

# **Preoperative Chemotherapy for Infiltrative Low-Grade Oligoastrocytoma: a Useful Strategy to Maximize Surgical Resection**

## **—Case Report—**

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### **Abstract**

**A 38-year-old woman presented with a large infiltrative left frontal low-grade glioma manifesting as partial seizures of the left arm and lower limb. First line chemotherapy with temozolomide reduced infiltration and volume, allowing subtotal surgical resection. The patient suffered postoperative supplementary motor area syndrome with right hemiparesis and mutism that resolved completely after approximately one month. She was able to return to her full-time job after 4 months. The residual tumor was stable, and the frequency of seizures had lessened dramatically at the last follow-up examination at 18 months. The present case demonstrates that this new therapeutic approach of chemotherapy followed by surgery can offer safer and more radical surgical resection, improving the quality of life of the patient.**

Key words: low-grade glioma, infiltrative tumor, chemotherapy, surgery, brain mapping

### **Introduction**

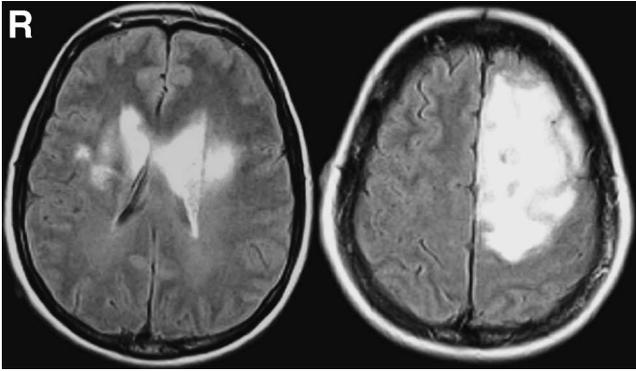
Cerebral low-grade gliomas (LGGs) of World Health Organization (WHO) grade II are slow-growing tumors that evolve at variable rates toward a higher grade of malignancy. Treatment options include surgery, chemotherapy, and radiotherapy. However, which treatment strategy is superior for different types of patients remains unclear. A balanced combination of different treatments seems to yield the best results in terms of prolonging the period during which the glioma does not grow and lengthening the time to progression to higher grade malignancy.

Given that evaluation of the overall survival may be difficult to assess because most patients have long survival, the principal goal of any treatment is to preserve patients' neurological functions and quality of life. Surgical resection has been found to have a valid impact on the natural history of LGG.<sup>1,5,11,21</sup> Unfortunately a large number of LGGs are located in eloquent brain regions, thus preventing effective extirpation. Moreover, in the case of a diffusive growth pattern, surgery offers limited benefits in terms of an oncologically useful extent of resection. In this group of patients, once biopsy has been performed, radiotherapy or chemotherapy is then administered. Chemotherapy can reduce volume and infiltration of LGGs,<sup>2-4,8,10,13,17,18,22,24,26,27</sup> and can permit total resection of an initially diffuse tumor.<sup>6</sup>

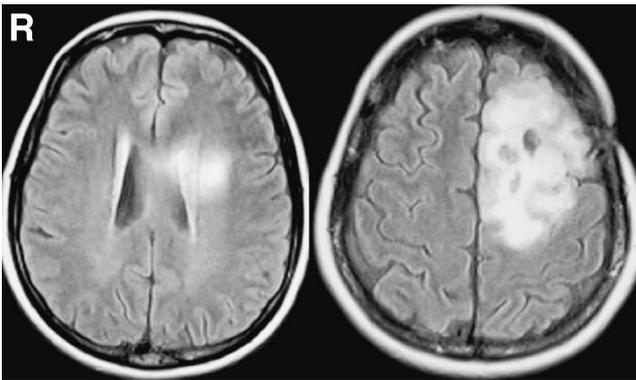
We report a case of a patient in which neoadjuvant chemotherapy allowed surgical treatment of a large infiltrating LGG.

### **Case Report**

A 38-year-old woman, with no history of neurological illness, experienced partial seizures of the left arm and lower limb in January 2007. Fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) imaging showed a large left frontal tumor involving the superior and middle frontal gyri, and the supplementary motor area (Fig. 1). The tumor deeply invaded the corpus callosum and infiltrated into the right hemispheric white matter. MR imaging showed no enhancement by contrast medium. The contralateral infiltration of the tumor contraindicated surgical resection. One week after, the patient underwent a biopsy that showed a pathological pattern of oligoastrocytoma of WHO grade II. No loss of heterozygosity for both 1p and 19q loci, no epidermal growth factor receptor amplification, and no *PTEN* deletion were detected. The cellular proliferation index expressed as Ki-67 was 3.8%. Promoter of the O<sup>6</sup>-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) was unmethylated. Considering the age of the patient, the absence of neurological impairment (apart from seizures) and the presence of an oligodendroglial component, radiotherapy was not the first choice. Consequently we started administration of temozolomide orally from days 1 through 5 at a starting



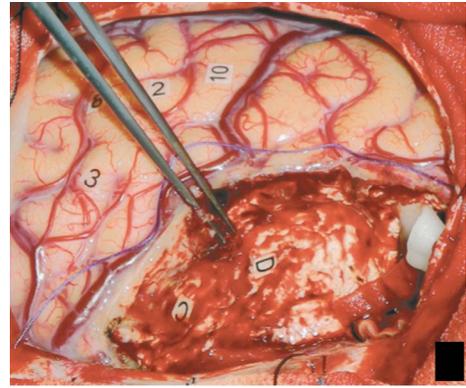
**Fig. 1** Pretreatment fluid-attenuated inversion recovery magnetic resonance images showing a large left frontal tumor invading the contralateral hemisphere through the corpus callosum.



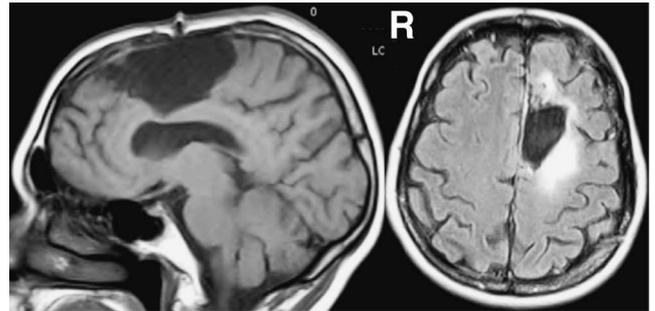
**Fig. 2** Cerebral fluid-attenuated inversion recovery magnetic resonance images after seven cycles of temozolomide showing markedly reduced mass effect and volume, and the contralateral infiltration has disappeared.

dose of 200 mg/m<sup>2</sup>, repeated every 28 days after the first daily dose of temozolomide.<sup>27)</sup> No corticosteroid therapy was prescribed. During chemotherapy the patient continued to work despite suffering about one seizure every 30 days.

After 4 cycles of temozolomide chemotherapy, we detected a clear shrinkage of the neoplasm with reduction of the mass effect and disappearance of the invasion of the corpus callosum (Fig. 2). After the seventh cycle, the tumor showed arrested involution, and the chemotherapy was suspended. At this point, since the regression of the size and infiltration of the tumor allowed surgical resection, the patient was counselled to undergo a craniotomy. Because of the eloquent location of the tumor, awake craniotomy with cortical and subcortical electrical stimulation was performed. During the cortical stimulation, no language site was found over the surface of the tumor (superior and middle frontal gyri). The motor strip corresponded to the posterior limit of the resection. Conversely, subcortical stimulation demonstrated that the tumor partially invaded the corticospinal tract (Fig. 3), so the



**Fig. 3** Intraoperative photograph showing the resection of the tumor was stopped at the subcortical level when stimulation revealed two points of motor response corresponding to the corticospinal tract (C: motor fibers of hand and forearm, D: motor fibers of face).



**Fig. 4** Postoperative fluid-attenuated inversion recovery magnetic resonance images showing subtotal resection of the tumor with residual infiltration in the corticospinal tract.

resection was stopped at this point to avoid a permanent deficit. Immediate postoperative MR imaging confirmed subtotal resection (Fig. 4). Histological examination confirmed the previous findings, with a slightly greater Ki-67 labeling index of 4%, and the promoter of the MGMT was unmethylated.

As expected, the patient suffered postoperative supplementary motor area syndrome with right hemiparesis and mutism that resolved completely after approximately one month. She was able to return to her full-time job after 4 months. At the last follow-up (18 months) without treatment, the residual tumor was stable, and the frequency of seizures had lessened dramatically (approximately 1 episode every 5 months).

## Discussion

Despite refinements in diagnosis and the development of more aggressive treatment strategies, survival in patients with LGG has not been significantly prolonged. Surgery can be useful in treating cerebral LGG, and a recent study found a statistically significant correlation between extent of resection and survival (both overall and malignant

progression-free).<sup>21)</sup> Resection should be as radical as possible where feasible, and confirmation by postoperative MR imaging (FLAIR) is mandatory. This rule is applicable to bulky lesions in non-eloquent region, but surgical resection has poor utility for infiltrative tumors in critical areas. For a long time, radiotherapy has represented the mainstay of treatment for this type of lesions, but radiation-induced toxicity still has to be carefully considered during decision-making.<sup>12)</sup> Although no consensus on the routine use of chemotherapy in treating LGG, and especially astrocytomas, has been reached yet, its efficacy has been demonstrated in terms of clinical and radiological response either as initial treatment<sup>2-4,8,10,13,15,24,27)</sup> or as salvage therapy after surgery and radiotherapy.<sup>17,18,22,23,26,27)</sup> Complete neuroradiological disappearance of a tumor is infrequent, so good response is defined as volumetric regression or stabilization over time. Since progression of LGG towards higher-grade malignancies has been associated with the accumulation of genetic abnormalities,<sup>19,29)</sup> the difference in response to chemotherapy among histologically similar tumors is probably due to the heterogeneity in the genetic pattern of neoplastic cells.<sup>8)</sup> So far, only loss of heterozygosity of 1p/19q has been demonstrated to statistically correlate with the response to chemotherapy and survival.<sup>3,10,14,20,24,25,28)</sup>

If neoadjuvant chemotherapy reduces tumor volume and infiltration, surgery allows further cytoreduction, as demonstrated in solid neoplasms of other tissues such as the lung, testicle, and breast.<sup>7,9,16)</sup> The combination of neoadjuvant chemotherapy and surgery to treat cerebral LGG has been reported only in a patient with a low-grade oligodendroglioma that progressed after prior partial surgical resection.<sup>6)</sup> Similar to our case, chemotherapy achieved regression of the contralateral diffusion, leading to a second radical surgery.

In our patient, postoperative MR imaging showed subtotal resection due to the infiltration of descending motor pathways. By using intraoperative cortical and subcortical electric stimulation, the resection of neoplastic tissue was guided by functional limits, thus avoiding permanent deficits. Although not radical, the surgery brought some benefit to the patient, such as reduction of tumor volume and mass effect, and seizure reduction. Of course, long-term follow up is needed to establish the real impact on survival.

This second case confirms the efficacy of a therapeutic strategy that combines first-line chemotherapy and surgery for LGG. In selected patients, chemotherapy can reduce tumor volume and infiltration, favoring a subsequent radical or subtotal surgical approach. Therefore, such a combination should be considered to postpone radiotherapy and to improve the quality of life. Further investigations are needed to identify new biological markers that can identify patients who respond well to chemotherapy.

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