Despite the lack of class I evidence, it is widely agreed that surgery can improve the functional and vital prognosis for WHO grade II gliomas when the resection is at least subtotal radiologically, that is, leaving less than 10 cm³ of visible residual tumor. Because these tumors frequently invade functional areas, the preoperative estimation of the probable residual volume remains challenging. This article presents a probabilistic map of postoperative residues, with the aim of predicting before the decision for surgical intervention whether the resection could be subtotal. We selected 65 patients who underwent surgery with intraoperative functional mapping between 1999 and 2004 for a WHO grade II glioma located in a sensorimotor and/or language area. For each case, the postoperative image was normalized on a standard atlas, and the residual tumor was segmented. A probabilistic map of residues was then computed. The fusion between the map and a preoperative image allowed a preoperative estimation of the expected extent of resection. The map enhances the regions where grade II glioma cannot be resected. The success rate for the preoperative classification of partial versus subtotal resection is 82%. Although both its reliability and accuracy have to be improved, this probabilistic map gives preoperatively an objective estimation of the expected extent of resection for grade II glioma resected under intraoperative functional mapping. This rationale will assist in decisions regarding surgical resection and may thus contribute to the elaboration of a therapeutic consensus for WHO grade II glioma.

Keywords: grade II glioma, intraoperative mapping, probabilistic map

Low-grade gliomas are slow-growing tumors, but they hamper functional prognosis, because they infiltrate functional areas, and vital prognosis, because they are ultimately prone to undergoing anaplastic transformation (Wessels et al., 2003). Although the treatment of these tumors remains controversial, there is growing evidence that the extent of resection is an important factor in outcome (Berger et al., 1994; Keles et al., 2001; Yeh et al., 2005). To achieve a resection as large as possible while preserving the functional areas usually located within the infiltrative part of the tumor, the safest technique is based on intraoperative functional mapping.
by cortical and subcortical direct electrical stimulation (Duffau et al., 2005a). As indicated by functional intraoperative testing, surgery is performed while the patient is under general anesthesia (motor functions) or local anesthesia (somatosensory, language, vision, working memory, spatial reasoning, calculation, and other cognitive functions). Intraoperative testing is planned preoperatively according to the anatomical location of the tumor and according to the results of neuropsychological assessment and noninvasive functional examinations, such as functional MRI (fMRI), PET, or magnetoencephalography.

Although these functional imaging techniques can help to anticipate preoperatively where the resection will be stopped because of functional responses encountered during intraoperative stimulations, they do not predict these functional cortical limits with good reliability. Moreover, they are restricted to the analysis of cortical sites and do not provide information about functional fiber tracts in white matter. Thus, according to these functional data and to the experience acquired with previous similar cases, estimation of the postoperative residual volume can be only subjective and qualitative. However, the decision for surgical resection is highly dependent on the size of this expected residue, because surgery probably does not influence prognosis if the resection cannot be at least subtotal.

In this article, we propose the creation of a probabilistic map, using standard computational methods of imaging, of postoperative residues of selected grade II glioma from a series of patients who underwent surgery with intraoperative functional mapping by electrical cerebral stimulation. As a direct application of this map, we present a method that enables a preoperative, objective estimation of the probable postoperative residual tumor volume. Data in this map could thus be of utmost importance in the elaboration of a therapeutic strategy for grade II gliomas.

**Patients and Methods**

**Intraoperative Direct Cerebral Stimulation**

Cortical and subcortical mapping was accomplished by using direct electrical stimulations with a bipolar electrode with 5-mm-spaced tips delivering a biphasic current (pulse frequency, 60 Hz; single-pulse phase duration, 1 ms; and amplitude, 2–8 mA) (Ojemann Cortical Stimulator 1; Radiomics, Inc., Burlington, Mass.).

In the first stage of the procedure, in order to avoid any damage to the eloquent area, cortical mapping was performed before resection. Sensorimotor mapping was systematically tested to confirm a positive response (e.g., the induction of movement and/or paresthesia in the contralateral hemibody when the primary sensorimotor areas were stimulated in a patient at rest). The minimal current intensity inducing a response was determined for each patient by progressively increasing the amplitude in 1-mA steps, from a baseline of 2 mA to an upper limit of 8 mA (to avoid generating seizures). For language testing, the patient while undergoing surgery with local anesthesia was asked to count (regularly, from 1 to 10, over and over) and to name pictures so that the essential cortical language sites known to be inhibited by stimulation could be identified. The patient was never informed when the brain was stimulated. Each stimulation lasted 4 s. For the picture-naming task, at least one picture was shown without stimulation, the display of a picture without stimulation followed each stimulation, and to avoid seizures, no site was stimulated twice in succession. A cortical site was considered essential for language if its stimulation induced speech disturbances during three trials, in accordance with previous studies (Ojemann et al., 1989).

During a second, surgical stage, the glioma was removed by alternation of resection and subcortical stimulations. The functional pathways were followed progressively, from the cortical eloquent sites already mapped, to the depth of the resection. To perform the best possible tumor removal while preserving the functional areas, all the resections were pursued until eloquent pathways (for motor function, as well as for language) were encountered around the surgical cavity, as determined by the subcortical stimulation.

**Patients**

This retrospective study initially included 154 patients whose cases had been followed for WHO grade II glioma (Kleihues and Cavenee, 2000) at the Pitié-Salpêtrière Hospital between 1997 and 2004 (Duffau et al., 2005a) and who underwent surgery performed by two of the authors (H.D. and L.C.). Histological types included 45 oligodendrogliomas, 6 astrocytomas, and 14 oligoastrocytomas. All of the patients had a tumor located in a functional site, requiring intraoperative functional mapping, which was accomplished with cortical and subcortical electrical stimulation. The resection was subtotal (residual volume < 10 cm³) for 75% of the patients. Permanent deficits were observed in 6.5% of the patients. Images meeting the Digital Imaging and Communications in Medicine (DICOM) standard were not available for each case, and the study was consequently restricted to a subspecies of 65 patients. In this subgroup, 65% of the patients had undergone subtotal resection, and 3% had incurred permanent deficits.

**Probabilistic Mapping of Residues**

The DICOM images that were available for the subgroup of 65 patients were used for mapping of residues. As much as possible, images produced three to six months after surgery (40 cases) were used rather than the immediately postoperative images (25 cases). Indeed, anatomical structures may be displaced on immediately postoperative images (because of edema or subdural collection), and after six months, the residual tumor, albeit in rare instances, could already have experienced regrowth. Magnetic resonance images were acquired with a 1.5 T...
scan, and the sequences were three-dimensional spoiled gradient, T1-weighted, usually with gadolinium injection. Slice thickness was 1 mm.

The methodology of spatial normalization relies on the same tools as those developed for lesion analysis in other neurological fields (especially for lesion analysis in stroke). Each postoperative MR image was spatially normalized in the Montreal Neurological Institute (MNI) atlas (Evans et al., 1992) by using the Lesion-mask procedure (Brett et al., 2001) (available at http://www.psychology.nottingham.ac.uk/staff/crl/mritut.html#Normalize2) and SPM2 software (available at http://www.fil.ion.ucl.ac.uk/spm/software/spm2) under Matlab 7.0 (MathWorks, Natick, Mass.). Such a process first requires a segmentation of the lesion (including residual tumor and resection cavity), which has to be excluded from the normalization itself. Indeed, introducing a cost-function masking reduces the distortions generated by the nonlinear transformation. Nonetheless, because of the great variability in the size of the ventricles, a mismatch is still present, especially for the periventricular white matter (Fig. 1). All segmentations were performed manually with MRICro software (available at http://www.psychology.nottingham.ac.uk/staff/crl/mricro.html). On each normalized image, the residual tumor was also manually segmented. Flair images were used to assist the interpretation of hypointense T1-weighted MRI as residual tumor. The statistical map was then computed (specific Matlab procedure, written by S.J.): A probability was associated with each voxel. This probability is the ratio of the number of residual tumors to the number of preoperative tumors occupying this voxel.

Preoperative Estimation of the Residual Volume

The resulting map can be tested to estimate preoperatively the residual tumor volume. A leave-one-out method (Shao, 1993) was used: The tested case was systematically excluded from the probabilistic map. For each patient, the estimation was obtained by multiplying the volume of a voxel (Fig. 2) by the sum of the probabilities contained in the segmented lesion (cavity + residual tumor, corresponding to the preoperative tumor). According to the amount of residual tumor, resections were classified (Berger et al., 1994) as subtotal (<10 cm³, thus including complete resections) and partial (>10 cm³). The success rate for the preoperative classification of subtotal versus partial resection was also calculated.

Results

Among the 65 lesions, the right hemisphere was involved in 21 cases and the left hemisphere in 44 cases. Patients with right-sided lesions displayed a right dominant hemisphere in four cases. Lesions were exclusively located in or near functional areas. (Thus, during intraoperative functional mapping, sensorimotor functions were systematically tested, and language functions were tested...
for 45 patients.) The median initial volume was 77 cm$^3$ (range, 20–290 cm$^3$).

Figure 3 shows the resulting map for some of the slices of the brain. (The entire map is available online as supplementary data at the DOI for this article.) As expected, only voxels situated near functional zones appear on the map. It is remarkable that the regions with a high probability of residual tumors are essentially located in the white matter.

To test the coherence of the resulting map, preoperative estimation of residual volume was computed. Figure 4 shows that the estimation is qualitatively good: The greater the effective segmented residual tumor was, the greater was the preoperative estimation (correlation coefficient = 0.78). The mean error is 6.2 cm$^3$ (range, 0.02–32.4 cm$^3$). The error is less than 5 cm$^3$ in 58% of cases and more than 10 cm$^3$ in 20%. The mean underestimation is 8.8 cm$^3$ (range, 0.02–32.4 cm$^3$), whereas the mean overestimation is 3.5 cm$^3$ (range, 0.16–10.0 cm$^3$). There is a greater tendency to underestimate the residual volume as it increases (only one patient showed overestimation of residual volume in the group of patients with partial resection).

To analyze the clinical relevance of this estimation, the success rate was calculated for the preoperative classification of subtotal versus partial resection. The value is 82%, indicating that only 18% of patients were misclassified. Among them, nine patients with partial resection had an underestimation of the residual volume (mean underestimation, 10.8 cm$^3$; range, 5–18 cm$^3$), and three patients with subtotal resection had an overestimation of the residual volume (mean overestimation, 7.7 cm$^3$; range, 2–10 cm$^3$).

Discussion

Methodology

Spatial normalization of brain images has been extensively used to infer brain function (Brett et al., 2002), both from normal brain (functional studies of healthy volunteers) and from pathological brain (lesion analysis in stroke). Nevertheless, such methods have never been applied to the field of neuro-oncology.

The spatial normalization used in this report is based on a cost-function masking (Brett et al., 2001). Other algorithms exist (Crivello et al., 2002), and another method (the full multigrid approach) could enable a better alignment of both white and gray matter. However, it has been proven that the functional intersubject variability is greater than the anatomical one (Crivello et al., 2002). The choice of the SPM algorithm is thus not crucial for the present purpose. Note that the Lesion-mask procedure has been developed on T1-weighted MRI without gadolinium injection. In this work, it has been used to normalize injected images. Given the small volume of vessels in comparison to the whole volume of the brain, this should not induce major bias in the transformation. Indeed, the alignment was systematically reviewed visually, and there were no aberrant results.

On the other hand, mechanical displacement of anatomical brain areas, due to the tumor and/or the resection, is a major limitation of this methodology. Indeed, most current algorithms have been dedicated to brain pathology without considering important displacement.
of anatomical areas (as in stroke). Theoretical biomathematical work on brain mechanical properties (Cuadra et al., 2004) should be a way to enhance the normalization process for the modeling of mass effect, when such mass effect is important. Indeed, the usual mathematical models of glioma growth have recently been improved by taking into account stresses and deformability of brain parenchyma (Clatz et al., 2005). This simulation can be used to correctly normalize a preoperative image on the probabilistic map and thus avoid errors in the residual volume estimation. Similarly, mechanical effects of tumor resection could be simulated, which would lead to improved normalization of the postoperative images and thus increase the spatial accuracy of the probabilistic map of residual tumors.

Finally, the statistical significance of the map is a very important issue. First, the significance is, of course, much greater for those voxels where a greater number of tumors have been observed. On the contrary, probability in voxels where only one or two lesions have been segmented is of poor significance. In the present map, 27% of the voxels contain only one lesion, 18% two lesions, 40% between three and five lesions, 14% between five and 10 lesions, and 1% more than 10 lesions. There are two ways to enhance the significance: by including more cases or, conversely, by restricting the analysis to different clinicoradiologically homogeneous subgroups. Statistical tools like bootstrapping (Efron and Tibshirani, 1993) could also be developed to quantify the reliability of the residual volume estimation.

**Interpretation of Residual Tumor**

The posterior part of the corpus callosum and the anterior perforated substance appear on the map (see Fig. 3) among regions with a high probability of residual tumor. These regions do not contain neural structures that are functionally essential, but their resection can lead to adverse effects. Indeed, they are either difficult to access (posterior part of corpus callosum) or are known to contain lenticulostriate vessels (anterior perforated substance). That these nonresectable anatomical structures are correctly visualized is a first validation of the map.

The relationship between tumor and functional cortical sites is usually investigated preoperatively by noninvasive functional examinations like fMRI, PET, or magnetoencephalography. Because the sensitivity and specificity of these techniques are limited (Roux et al., 2003) (essentially because of perturbations induced by the tumor on local hemodynamics and coupling between metabolism and electrical activity [Aubert et al., 2002]), intraoperative electrical stimulation remains the gold standard. In the present map, cortical areas are as a rule associated with a low probability of residual tumor. This result is consistent with the well-known individual anatomical-functional variability. This variability, eventually enhanced by the interaction with tumor growth, can be viewed as the macroscopic remapping of brain function (Duffau, 2005). This map thus illustrates clearly the concept of plasticity.

As it has been recently modeled (Jbabdi et al., 2005), low-grade gliomas migrate along white matter fiber tracts. Diffusion tensor imaging (DTI), combined with neuronavigation, or intraoperative MRI, may eventually enable the anatomical location of the tracts (Nimskey et al., 2005), but this technique—whose reliability remains to be evaluated—does not provide information about the functional role of these fasciculi. Intraoperative electrical stimulation is presently the only way to test the role of these pathways, which are often still functional, albeit invaded. As mentioned in the Results section, most of the regions with a high probability of residual tumor are located in white matter. They probably correspond to the functional subcortical pathways already described (Duffau, 2000; Duffau et al., 2002, 2003a, b, 2004, 2005b).

To further test the accuracy of the resulting map, we have focused our attention on the regions with a probability of residual tumor greater than 70%. They clearly include the pyramidal tract, both at its origin (Fig. 5A), just under the primary motor area, and deep within the internal capsule (Fig. 5B). Other tracts are also recognizable: the inferior occipitofrontal fasciculus (Fig. 5C), involved in semantic processes of language, and the arcuate fasciculus (Fig. 5D). Of interest, the location of residual tumors along white matter tracts indicates that subcortical areas seem to be less subject to reorganization by plasticity than are cortical sites.

**Oncological Interest**

The optimal therapeutic strategy for low-grade gliomas is still a matter of debate (Ashby and Shapiro, 2004). It is usually believed that postoperative tumor volume influences the prognosis for patients with this disease (Berger et al., 1994; Duffau et al., 2005a; Keles et al., 2001; Yeh et al., 2005). However, it seems that there is only a limited prognostic influence if the residual volume is greater than 10 to 15 cm³. In this case, it could be more advantageous to start active treatment with radiotherapy or even chemotherapy (Byrne, 2004). It is therefore of utmost importance to develop a standard tool that enables an objective preoperative estimation of the postoperative tumor volume.

With the present mapping method, 82% of patients are preoperatively classified correctly in terms of a probable subtotal versus partial resection. This high rate of success indicates that this map is a promising tool for use in the decision-making process of whether to operate on a grade II glioma.

Moreover, recent clinical studies of gliomas stress the importance of quality of life in the elaboration of a therapeutic management. Treatment efficacy should be evaluated not by survival probabilities only, but rather by a composite benefit-risk ratio. Because intraoperative stimulation guarantees the functional role of the area in which the residual tumor is located, regions with a high probability on the map are most often associated with essential sensorimotor and/or language areas. Of course, this methodology could be applied to other brain functions such as visuospatial perception, vestibular function, or calculation.
This map could therefore be used in the planning of other treatment modalities, like radiotherapy. Indeed, this approach could be taken to tailor the radiation regimen, taking into account the regions of high functional probability, to limit adverse cognitive effects (Taphoorn and Klein, 2004).

Conclusion and Perspectives

Using current tools of neuroimaging normalization, we have computed a probabilistic map of tumoral residues for grade II gliomas resected with intraoperative functional mapping. As a direct application, the resulting map enables an 82% rate of success for the preoperative classification of subtotal resection (<10 cm³) versus partial (>10 cm³) resection. This map could be provided as a new tool to help with surgical decision making and hence standardize the therapeutic strategy in low-grade gliomas. Moreover, the normalization in the standard MNI atlas could enhance its use with DTI, with the aim of identifying the functional role of the white matter tracts. Finally, the online availability of the atlas could facilitate both its use and its continual improvement. Indeed, by increasing the number of patients in other centers and ours, by restricting the analysis to clinicoradiologically homogeneous subgroups, and by improving normalization accuracy with biomathematical modeling, both the reliability and the accuracy of the present map should be greatly enhanced.

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References


