

SEIZURES IN PATIENTS UNDERGOING RESECTION OF LOW-GRADE GLIOMAS

Seizure Characteristics and Control Following Resection in 332 Patients with Low-Grade Gliomas. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, Berger MS. *J Neurosurg* 2008;108(2):227–235. **OBJECT:** Seizures play an important role in the clinical presentation and postoperative quality of life of patients who undergo surgical resection of low-grade gliomas (LGGs). The aim of this study was to identify factors that influenced perioperative seizure characteristics and postoperative seizure control. **METHODS:** The authors performed a retrospective chart review of all cases involving adult patients who underwent initial surgery for LGGs at the University of California, San Francisco between 1997 and 2003. **RESULTS:** Three hundred and thirty-two cases were included for analysis; 269 (81%) of the 332 patients presented with ≥ 1 seizures (generalized alone, 33%; complex partial alone, 16%; simple partial alone, 22%; and combination, 29%). Cortical location and oligodendroglioma and oligoastrocytoma subtypes were significantly more likely to be associated with seizures compared with deeper midline locations and astrocytoma, respectively ($p = 0.017$ and 0.001 , respectively; multivariate analysis). Of the 269 patients with seizures, 132 (49%) had pharmaco-resistant seizures before surgery. In these patients, seizures were more likely to be simple partial and to involve the temporal lobe, and the period from seizure onset to surgery was likely to have been longer ($p = 0.0005$, 0.0089 , and 0.006 , respectively; multivariate analysis). For the cohort of patients that presented with seizures, 12-month outcome after surgery (Engel class) was as follows: seizure free (I), 67%; rare seizures (II), 17%; meaningful seizure improvement (III), 8%; and no improvement or worsening (IV), 9%. Poor seizure control was more common in patients with longer seizure history ($p < 0.001$) and simple partial seizures ($p = 0.004$). With respect to treatment-related variables, seizure control was far more likely to be achieved after gross-total resection than after subtotal resection/biopsy alone (odds ratio 16, 95% confidence interval 2.2–124, $p = 0.0064$). Seizure recurrence after initial postoperative seizure control was associated with tumor progression ($p = 0.001$). **CONCLUSIONS:** The majority of patients with LGG present with seizures; in approximately half of these patients, the seizures are pharmaco-resistant before surgery. Postoperatively, > 90% of these patients are seizure free or have meaningful improvement. A shorter history of seizures and gross-total resection appear to be associated with a favorable prognosis for seizure control.

COMMENTARY

Seizures occur in about half of children and 35 to 40 percent of adults with supratentorial tumors (1). Known risk factors for seizures in patients with tumors include low-grade tumors (rather than high grade), cortical involvement, and either a perirolandic or temporal lobe location (2). Seizures are usually the first symptom in patients with low-grade gliomas, especially oligodendrogliomas (1). Brain neoplasms account for 10 to 30 percent of adult epilepsy surgery candidates (3). Nonneuronal tumors, such as gliomas, are thought to cause seizures in peritumoral cortex via one or more of the following mechanisms: 1) alteration of the number and organization of excitatory and inhibitory synapses; 2) changes in neurotransmitters, their receptors, and related enzymes; and 3) development of secondary hippocampal sclerosis, also known as dual pathology, for tumors located in or near the medial temporal lobe (3).

Seizures and their treatment play a major role in the quality of life among patients with low-grade tumors. Patients with epilepsy and tumors seem to be particularly prone to adverse effects from antiepileptic medications (especially rash) and are at risk for significant drug interactions, notably those involv-

ing steroids and chemotherapy (1). Evidence from a controlled study indicates that cognitive dysfunction in patients with low-grade glioma is ascribed primarily to the use of antiepileptic drugs, whereas declines in health-related quality of life are related more to incomplete seizure control (4).

In the current paper, Chang and colleagues provide extensive seizure-related information for a large cohort of patients (over 300) undergoing surgery for histologically proven low-grade gliomas. Many of their findings confirmed prior studies: risk of seizures was greater with cortical involvement and an oligodendroglial component to the tumor; seizures were more likely to be refractory if there was temporal lobe involvement or a longer duration of epilepsy; and postoperative seizure control was better with complete lesion resection or with shorter duration of seizures preoperatively.

From the epileptologist's standpoint, it is noteworthy that half (137/269) of the patients with preoperative seizures were fully controlled medically and half of that subgroup (61/137) had experienced only one seizure preoperatively. Thus, those patients were undergoing tumor surgery, not epilepsy surgery. Eighty percent of this subgroup had achieved seizure freedom for at least 6 months at the 1-year postoperative follow-up. Among those patients who never had seizures prior to resection, 2/53 developed new-onset seizure(s) postoperatively. Of the 132 patients with refractory seizures prior to surgery, 54%

were seizure free for at least 6 months at 1-year follow-up. Although gross total resection was clearly a positive predictor of seizure freedom postoperatively in all patients with seizures (almost 90% were seizure free), it is not clear what percent of *refractory* patients with complete resection became seizure free. Prior studies have addressed this question and also have found that complete resection improves seizure outcome. For example, Zaatreh et al. reviewed 68 patients with intractable temporal lobe tumoral epilepsy, almost all of whom had low-grade tumors (5). Seizure freedom was achieved in 43/60 patients with total resection (with tumor-free margins confirmed by intraoperative frozen sections) compared with only 1/8 without complete resection.

This study does not and was not intended to shed light on the role of electrocorticography or intracranial monitoring for patients with tumors and refractory seizures. Nonetheless, electrocorticography was used for 63 cases, not necessarily refractory cases. Seizure foci, although never specifically defined, were identified in 26 of those having electrocorticography. These foci were resected if considered safe to do so, but the authors do not state how often resection occurred. Of the 26 cases, 15 (58%) were seizure free at 6 months; the percent of patients who were seizure free and had the identified seizure focus resected was not provided. While prior studies have specifically evaluated the use of electrocorticography, the role of extending resections based on intraoperative electrocorticography or prolonged intracranial monitoring (with its own significant risks and morbidity) to capture seizure onsets remains unclear. There is certainly room for improvement in seizure freedom outcome given that lesionectomy, as applied in this study and several others with a variety of low-grade lesions, results in long-term seizure freedom for just over half of patients with refractory epilepsy prior to surgery. Only a large, multicenter randomized study would be able to address this issue meaningfully. Similarly, the current study does not speak to dual pathology. In fact, Chang and colleagues do not mention mesial temporal sclerosis or hippocampal resections. Prior studies have strongly suggested that resection of both the lesion and mesial temporal structures are required for long-term seizure freedom in these cases, though the risks and benefits must be weighed carefully in each case (3,6).

There are other valuable findings from this study. First, Karnofsky performance scores were inversely related to seizure control, which again, shows the importance of seizure control for quality of life. Second, seizure recurrence predicted tumor recurrence. Thus, in someone who has been seizure free for some time, a recurrent seizure should prompt a repeat of neuroimaging. As Yogi Berra might say, "If your patient has recurrence, you should worry about recurrence."

There are additional limitations to the current study. Only those patients with proven gliomas were included. Histologic

confirmation often is unavailable when making surgical decisions in this patient population, and other types of tumors can appear very similar on imaging but have different pathophysiology. For example, dysembryoplastic neuroepithelial tumors, which often resemble low-grade gliomas on imaging, seem to be highly associated with neighboring cortical dysplasia, which may affect the surgical approach (3,7). In addition, the Chang et al. study only included patients who underwent resection for their tumor. There may be many other patients with low-grade gliomas and seizures who never came to surgery and were thus excluded from the analysis. Accordingly, some of the conclusions should be interpreted with this caveat in mind: for instance, although resection following a short duration of seizures is associated with better seizure outcome in this and other studies of benign lesions that are ultimately resected (including cavernous malformations), it does not necessarily mean that surgery needs to be performed after the first seizure or when seizures are easily controlled. Some of these patients will never require surgery.

Therefore, patient preference continues to play an important role in the management of seizures associated with low-grade lesions. For those individuals who have the "get it out of there" approach (especially for patients with lesions that have the potential for growth, transformation, or bleeding) or who want to have an increased chance of eliminating chronic antiepileptic medication (which is higher with complete resection than with no resection), early surgery is likely the best option for them. Yet, there are others who have the "no one is going in my head" attitude, do not mind long-term serial neuroimaging studies and accept taking chronic medication. For the latter group, early surgery makes less sense; thus, watching and waiting is probably the most reasonable approach. Once it is clear that seizures are difficult to control, rapid consideration of surgery is recommended for both types of patients, as it is for all patients with refractory seizures.

by Lawrence J. Hirsch, MD

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