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PATIENTS AND METHODS

Patients

Between 1985 and 2003, 222 patients underwent surgical resection for a supratentorial LGG in our institution, without any previous therapy. Two consecutive periods were identified for the present study:

- (1) from 1985 to October 1996, during which 100 patients were operated on without intraoperative electrophysiological mapping (retrospective study—series 1 (S1))
- (2) from November 1996 to 2003, during which 122 patients were operated on with the use of DES (prospective study—series 2 (S2)).

A part of this experience has been described previously, with special attention to the detailed neurological outcome in series 2, but no comparison was made with a surgical series in which intraoperative functional mapping was not done.

Preoperative evaluation

For both S1 and S2, we reviewed the presenting symptoms and preoperative neurological examination. Patients were classified in two groups:

- Group I: no or mild deficit, with Karnofsky Performance Status (KPS) score ranging between 80 and 100
- Group II: a severe deficit, which led to deterioration in the quality of life, with the patient unable to carry out normal activities (that is, KPS of 70 or less).

In both series, we analysed the topography of the tumour on a preoperative magnetic resonance (MR) image (T1-weighted and/or spoiled gradient images before and after
gadolinium enhancement in the three orthogonal planes and T2-weighted axial images. Fluid attenuated inversion recovery (FLAIR)-weighted axial images were taken in the last three years of series 2). The volume of the tumour was evaluated using the method proposed by Berger et al—that is, the product of the three largest diameters (two measured in the axial plane, the third measured in the sagittal plane, as we have previously reported) divided by 2. All tumours were graded functionally, relative to their location with respect to the eloquent brain, into two groups:

- tumours involving functional regions, according to the definition previously proposed by us—for example, motor cortex/supplementary motor area, somatosensory cortex, speech centres, visual cortex, insular lobe, internal capsule and deep grey nuclei
- tumours near or remote from eloquent areas and not invading these areas.

**Intraoperative technique**

In both series, we used the same surgical equipment (ultrasonic aspirator, bipolar coagulation, ultrasonography, operative microscope), except for the intraoperative functional mapping methods, which were not used in series 1. In series 2, intraoperative real-time functional cortico-subcortical mapping was performed during all the surgical procedures (motor mapping in 49 patients under general anaesthesia; sensorimotor and language mappings in 73 patients under local anaesthesia), using the technique of DES. We have described this technique in detail in previous reports, and it is based on the methodology described by Berger and Ojemann. Our aim was first to track and encounter so as not to interrupt the surgery prematurely, to continue LGG removal until functional areas were delineated before its removal but also to control the residual amount during the resection.

**Results**

The clinical, radiological, and surgical data of both series are summarised in table 1.

**Clinical and radiological findings**

Seizures were the presenting symptoms in 95% of patients in both series. Clinically, the neurological examination was normal in 94 patients in S1 and 112 patients in S2. However, on the basis of the KPS scores, all patients from S1 and S2 were classed into group I—that is, with KPS between 80 and 100. In S1, 35 tumours involved functional areas (table 1 and fig 1A) whereas in S2, 76 tumours were located within eloquent regions (table 1 and fig 2A) (p<0.0001).

Of the tumours not invading eloquent areas, 29% were near functional regions in S1 versus 32.7% in S2 (not significant), whereas 36% were remote from eloquent areas in S1 versus 5% in S2 (p<0.0001). There was no significant difference between the groups with regard to preoperative tumour volumes (p = 0.09) (see table 1 for details).

**Surgical findings**

In S2, intraoperative electrical mapping was used for the removal of all tumours located within and near eloquent areas (95% of cases). Only six resections were performed without stimulation in this series. In all 116 surgeries with mapping, the stimulations allowed detection of the eloquent cortico-subcortical areas, systematically used as boundaries of the resection. However, the mean duration of surgery was longer in S2 (five v three hours in S1) and the incidence of bone flap infection was 0.86% (1/116) in S2.

**Postoperative neurological results**

In S1, mortality was 2%, and 17% with a severe permanent deficit were in group II (see table 1). In S2, there were no deaths, and 6.5% of patients with severe sequelae were in group II (p<0.019, two tailed test) (figs 1B and 2B).

**Postoperative radiological results**

The difference between the quality of resections as evaluated on the postoperative control MRI in S1 and S2 (see table 1) was statistically significant (p<0.001).

**Histological results**

On histopathological examination, a low grade glioma (WHO grade II) was diagnosed in all patients in both series.
Table 1  Clinical, radiological, and surgical characteristics of 222 patients operated on for a low grade glioma (LGG) without (series 1) and with (series 2) intraoperative direct electrical stimulation (DES)

<table>
<thead>
<tr>
<th>DES used</th>
<th>Period</th>
<th>No.</th>
<th>Sex and age (range)</th>
<th>Preoperative volume</th>
<th>Location of glioma</th>
<th>Preoperative examination</th>
<th>Severe complications</th>
<th>Quality of resection</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series 1</td>
<td>1985–Oct 1996</td>
<td>100</td>
<td>56 Men 44 Women 38 Years (19–66)</td>
<td>Median: 69 ml 4% &lt;14 ml 23% &gt;13.5 and &lt;32 ml 21% &gt;32 and &lt;62.5 ml 52% &gt;62.5 ml</td>
<td>Within eloquent areas</td>
<td>1 Sight motor deficits 1 Sight hypoplasia 4 Sight dysphasia</td>
<td>5 Severe motor deficits 3 Severe language deficits 2 Severe language + motor deficits</td>
<td>T 11 ST 23 P</td>
<td></td>
</tr>
<tr>
<td>DES not used</td>
<td>Oct 1996</td>
<td>44 Women</td>
<td>14 ml</td>
<td>35 (35%)</td>
<td>9 Primary sensorimotor areas (4R, 5L) 5 Broca’s areas (L) 7 Left posterior temporal language areas</td>
<td>No deficit</td>
<td>3 Severe motor deficits 2 Severe language deficits 2 Severe language + motor deficits</td>
<td>T 26 ST 34 P</td>
<td></td>
</tr>
<tr>
<td>Series 2</td>
<td>Nov 1996–Feb 2003</td>
<td>122</td>
<td>67 Men 55 Women 36 Years (17–63)</td>
<td>Median: 55 ml 11% &lt;14 ml 21% &gt;13.5 and &lt;32 ml 25% &gt;32 and &lt;62.5 ml 43% &gt;62.5 ml</td>
<td>Within eloquent areas</td>
<td>1 Sight motor deficits 1 Sight hypoplasia 4 Sight dysphasia</td>
<td>5 Severe motor deficits 3 Severe language deficits 2 Severe language + motor deficits</td>
<td>T 11 ST</td>
<td></td>
</tr>
<tr>
<td>Systematic DES use (except in the 5% of patients with LGGs remote from eloquent areas)</td>
<td>Nov 1996–Feb 2003</td>
<td>122</td>
<td>67 Men 55 Women 36 Years (17–63)</td>
<td>Median: 55 ml 11% &lt;14 ml 21% &gt;13.5 and &lt;32 ml 25% &gt;32 and &lt;62.5 ml 43% &gt;62.5 ml</td>
<td>Within eloquent areas</td>
<td>1 Sight motor deficits 1 Sight hypoplasia 4 Sight dysphasia</td>
<td>5 Severe motor deficits 3 Severe language deficits 2 Severe language + motor deficits</td>
<td>T 11 ST</td>
<td></td>
</tr>
<tr>
<td>No deficit</td>
<td>3 Severe motor deficits 2 Severe language deficits 2 Severe language + motor deficits</td>
<td>T 26 ST 34 P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

KPS, Karnofsky Performance Status; T, total; ST, subtotal; P, partial; SMA, supplementary motor area; R, right; L, left.
Survival
Based on the quality of resection, mortality in the two series was as follows.

- Series 1 (p = 0.04)
  - Partial resections: 30/57 (52.6%), median follow up 72 months
  - Subtotal resections: 13/37 (35%), median follow up 87 months
  - Complete resections: 0/6 (0%), median follow up 75 months

- Series 2 (p = 0.02)
  - Partial resections: 6/29 (20.6%), median follow up 49 months
  - Subtotal resections: 5/62 (8%), median follow up 45 months
  - Complete resections: 0/31 (0%) median follow up 48 months

DISCUSSION
Recent literature reveals a more frequent use of intraoperative electrostimulation mapping during tumour surgery in eloquent brain areas, in particular for poorly demarcated lesions such as infiltrative LGGs. However, this method still remains controversial first, because of the alternative use of intraoperative electrophysiological monitoring techniques (evoked potentials) proposed by several authors; second, since it is necessary to perform the surgery under local anaesthesia to allow language mapping; and third, because of the recent development of neurofunctional imaging, which can be integrated into a neuronavigation system.

We believe that none of these criticisms is really well founded, since (a) evoked potentials do not allow the mapping of language and other cognitive functions, (b) good tolerance of awake craniotomies has been well demonstrated, (c) neurofunctional imaging still lacks reliability, especially with regard to language mapping. In fact, the real problem seems to be that only few studies have compared the results of surgery without and with the use of DES to evaluate the exact contribution of intraoperative electrostimulation. Moreover, in these rare reports, the impact of DES and other methods, such as somatosensory evoked potentials and/or neuronavigation, has been evaluated together, so it is difficult to assess the exact role of sole DES. Also, in these studies, intraoperative motor mapping was done only during tumour surgery within the central region and language mapping was not reported (except in rare series of dominant temporal lobectomies in epilepsy surgery, which present not exactly the same

Figure 1  (A) Preoperative axial T1-weighted magnetic resonance imaging (MRI) scan, showing a left precentral low grade glioma invading the dominant superior frontal gyrus (series 1). (B) Postoperative axial T1-weighted MRI, after a surgery performed without intraoperative electrical mapping, showing the resection of the anterior part of the tumour, with a residue in contact with the primary motor area posteriorly. Arrow: precentral sulcus.

Figure 2  (A) Preoperative axial T1-weighted magnetic resonance imaging (MRI) scan, showing a similar left precentral low grade glioma invading the dominant superior frontal sulcus (series 2). (B) Postoperative axial T1-weighted and fluid attenuated inversion recovery (FLAIR)-weighted MRI, after a surgery performed with intraoperative electrical mapping, showing total resection of the tumour—the cavity coming into contact with the primary motor area posteriorly, identified by stimulations. Arrow: precentral sulcus.
problem as in surgery for infiltrative cortico-subcortical gliomas). Finally, the tumours operated on have not all been the same, since the recent series of Reithmeier et al\(^2\) included not only low and high grade gliomas but also metastasis and meningiomas.

In the present study, we included a uniform consecutive sample to try to quantify the impact of DES during surgery of supratentorial LGGs, whatever their location, on (a) surgical indications, (b) functional results, and (c) quality of tumour resection.

**Extension of surgical indications**

Although surgery for infiltrating LGGs has been the subject of much controversy in the literature,\(^34\) a growing number of recent series have provided evidence for the favourable impact of resection on the natural history of this kind of lesion.\(^34\) Consequently, a patient who is not selected for resective surgery for technical reasons (for example, the location of the lesion) by a team which performs surgical resection for LGGs, if the tumour is in fact “operable”, could potentially lose the chance of a favourable outcome.

In our experience, the definition of “operability” significantly changed between the first and the second series, since 62% of LGGs resected in S2 were located within eloquent areas, whereas only 35% of LGGs involved functional regions in S1. Indeed, during the earlier period, there were patients in whom surgical resection was not considered an option: this was typically the case for insular LGGs, which were almost never removed in S1, being documented as “inoperable”. However, we must point out the fact that the extension of surgical indications in S2 was partly due to the following confounding factors:

- evolution of the management of LGGs in the last decade, favouring aggressive treatment rather than a “wait and see” attitude, due to a better knowledge of the natural history—in particular with regard to the high risk of anaplastic transformation leading to death.\(^34\)\(^35\)
- development of preoperative neurofunctional imaging techniques, which allow better prediction of the individual functional surgical risk and improved surgical planning.\(^34\)
- improvement of the surgeon’s experience, with a tendency towards “hyper-specialisation” in the second period, and thus a slight modification of the population of patients treated at our institution in S2 as reflected in the lower rate of LGG surgeries remote from eloquent regions.

Nevertheless, it seems that the use of intraoperative DES itself has had an actual impact on the modulation of our criteria of “operability”. First, these methods of intraoperative mapping permit identification and preservation of the functional areas at each moment and each site of the resection. Thus, surgery within the eloquent area is not much more difficult than in “non-eloquent” regions, since the boundaries of the resection are defined in real time using objective and not subjective individual functional data. Second, DES has allowed us to understand better the pathophysiology of eloquent areas in which surgery was rare until recently—despite the fact that LGGs are often located in these areas, such as the insular lobe.\(^37\)\(^38\) Indeed, an increase in the knowledge of the functional role of the critical brain regions using DES has permitted us to perform surgery in these structures with minimal risk.\(^39\)\(^40\) Third, DES allows the study of individual plasticity,\(^52\)\(^53\) a brain potential often described in functional compensation in patients harbouring an LGG, thus leading to an extension of the limits of resection in eloquent areas without induction of permanent deficit.\(^59\)\(^54\)

**Improvement of postoperative functional results**

Taking into account the fact that an LGG is usually revealed by seizures, in young patients leading an active social-professional life with a normal neurological examination or only a slight deficit, surgery should be considered on the sole condition that the risk of inducing a permanent deficit is low.

Clearly, in our experience, DES has significantly decreased the rate of sequelae (6.5% in S2 vs 17% in S1), despite a higher number of surgeries performed within eloquent areas in S2. Indeed, the rest of the surgical methodology was the same in both series, and we did not use neurofunctional imaging data intraoperatively, integrated into an image-guided surgery system, even in S2.

Interestingly, our results are similar to those reported in the literature. In series where intraoperative electrical mapping was not used, the rate of sequelae ranged from 13% to 27.5%, with a mean of 19%,\(^55\)\(^62\) which is comparable to the results of our S1. In contrast, the rate of postoperative severe permanent deficit reported in the many studies describing the use of DES during surgery of LGG was quite similar at around 4%, again close to our experience (S2). These comparisons are important since they show that DES represents a reliable and reproducible technique with consistent good results—whichever surgical team performs the resection (even in different countries). Our review covers 834 patients operated on for a glioma, including 358 LGGs, in 21 different neurosurgical departments distributed in nine countries (table 2).\(^7\)\(^13\)

Furthermore, intraoperative electrical mapping excludes neither simultaneous electrophysiological monitoring by evoked potentials nor integration of preoperative neurofunctional imaging data in an image-guided system.\(^11\)\(^23\) On the contrary, cortical DES may allow validation of positron emission tomography (PET), magnetoencephalography (MEG), functional (f)MRI, and even the recent method of fibre tracking by diffusion tensor imaging.\(^83\)

**Improvement of the quality of resection**

Since intraoperative DES allows individual identification of the cortical and subcortical eloquent structures, it seems logical to perform a resection according to functional

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>No. of gliomas (No. of LGGs, if available)</th>
<th>Permanent severe postoperative deficits</th>
</tr>
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<tbody>
<tr>
<td>Berger et al (1994)(^3)</td>
<td>53 (53)</td>
<td>0</td>
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<tr>
<td>Cubert et al (1995)(^3)</td>
<td>5 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Ebel et al (2000)(^3)</td>
<td>26 (10)</td>
<td>1 (4)</td>
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<tr>
<td>Ebeling et al (1995)(^4)</td>
<td>11 (7)</td>
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<tr>
<td>Etser et al (2002)(^4)</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Fardini et al (1999)(^4)</td>
<td>8 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Freytag et al (2001)(^5)</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Haglund et al (1994)(^5)</td>
<td>40 (25)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Krambach et al (1998)(^5)</td>
<td>6 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Meyer et al (2001)(^5)</td>
<td>65 (18)</td>
<td>3 (4.5)</td>
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<td>Nikas et al (1998)(^5)</td>
<td>175 (175)</td>
<td>10 (6)</td>
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<td>Peraud et al (2002)(^5)</td>
<td>24 (24)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Reuten et al (1997)(^5)</td>
<td>30</td>
<td>4 (13)</td>
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<tr>
<td>Rostomily et al (1999)(^5)</td>
<td>5 (4)</td>
<td>0</td>
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<td>Roux et al (2001)(^5)</td>
<td>15 (9)</td>
<td>0</td>
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<td>Schiffbauer et al (2002)(^5)</td>
<td>183</td>
<td>6 (3)</td>
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<td>Sobotka et al (2002)(^5)</td>
<td>7 (4)</td>
<td>0</td>
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<tr>
<td>Taylor et al (1999)(^5)</td>
<td>121 (21)</td>
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<td>Wagner et al (1997)(^5)</td>
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<td>Walsh et al (1990)(^5)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Whittle et al (2003)(^5)</td>
<td>25</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

| Total | 834 (358) | 35 (4.2) |

LGG, low grade glioma.
boundaries. Indeed, we suggest continuing the resection until after the functional structures are detected by DES, and not stopping before, in order to optimise the quality of resection without increasing the risk of inducing postoperative permanent deficit.

This surgical strategy based on the extensive use of DES during the resection, in our experience has significantly improved the quality of LGG removal. Only 37% of resections were defined as subtotal and 6% as total on postoperative MRI in series 1, whereas 50.8% of resections were subtotal and 25.4% total in series 2—despite a higher number of surgeries within the critical areas—with a parallel decrease of the rate of sequelae.

Moreover, whereas extensive surgery is still controversial in LGG, the series’ supporting the positive impact of such a surgical strategy argue that this benefit seems directly related to the quality of resection.\(^1\)\(^{61-45}\) Our present oncological results provide the basis for strong arguments in this direction, since the rate of deaths was significantly decreased in cases of subtotal and total glioma removal, in comparison with partial removal. Interestingly, this observation was true for both our series (median follow up: S1 77 and S2 47 months) even though there were more patients with a complete or subtotal resection in S2.

**CONCLUSIONS**

The present work allows for the first time quantification of the contribution of intraoperative DES during LGG resection. Indeed, our results show that the use of this method leads to:

- extension of indications of LGG surgery within eloquent areas
- decrease of the risk of sequelae
- increase of the quality of tumour resection itself, with an impact on survival.

Thus, DES seems to represent a valuable adjunct to LGG surgery based on the premise that only radiologically total or subtotal resection has a positive impact on the natural history of these tumours.

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Contribution of intraoperative electrical stimulations in surgery of low grade gliomas


