Surgical management of multicentric diffuse low-grade gliomas: functional and oncological outcomes

Clinical article

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Object. Multicentric diffuse low-grade gliomas (DLGGs) are defined as widely separated lesions in different lobes or hemispheres where there is no anatomical continuity between lesions. This condition is rare and its clinicopathological characteristics have been scarcely described in the literature. Here, the authors report the first consecutive surgical series of multicentric DLGGs with functional and oncological outcomes.

Methods. A retrospective review of patients surgically treated for histopathologically confirmed multicentric DLGGs between 2000 and 2012 was performed. Information regarding clinical features, surgical procedures, histopathological results, and clinical outcomes was collected and analyzed.

Results. Five consecutive patients were included in this study. There were 3 men and 2 women, whose mean age was 27.4 years (range 23–35 years). The mean follow-up period after surgery was 46 months (range 11–138 months). Gross-total or subtotal resection was achieved in all cases, using a single surgery in 3 patients and a 2-stage surgery in 2 patients. There was no mortality or permanent morbidity associated with surgery. The Karnofsky Performance Scale score ranged between 90 and 100 in all cases. Adjuvant chemotherapy was administered in 2 patients because of tumor regrowth with no malignant transformation.

Conclusions. Multicentric DLGGs can be removed safely without inducing severe permanent neurological deficits. Interestingly, a single-stage resection of multiple lesions within different lobes may be performed if tumors are located in the same hemisphere. Therefore, the authors suggest considering surgery as the first therapeutic option for multicentric DLGGs, as in solitary DLGGs.

Key Words • multicentric tumor • low-grade glioma • awake surgery • surgical management • outcome • oncology

Abbreviations used in this paper: DLGG = diffuse low-grade glioma; GTR = gross-total resection; KPS = Karnofsky Performance Scale; STR = subtotal resection.

To date, only a few series of multicentric gliomas have been described in the literature. In addition, most of those reported cases are associated with high-grade gliomas (Grade III and IV gliomas according to the WHO classification) while descriptions of pure multicentric LGGs (WHO Grade I and II gliomas) are sparsely available. In this context, little is known regarding the clinicopathological features of multicentric DLGGs (that is, WHO Grade II gliomas) and consequently, appropriate management has not yet been optimized. Here, we present clinical characteristics, surgical procedures, histopathological findings, and clinical outcomes.
of 5 consecutive cases of multicentric DLGGs. We also discuss the role of surgery in the management of this rare entity.

Methods

Selection of Patients

We performed a retrospective review of patients’ medical records to identify those who were surgically treated for DLGGs between October 2000 and July 2012. Patients with multicentric DLGGs on the basis of criteria outlined by Batzdorf and Malamud were included in this study. Clinical, surgical, and histopathological characteristics as well as clinical outcomes were collected and analyzed.

Surgical Procedure

Surgery was proposed with the aim of maximal resection of tumors and preservation of brain function. To achieve this goal, awake surgery with intraoperative functional brain mapping using cortical and subcortical electrical stimulation was performed. Technical details of our functional-guided surgical procedure have been described in previous reports.

Extent of Resection and Clinical Outcomes

The extent of resection was determined on early postoperative FLAIR MRI obtained within 24 hours after surgery. Complete removal of the hyperintense area on postoperative FLAIR MRI was considered as GTR, whereas a residual volume of less than 10 ml on FLAIR imaging was defined as STR. All other cases were considered a partial resection.

Postoperatively, patients were observed regularly in the outpatient clinic at 3 months after surgery and every 6 months thereafter to evaluate neurological function and observe tumor behavior using MRI. The KPS score was also evaluated at the time of follow-up.

Results

Clinicopathological features of the 5 patients are summarized in Table 1.

Patient Population

Among 350 patients reviewed, 5 patients met the Batzdorf criteria and were included in this study. These 5 patients accounted for 1.4% of the surgically treated patients with DLGGs in our series. The patients consisted of 3 men and 2 women, whose mean age was 27.4 years (range 23–35 years). Four of the 5 patients were right-handed.

Seizure was noted as the initial clinical symptom in all patients except 1, in whom the discovery was made following imaging for headache symptoms.

Tumor Location

A total of 10 tumors were identified in our series of 5 patients (2 tumors per patient). The lesions were all synchronous and detected on initial neuroimaging. The tumors involved the same hemisphere in 4 patients (the
right hemisphere in 1 patient and left hemisphere in 3 patients), and they involved both hemispheres in 1 patient. The most commonly affected regions were the frontal lobe and temporal lobe, followed by the parietal lobe. No DLGGs were identified within the occipital lobe, brainstem, or cerebellum in this series.

Surgical Outcome

A total of 9 operations were performed, including 1 partial tumor resection that had been performed at another hospital before our consultation (Case 3). In our first patient (Case 1, who underwent her first operation 138 months ago) we performed 2 surgeries: the first for a right temporal lesion, and the second 2 years later for a right frontal lesion. Because of a relapse 10 years after the first operation, a third surgery was performed under awake conditions at which time both tumors were resected (Fig. 1). Similarly, a single surgery was performed in the more recent cases for multicentric tumors located in the same hemisphere (Cases 2–4, Figs. 2–4). For Case 5, a planned 2-stage surgery was performed (interoperative interval 52 days) because the tumors were located in opposite hemispheres (Fig. 5).

For the total of 12 resections at our hospital, GTR was achieved in 6 surgeries and STR in the remaining 6 (there were no cases of partial resection). There was no death or severe permanent neurological deficit associated with any of the surgeries. Of note, a left upper quadrant-tanopia persisted after the first surgery for resection of the temporal lesion in Case 1; however, the patient’s quality of life was not significantly affected and she was able to continue working.

The mean follow-up period after surgery was 46 months (range 11–138 months). At the most recent follow-up, seizures had been controlled with medications in 3 cases and without medications in 2 cases. All patients returned to their normal social and professional life and all had a KPS score of 90 or 100 at the most recent follow-up.

Histopathological and Molecular Examinations

Histopathological examination was performed on each lesion in all cases. Multicentric tumors were histopathologically identical in 4 cases: 3 patients had multicentric WHO Grade II oligodendrogliomas and 1 had a multicentric WHO Grade II astrocytoma. In contrast, the tumors in Case 5 had different histopathological features (a WHO Grade II oligodendroglioma and WHO Grade II astrocytoma).

All tumors were classified as WHO Grade II gliomas, although in Case 4 part of the pathological specimen exhibited a microfocus of anaplastic features. The Ki 67 labeling index varied between 1% and 15%.

In 4 patients both tumors had the same genetic profile
IDH1 mutation and no 1p19q codeletion). In 1 patient, although IDH1 mutation was found in both tumors, there was no 1p19q codeletion in the first glioma whereas there was a dissociation in the second glioma (that is, no 1p deletion and 19q deletion).

Adjuvant Therapy

Given that all tumors were pathologically confirmed DLOGs and resected either totally or subtotally, adjuvant therapy (chemotherapy and/or radiotherapy) was not administered routinely after surgery. However, in the patient in Case 1 the frontal lesion recurred 6 months after the resection despite GTR. Accordingly, temozolomide was administered for 18 months, which resulted in not only stabilization of the frontal tumor but also a partial reduction of the temporal residual tumor subtotally removed 2 years before. Nevertheless, both the frontal and temporal lesions evolved gradually on regular MRI after the withdrawal of the above-mentioned chemotherapy. Therefore, a third surgery was performed 10 years after the first operation to resect both lesions simultaneously (although the patient was still asymptomatic at the time of the third surgery).

Discussion

To the best of our knowledge, this is the first consecutive surgical series of multicentric DLGGs reported in the literature.

Incidence of Multicentric DLGGs

The incidence of multicentric DLGGs has not yet been well documented in the literature, but they are considered to be extremely rare entities. A previous autopsy study of 241 patients with gliomas revealed 18 cases of multicentric gliomas. Of these 18 cases, pure multicentric DLGGs consisting of solely low-grade lesions were found in only 1 case, indicating that the incidence was 0.41% among all glioma patients. In our series, the incidence of multicentric DLGGs was 1.4% of our DLGG cases. This scarcity explains why few cases have been reported and why management of this entity has not been well established. Of note, multicentric DLGGs and gliomatosis are 2 distinct entities, resulting in different therapeutic strategies.

Clinicopathological Features

Age distribution, clinical manifestation, and tumor location in our series of multicentric DLGGs did not differ from those characteristics previously described in solitary DLGGs. Interestingly, although the diagnosis was made because of seizures in 4 patients, the tumor was incidentally discovered in 1 patient (Case 1). However, during the follow-up of 138 months of this patient (who is still asymptomatic) tumor growth (and even regrowth after surgery) was observed. This suggests that the natural course of incidental multicentric DLGGs is the same as that of incidental unicentric DLGGs, which can demonstrate a constant progression of the tumor despite no neurological symptoms.

Regarding neuropathological features, although the histological characteristics were the same between the 2 tumors in 4 cases, different histopathological features were found in 1 patient (one tumor was an oligodendroglioma and the other tumor was an astrocytoma). In a relatively large series of 18 cases of multicentric gliomas, 6 cases had different histopathological appearances. Neuropathological heterogeneity has also been described in several other case reports. These previous findings along with our data highlight the uncertainty of a histopathological diagnosis determined from only a single lesion. Interestingly, molecular heterogeneity was also observed in 1 patient. This issue is important to adapt the optimal therapeutic management, which could be different for each tumor.

The Role of Extensive Resection in Multicentric DLGGs

Appropriate management of multicentric DLGGs is yet to be established. In solitary DLGGs mounting evidence suggests that extensive resection is significantly associated with a greater overall survival by delaying malignant transformation. Based on these previous studies, maximal resection while preserving brain function was performed when the lesions were less than 3 cm in diameter. In Case 1, however, a third surgery was performed 10 years after the first operation to resect both lesions simultaneously (although the patient was still asymptomatic at the time of the third surgery).

Fig. 3. Case 3. Upper: Preoperative axial FLAIR MR images demonstrating 2 multicentric lesions located in the left temporoparietal region and the left frontal lobe. Lower: Postoperative axial FLAIR MR images obtained 3 months after surgery showing removal of both lesions.

(IDH1 mutation and no 1p19q codeletion). In 1 patient, although IDH1 mutation was found in both tumors, there was no 1p19q codeletion in the first glioma whereas there was a dissociation in the second glioma (that is, no 1p deletion and 19q deletion).
Surgery for multicentric diffuse low-grade gliomas

function is considered the optimal treatment of DLGG.\textsuperscript{11,38} Accordingly, maximal resection may also be indicated for patients with multicentric DLGGs. Indeed, in our series no patient died and none experienced malignant transformation during a mean follow-up of 46 months after surgery. Moreover, reoperation can also be considered in recurrent multicentric DLGGs, as already recommended in recurrent solitary DLGGs.\textsuperscript{22} As an example, in the patient in Case 1 of the present series, the patient has survived longer than 11 years and 3 surgeries and currently has stable disease. In addition, this case indicates that when the resection is not complete for functional reasons, chemotherapy may also be used before performing a subsequent resection, as already reported in unicentric DLGGs.\textsuperscript{17}

Beyond oncological issues, it should be noted that all patients in the present series continue to enjoy their nor-

Fig. 4. Case 4. Preoperative axial FLAIR MR images (A and B) and coronal T2-weighted MR image (C) demonstrating 2 multicentric lesions located in the left mesial temporal lobe and the left superior frontal gyrus. Intraoperative photograph of the surgical field obtained before resection of tumor (D), indicating functional areas identified by cortical electrical stimulations: ventral premotor cortex (tags 1, 2, and 7) that provoked dysarthria with facial deviation when stimulated, primary motor cortex of the face (tags 3 and 4) and hand (tags 5 and 6), and an area in the posterior part of the superior temporal gyrus that elicited anomia (tag 10). Intraoperative photograph of the surgical field obtained after resection of tumor (E), indicating functional boundaries detected by subcortical electrical stimulations: the pyramidal tract that disturbed movement of the upper extremity (tag 50) and the superior longitudinal fasciculus (tags 46 and 47) that provoked anomia. Note that both lesions were successfully resected through a single frontotemporal craniotomy window. Follow-up axial FLAIR MR images (F and G) and a coronal T2-weighted MR image (H) obtained 19 months after surgery, demonstrating a small hyperintense lesion on FLAIR image at the lateral margin of the frontal tumor cavity.
mal life after surgery despite multiple tumors and multiple surgeries. First, this means that intraoperative mapping with functional-guided resection may allow preservation of the quality of life while maximizing the extent of resection in multicentric DLGGs (supported by the fact that there was no partial resection in this series), as previously demonstrated in solitary DLGGs. Second, it also means that simultaneous resection of multiple gliomas located within different lobes but in the same hemisphere (including in the left hemisphere in right-handed patients) can be achieved with no addition risk. Finally, our results demonstrate that incidental multicentric DLGGs can be resected with no consequences on the quality of life as shown in the patient in Case 1, in agreement with previous reports in unicentric DLGGs.

Conclusions

Despite the small number of patients in this retrospective study, we demonstrate that multicentric DLGGs can be managed similarly to unicentric DLGGs. They can be extensively and safely removed without inducing permanent functional deficits thanks to the use of awake intraoperative brain mapping. Therefore, we suggest considering early surgery as the first therapeutic option in multicentric DLGGs, with reoperation(s) in cases of glioma relapse.

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. Conception and design: Duffau. Acquisition of data: all authors. Analysis and interpretation of data: Duffau, Terakawa. Drafting the article: Duffau, Terakawa. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Duffau. Administrative/technical/material support: Duffau. Study supervision: Duffau.

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