Characteristics and Treatment of Seizures in Patients with High-Grade Glioma: A Review

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High-grade gliomas (HGGs), including anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM), are the most common primary tumors of the central nervous system.[1,2] Despite medical and surgical advances, the prognosis of patients with HGGs remains poor, with a median survival of approximately 22 months for AA and 12 months for GBM, even after surgery, irradiation, and chemotherapy.[2–4] Seizures are common in these patients, affecting between 25% and 60% of individuals with HGGs, and they are frequently the presenting symptom.[5–9] Tumor-related epilepsy affects patients' quality of life significantly, causes cognitive deterioration, and may result in significant morbidity.[5,10–13] However, the importance of seizure control in patients with HGG remains underappreciated because most neuro-oncologic studies and practices focus primarily on tumor progression and the overall survival. An understanding of the underlying risk factors and treatment options for seizures in patients with HGG is critical in their evaluation and treatment. This review briefly discusses the potential mechanistic underpinnings and predictors of seizures in HGGs, and focuses primarily on important therapeutic considerations.

PREDICTORS, MECHANISMS, AND CHARACTERISTICS OF EPILEPSY IN PATIENTS WITH HGG

The predilection for seizures in patients with brain tumor has long been recognized, and was described by Hughlings Jackson in 1882.[14] Across various clinical series, 25% to 60% of individuals with HGGs experience seizures, suggesting that brains harboring these lesions possess a strong predisposition to epileptogenicity,[5,10–13] but seizures are not equally common among different types of gliomas. The highest rates of epilepsy are

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observed in patients with low-grade gliomas (LGGs) (World Health Organization [WHO] grade I–II), whereas among patients with HGGs, seizures are more common in patients with AAs (WHO grade II) than in those with GBMs (WHO grade IV).[15–17] Smaller tumors and those growing less quickly are associated with higher rates of seizures than large tumors and rapidly growing lesions.[5–9,17,18] Although the reason for this trend is not known, proposed explanations include the predilection of HGG for white matter locations, the possibility that rapid growth might preclude the development of epileptogenesis, and the prospect that some patients with HGG do not survive long enough to develop epilepsy.[17–19]

HGGs located in superficial cortical areas are most likely to produce seizures,[17,20–23] as are tumors centered in the temporal or frontal lobes or the insula.[17,20,21,24–26] Lee and colleagues[17] analyzed tumor location in 124 glioma patients with seizures, and mapped aggregate tumor location using a summed-statistic image, as depicted in **Fig. 1**. These investigators also found that many HGGs causing seizures were located in the temporal lobe, followed by the frontal lobe. The inherent epileptogenicity of mesial temporal structures making seizures more likely in the temporal region is a possibility.[27,28] Furthermore, Spencer and colleagues[29,30] have suggested that "dual pathology," including any combination of foreign-tissue lesions, cortical dysgenesis, gliosis, or hippocampal sclerosis, further drives epileptogenesis in tumoral temporal lobe epilepsy. Some investigators have found

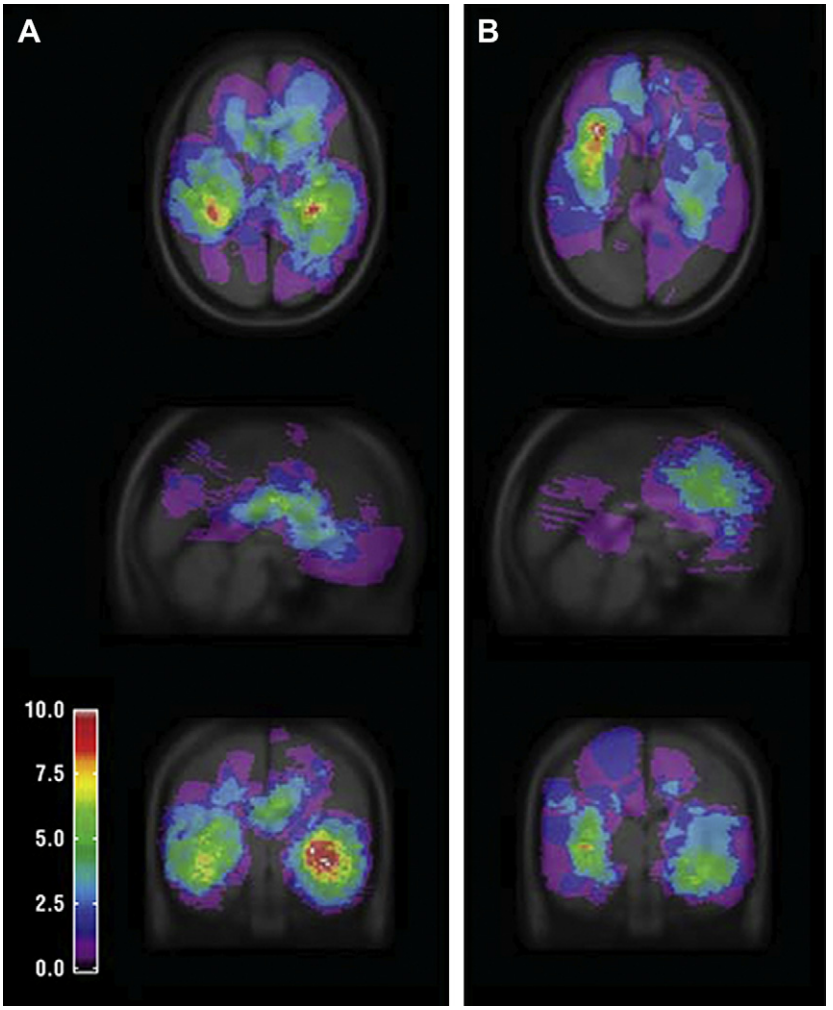

Fig. 1. Summed-statistic image showing the aggregate location of 124 tumors. At each voxel, the number of patients presenting with tumors is calculated. Maps are generated from the sum of the binary tumor masks for high-grade (*A*) and low-grade (*B*) gliomas. (*From* Lee JW, Wen PY, Hurwitz S, et al. Morphological characteristics of brain tumors causing seizures. Arch Neurol 2010;67:339; with permission.)