Intractable epilepsy in paralimbic Word Health Organization Grade II gliomas: should the hippocampus be resected when not invaded by the tumor?

Clinical article

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Object. Beyond its oncological benefit, surgery could improve seizure control in paralimbic frontotemporalinsular or temporoparietal WHO Grade II gliomas generating intractable seizures. However, no studies have examined the impact of hippocampal resection on chronic epilepsy when the hippocampus is not invaded by Grade II gliomas. Here, the authors compared the epileptological outcomes and return to work in 2 groups of patients who underwent surgery with or without hippocampectomy for paralimbic Grade II gliomas eliciting intractable epilepsy despite no tumoral involvement of the hippocampus.

Methods. Surgery was performed in 15 consecutive patients who were unable to work (median Karnofsky Performance Scale [KPS] Score 70) because of refractory epilepsy due to paralimbic Grade II gliomas that were not invading the hippocampus. In Group A (8 patients), the hippocampus was preserved. In Group B (7 patients), glioma removal was associated with hippocampectomy.

Results. No patient died or suffered a permanent deficit after surgery. Postoperatively, in Group A, no patients were seizure free (4 patients were in Engel Class II and 4 were in Class III). In Group B, all 7 patients were seizure free (Class I) (p = 0.02). Only 62.5% of patients returned to work in Group A, whereas all patients are working full time in Group B. The postsurgical median KPS score was 85 in Group A, that is, not significantly improved in comparison with the preoperative score, while the postsurgical median KPS was 95 in Group B, that is, significantly improved in comparison with the preoperative score (p = 0.03).

Conclusions. The authors’ data support, for the first time, the significant impact of hippocampectomy in patients with intractable epilepsy generated by a paralimbic Grade II glioma, even if it does not invade the hippocampus. Hippocampal resection allowed seizure control in all patients, with an improvement in KPS scores, since all patients resumed their social and professional activities. Thus, the authors suggest performing a resection of the nontumoral hippocampus in addition to resection of the tumor in patients with refractory epilepsy due to paralimbic Grade II gliomas.

KEY WORDS • glioma • intractable epilepsy • hippocampectomy • surgery • paralimbic tumor • oncology

Approximately 10%–15% of epilepsy cases are caused by cerebral neoplasms in adults.13,82 Seizure represents the initial symptom in approximately one-third of primary brain tumors,13,82 with a higher rate of initial epilepsy (around 80%) in WHO Grade II gliomas.12,74 Moreover, numerous patients with Grade II gliomas experience intractable epilepsy, especially when the glioma involves the insular/paralimbic system,15,27,81 with a negative impact on cognition and quality of life.46 Recently, a large number of surgical studies based on objective evaluation of the extent of resection on postoperative MRI found that an extensive (total or at least subtotal) resection of Grade II gliomas was significantly associated with an increase in overall survival by delaying malignant transformation.25,53,69,70,72,75 Thus, maximal resection with preservation of quality of life is currently the first therapeutic option to consider in Grade II gliomas.76 However, even in cases of maximal resection, seizure control is usually achieved in only 70%–80% of patients, especially for insular/paralimbic Grade II gliomas.15,27,29,74 Interestingly, it was suggested that the majority of long-term epilepsy-associated tumors are temporal in origin, with the hippocampus by itself, perhaps representing an epileptogenic focus,50,58,62,66,87,89 as already shown in nonlesional temporal lobe epilepsy.8 In addition, strong relationships have been demonstrated between the insula/paralimbic system and the mesiotemporal/limbic structures.5,18,28,90 In an extensive literature review, all the

Abbreviations used in this paper: AED = antiepileptic drug; ILAE = International League Against Epilepsy; KPS = Karnofsky Performance Scale; MMSE = Mini-Mental State Examination.
achievements in epilepsy control related to brain tumors occurred when hippocampectomy was added because of tumor infiltration or the presence of dual pathology. Yet, to the best of our knowledge, in surgery for paralimbic frontotemporointrisular or temporointrisular Grade II gliomas, no study has specifically examined the impact of additional hippocampectomy on medically refractory epilepsy, when the hippocampus was not invaded by the glioma.

Here, we compared the epileptological outcomes in 2 groups of patients who underwent surgery with or without hippocampal resection for a paralimbic frontotemporointrisular or temporointrisular Grade II glioma that generated intractable epilepsy despite the absence of tumoral involvement within the hippocampus. We hypothesized that hippocampectomy, in addition to glioma removal, might have a positive impact on seizure control. We also studied the consequences of surgery on KPS score and return to work, but our goal was not to investigate neurocognition in this study.

**Methods**

**Patient Selection**

We analyzed a consecutive series of 15 right-handed adult patients with intractable epilepsy who underwent surgery between June 2006 and February 2010 for a paralimbic frontotemporointrisular or temporointrisular Grade II glioma that was not involving the hippocampus (Table 1). All patients experienced intractable seizures for a median duration of 12 months (range 6–17 months) despite taking 2–3 AEDs. As a consequence, no patient was able to work before surgery (median KPS Score 70). The MMSE scores were between 28 and 30 in all cases.

According to Yaşargil’s classification of paralimbic tumors, all patients harbored a Type 5A glioma with infiltration of the insula and the anterior temporal lobe (with or without the orbitofrontal area) but with no invasion of the hippocampus, as demonstrated on the preoperative T2-weighted/FLAIR MRI sequences.

**Imaging Evaluation**

In the first period of this series, preoperative tumor volume was calculated on the basis of the 3 largest diameters (D1, D2, and D3) of areas of signal abnormality on FLAIR MRI according to the 3 orthogonal planes (axial, sagittal, and coronal). An estimation of tumor volume was calculated by the ellipsoid approximation ([D1 × D2 × D3]/2), as previously reported. Postoperatively, the volume of the residual tumor (if any) was calculated using the same method on the FLAIR MRI studies obtained 3 months after surgery. In the second period of the series, pre- and postsurgical volumes were calculated using dedicated software (Myrian, Intrasense).

**Surgical Procedure for Tumor Resection**

All patients benefited from intraoperative functional electrostimulation mapping, as extensively described in previous reports. A bipolar electrode with a 5-mm space between the tips (Nimbus, Newmedic) and delivering a biphasic current (pulse frequency 60 Hz, single-pulse phase duration of 1 msec, amplitude 2–8 mA depending on the conditions of anesthesia) was applied to the brain. These procedures were performed under general anesthesia in all patients with a right-sided tumor (to allow motor mapping) and in awake patients in all other cases (to allow both sensorimotor and language mapping).

In a first stage, the tumor and cerebral sulci/gyri were identified using ultrasonography. Cortical mapping was performed subsequently to detect the eloquent areas.

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<th>Extent of Resection (%)</th>
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<th>ILAE Class (postop)</th>
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Hippocampectomy in epileptogenic paralimbic glioma

Taking these individual landmarks into account, the resection was initiated with an operculo- and/or polar temporal tumor removal in all cases (eventually associated with an operculo- and/or orbitofrontal resection in cases of frontal invasion), which provides a good exposure of the insular surface without opercular retraction. Stimulation mapping was then performed in the insular cortex. Subpial resection (to avoid the middle cerebral artery and its branches) was performed according to these functional boundaries. Insular mapping particularly concerned the distribution of language areas in the dominant hemisphere. The awake patient was asked to perform counting and naming tasks throughout the tumor removal, regularly alternated with stimulation eliciting disruption of language when performed at the level of a critical structure. In a second stage, using repetitive subcortical stimulation, we detected the motor descending pathways in the internal capsule in all patients (and in the centrum semiovale when the frontal lobe was also invaded by the glioma), as well as the language tracts in awake patients, especially the inferior occipitofrontal fascicle coursing in the roof of the sphenoidal horn of the ventricle and eliciting semantic paraphasia when stimulated, as previously detailed. To obtain the best possible tumor removal with preservation of eloquent structures, the resection was performed according to cortical and subcortical functional boundaries at each stage, thus without margin, except deep to the bifurcation of the sylvian artery, where removal of the limen insulae leads to the anterior perforating substance. Indeed, the lenticulostriate arteries run at this level, and this region represents an anatomical limit for resection. After completing maximal resection of the tumor involving the insula and anterior temporal lobe in all cases, we performed an additional hippocampectomy in 7 patients, with a subpial resection into the contact of the lateral part of the brainstem medially, and until the posterior part of the brainstem posteriorly (sphenoidal horn of the ventricle as the upper limit).

It is worth noting that no electrocorticography was performed during the procedure.  

Definition of the Groups

The 15 patients were divided into 2 groups (Table 1). In the first part of our study, we did not perform hippocampectomy. Because intractable epilepsy was not controlled in several patients, we decided to remove the hippocampus in a second period. In the first group (Group A), no hippocampectomy was performed at the end of tumor resection. This group included 8 patients. In the second group (Group B), additional hippocampectomy was performed at the end of glioma resection. This group comprised 7 patients. One of these patients underwent an initial surgery with glioma resection but without hippocampal removal. He underwent reoperation 11 years later with additional hippocampectomy due to chronic seizures, but with no tumor recurrence.

Evaluation Method of Seizure Outcome

Seizure outcome was evaluated using the Engel and the ILAE classifications.

The 4 classes of Engel classification include the following: Class I, free of disabling seizures; Class II, rare disabling seizures (almost seizure free); Class III, worthwhile improvement; and Class IV, no worthwhile improvement. The 6 classes of new classification by ILAE include the following: Class 1, completely seizure free, no auras; Class 2, only auras, no other seizures; Class 3, 1–3 seizure days per year with or without auras; Class 4, 4 seizure days per year to 50% reduction of baseline seizure days with or without auras; Class 5, less than 50% reduction of baseline seizure days to 100% increase of baseline days with or without auras; and Class 6, more than 100% increase of baseline seizure days with or without auras.

Evaluation Method for Functional Outcome

The functional outcome was evaluated by neurological examination immediately after surgery and 3 months later, the KPS score 6 months after surgery, and return to work status.

Statistical Analysis

The Fisher exact test was used to assess the relationship between the binary response (hippocampectomy vs no hippocampectomy) and the postoperative seizures. A significance level of 5% (p < 0.05) was accepted in each case.

Results

Clinical and Radiological Presentation

Patient characteristics are summarized in Table 1. Our series consisted of 15 right-handed patients (7 males and 8 females) with a mean age of 35.5 years (range 19–62 years).

Group A (no hippocampectomy) included 8 patients (4 males and 4 females), with a median age of 30 years (range 19–53 years). The neurological examinations revealed normal findings before surgery. The MMSE scores were between 28 and 30 in all cases. Four tumors involved the left dominant hemisphere, and 4 were located in the right side.

Group B (with hippocampectomy) comprised 7 patients (3 males and 4 females), with a median age of 37 years (range 26–62 years). There were no neurological deficits before surgery. The MMSE scores were between 28 and 30 in all cases. Two tumors involved the left dominant hemisphere, and 5 were located on the right side.

None of the 15 patients underwent radiotherapy or chemotherapy before the resection. None of the patients were able to work before surgery due to intractable seizures.

Postoperative Results

Functional Outcome. No patient died or suffered postoperative permanent neurological worsening in this series.

In Group A, immediately following surgery, 3 patients had a slight hemiparesis and 4 patients had a language deficit. All patients completely recovered within 3 months. In Group B, immediately after surgery, 3 patients...
experienced a slight hemiparesis and 2 patients had language deficits. All patients completely recovered within 3 months. There were no significant differences between the 2 groups.

The median KPS score in Group A improved after surgery from 70 to 85 (not significant). In Group B, the median KPS score significantly improved after surgery from 70 to 95 ($p = 0.03$). Postoperative MMSE scores were between 28 and 30 in all cases. There were no significant differences between the groups, and there were no significant differences before and after surgery.

**Epileptological Outcome.** In Group A, even if a decrease in seizures was observed in all patients, no patient was seizure free with a mean follow-up of 36 months (range 22–51 months) (Fig. 1). Four patients were in Engel Class II, and 4 patients were in Class III. All patients are still taking AEDs. The 8 patients have resumed their social activities. However, only 5 patients returned to work (62.5%), and 3 did not resume their professional activities. The mean extent of resection in this group was 86.3% (range 64%–95%).

In Group B, the 7 patients were completely seizure free (Engel Class I) with a mean follow-up of 20.5 months (range 19–33 months) (Fig. 2). There was a significant difference concerning the epileptological outcome between the 2 groups ($p = 0.02$). Six patients are still taking 1 AED, 2 of whom are taking decreased doses, and 1 patient stopped treatment in Group B. In addition, all patients have resumed their social activities and are working full time. The mean extent of resection in this group was 92.4% (range 86%–100%), with no significant difference between the groups.

The neuropathological examination diagnosed a WHO Grade II glioma in the 15 tumors. In Group B, no sign of tumoral invasion was observed in the 7 hippocampi, and there was no sclerosis or dysplasia. No adjuvant treatment was administered after surgery in Group B, whereas chemotherapy was given in 3 patients in Group A more than 2 years after surgery.

**Discussion**

**Intractable Epilepsy in Paralimbic Grade II Gliomas**

Grade II gliomas are known to be more often associated with chronic epilepsy than high-grade gliomas. In particular, intractable seizures are very frequent for gliomas involving the paralimbic system, a region often involved by Grade II gliomas. Several factors are believed to cause epilepsy-associated tumor. Mass lesions with increased pressure on surrounding brain parenchyma, ischemia, voltage-gated ion channels controlling cell excitability, or specific trophic factors may be involved in seizures. Morphological changes in peritumoral tissue may also participate in epileptogenesis, including aberrant neuronal migration, changes in synaptic vesicles, enhanced intercellular communication through increased expression of gap-junction channels, or imbalance between inhibitory and excitatory mechanisms through changes in local concentrations of $\gamma$-aminobutyric acid, glutamate, and lactate. In addition, the tumor microenvironment, due to hypoxia, can be associated with changes in gene expression with negative effects on the stability of DNA repair mechanisms and on the likelihood of mutation.
Under these conditions, the astrocytic cell membrane becomes more prone to inward sodium currents, leading to risk of epilepsy. A possible explanation of this interaction between glial cells and neurons is that they share the same transitional structural and functional profile.

Interestingly, the tumor could also modify synchronization within cerebral networks, with randomization in neural dynamics, causing seizure onset. The small-world network theory suggests that synchronization of neurons in a network is mandatory for normal brain functioning and information processing, but it may also explain abnormal dynamics related to epilepsy. This mechanism seems to involve not only local but also global dysfunction in cerebral connectivity. Indeed, according to the theory of complex networks, which derives from the graph theory, it is hypothesized that a brain tumor interferes with widespread functional circuits rather than with only the site of the lesion itself. This network imbalance does convert a healthy into a pathological neural circuit with random processing, which may lead both to cognitive impairment and lowering threshold, and thus to epilepsy. Of note, in this “epileptic network,” remote areas such as the hippocampus can be recruited, even if not involved by the tumor initially.

As a consequence, the strong connections of the paralimbic system with both the neocortex and the limbic system might explain the high rate of intractable seizures in cases of tumor such as Grade II gliomas.

Epileptological Outcomes in Paralimbic Grade II Gliomas

Traditionally, the goal for neurosurgeons involved in oncology is to remove only the tumor, even if the patient experiences chronic epilepsy. It seems that there is a relationship between the extent of glioma resection and seizure control, likely due to the decrease or elimination of the factors believed to cause epilepsy. Indeed, beyond the reduction of the compression effect due to the tumor removal, it has been hypothesized that the cortex surrounding the glioma probably loses the ability to independently initiate or propagate seizures once the tumor itself is resected. However, even after total or subtotal resection, only 65%–80% of patients are seizure free. This might be explained by the presence of residual tumor cells acting as an epileptic focus, since it has been demonstrated that gliomas involve the brain beyond the signal abnormality visible on MRI, both in high-grade and low-grade gliomas. Nonetheless, according to this hypothesis, it is difficult to understand why more than two-thirds of patients are seizure free after surgery, because in essence, tumoral cells have probably been left in the majority of cases, even in cases of “complete” removal on FLAIR MRI, explaining why “supratal” resection, that is, with a margin around the MRI signal abnormality, has recently been proposed as having a greater impact on the natural history of Grade II gliomas, especially by avoiding anaplastic transformation.

The alternative explanation could be that chronic seizures before surgery develop an aberrant network including temporomesial structures, even far from the location of the tumor itself, as discussed above. This idea of recruitment of areas not involved by the tumor was reported in many series with temporal mass lesions, which induced secondary epileptogenicity in the mesiotemporal structures (as demonstrated by EEG results) and which...
led to refractory seizures after lesionectomy alone. On the basis of these observations, Sugano et al. suggested that seizure control could be better if the zone of seizure origin and the zone of maximal interictal spiking were completely excised. Morioka et al. also proposed to perform hippocampectomy in the surgical management of intractable temporal lobe epilepsy associated with glioneuronal tumors. Nevertheless, to our knowledge, no previous series has evaluated the role of such a hippocampectomy in a homogeneous series of patients who experienced intractable seizures due to a paralimbic frontotemporoparietal or temporoinsular Grade II glioma, despite the absence of involvement of the hippocampus by the tumor.

The Impact of Resection of the Nontumoral Hippocampus in Paralimbic Grade II Gliomas Associated With Chronic Epilepsy

Here, we demonstrated for the first time that resection of the hippocampus, when not invaded by the glioma (as confirmed on preoperative T2-weighted and FLAIR MRI and by postoperative neuropathological examination) in paralimbic frontotemporoparietal or temporoinsular Grade II gliomas eliciting chronic seizures, had a significant impact on epilepsy in comparison with a similar group of patients in whom no hippocampectomy was performed in addition to glioma resection. Indeed, in the group without hippocampectomy, even if a decrease in seizures was observed in the 8 cases, no patients were seizure free (4 patients in Engel Class II and 4 patients in Class III), while in the second group with hippocampal resection, the 7 patients were completely seizure free (7 patients in Class I) (p = 0.02) with a mean follow-up of 23 months. Furthermore, in Group B with hippocampectomy, the dosage or number of AEDs was decreased in 2 cases and stopped in 1 case.

A remarkable case is the patient in Case 15 who benefitted from a first surgery with a complete resection of the paralimbic Grade II gliomas without hippocampal removal. There was no tumor recurrence with 11 years of follow-up. Nonetheless, the patient continued to have intractable seizures. Then, a second surgery was performed and consisted of a single hippocampectomy, that is, with no additional glioma removal because no tumor residue was visible after the first operation. Even if the neuropathological examination confirmed the absence of tumoral invasion within the hippocampus, the patient had no more seizures after the second surgery.

These original findings plead in favor of the involvement of the hippocampus (even if not invaded by the glioma) in chronic epilepsy in paralimbic Grade II gliomas, likely due to its recruitment in an “epileptic network” initially generated by the tumor, as previously discussed. Indeed, this difference in epileptic outcomes in the 2 groups is not due to the extent of tumor removal, since the extent of resection was almost similar (86.3% vs 92.4%, not significant). Therefore, these results also show that it is possible to be seizure free despite incomplete removal of paralimbic Grade II gliomas, thanks to an additional hippocampectomy.

Last but not least, hippocampectomy did not increase the mortality or the morbidity in our series, since no patient experienced permanent neurological worsening after surgery. Rather, due to epilepsy control in Group B, the quality of life was improved in all 7 patients. This crucial point is supported by the fact that 100% of patients are now working full time after hippocampectomy, whereas only 62.5% of patients resumed their professional activities in Group A because of their seizures. As a consequence, postoperative KPS scores were significantly increased in comparison with presurgical KPS scores only in Group B after hippocampectomy (p = 0.03).

Limitations and Perspectives

The main limitations of our study are the small number of patients and a short postoperative follow-up (mean 30 months), especially in Group B (mean 20.5 months). However, Jutila et al. analyzed the long-term results of temporal lobe epilepsy surgery in 140 consecutive patients for a mean follow-up of 5.2 years (range 1–10.5 years); 83 (59%) of 140 patients had recurrent seizures during the follow-up period, and 86% (71 of 83 cases) of all seizure relapses occurred within 1 year postoperatively. Interestingly, epileptological results at 1 year after surgery were analogous to the long-term outcome. This was true in Group A, since all patients had seizures within the 1st year following surgery. It also means that the probability of seizure-freedom continuation is high when patients have a 1-year postoperative period of complete seizure freedom. As a consequence, we can hypothesize that our patients in Group B will remain seizure free during long-term follow-up, since the follow-up is now more than 1 year in all patients, at least if the residual tumor can be controlled. It is worth noting that no patient had adjuvant treatment in Group B, demonstrating that epilepsy control was not due to chemotherapy and/or radiotherapy.

In addition, we did not use intraoperative electrocorticography, for 3 reasons. First, the reliability of this technique is still controversial in the literature. In temporal lobe tumors, recording over the hippocampus was positive in only 86.4% in the best series. Second, as mentioned, the likely involvement in “secondary epileptogenicity” of mesiotemporal structures not invaded by the tumor was already reported in many series with temporal lesions, explaining intractable seizures after lesionectomy alone. Third, because in our previous experience concerning paralimbic Grade II gliomas that caused intractable epilepsy, seizure freedom was obtained when the hippocampus (invaded by the glioma) was removed.

Nonetheless, beyond these limitations, in cases of intractable epilepsy due to paralimbic Grade II gliomas, the present data give strong arguments in favor of an additional resection of the hippocampus not invaded by the tumor, even if glioma removal cannot be complete for functional reasons (for example, invasion of the motor or language pathways, or involvement of the anterior perforating substance). It means that one could consider performing surgery in a patient with paralimbic glioma eliciting refractory epilepsy not only for oncological reasons but also to improve his or her quality of life, that is,
to increase the KPS score and to allow a return to work, due to a relief of seizures. Of note, despite the lack of extensive neuropsychological examination in this study, it is important to underline that MMSE scores were not significantly modified by the hippocampectomy. It also means that in patients who already underwent surgery for paralimbic Grade II gliomas but who continued to experience chronic epilepsy, a second surgery with the goal of removing only the hippocampus might be considered, as shown in 1 patient in the present study.

Conclusions

Our data support for the first time the significant impact of hippocampectomy in patients with intractable epilepsy generated by a paralimbic (fronto)-temporo-insular Grade II glioma, even if it does not invade the hippocampus. Indeed, in the present series, hippocampal resection allowed a complete control of seizure in all cases, with an improvement of the KPS scores. All patients in Group B resumed their social and professional activities even though they were not able to work before surgery. Thus, we suggest performing resection of the nontumoral hippocampus in addition to glioma removal in patients with medically refractory epilepsy due to a paralimbic (fronto)-temporo-insular Grade II glioma, and also suggest adding new surgical indications in this kind of tumor, that is, for functional reasons and not exclusively for oncological reasons. These preliminary results need to be validated by increasing the number of patients and the follow-up period using multicenter prospective and randomized studies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Concept and design: Duffau. Acquisition of data: Duffau. Analysis and interpretation of data: both authors. Drafting of the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of all authors: Duffau. Statistical analysis: both authors. Study supervision: Duffau.

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