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Young-Hoon Kim and Chae-Yong Kim

The insula is a functionally and anatomically complex cortical structure that can be affected by both low-grade and high-grade gliomas. This complexity often prevents many neurosurgeons from attempting to surgically manage insular gliomas. This article reviews the anatomic and functional uniqueness of the insula and the surgical outcomes and lessons learned from previously reported surgical series. Successful management of insular gliomas, defined as maximal resection of the tumor without postoperative neurologic morbidity, can be achieved through a sophisticated understanding of the neurovascular structure of the insular region and an intraoperative functional mapping using cortico-subcortical electrical stimulation.

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Seunggu J. Han and Michael E. Sughrue

Many neurosurgeons take a nihilistic approach to surgical treatment of gliomas, stating the inability to achieve a cure. Where this idea comes from is somewhat nebulous to most neurosurgeons. A review of the scientific studies supporting the commonly held beliefs about gliomas shows that these ideas regarding the surgical treatment of gliomas are based on overgeneralizations of data from older studies. One should avoid the temptation to apply them to the greater concept of what gliomas are, how they behave, and what should be done, but rather we should continue to scientifically evaluate the role of surgical resection in glioma treatment.

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Bryan D. Choi, Ankit I. Mehta, Kristen A. Batich, Allan H. Friedman, and John H. Sampson

Surgery remains one of the oldest and still most important forms of treatment for patients with glioma. The advantages of surgical resection for glioma must be balanced with the potential of operative morbidity to surrounding eloquent brain. To that end, advances in functional brain mapping allow for safer operations with more aggressive surgical resections. A brief history of motor mapping as well as its present day use in aiding resection of eloquent gliomas is discussed.

Characteristics and Treatment of Seizures in Patients with High-Grade Glioma: A Review	227
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Dario J. Englot, Mitchel S. Berger, Edward F. Chang, and Paul A. Garcia

High-grade gliomas (HGGs), including anaplastic astrocytoma and glioblastoma multiforme, are the most common primary brain tumors, and are often associated with seizures. Seizure control is a critical but often underappreciated goal in the treatment of patients harboring these malignant lesions. Patients with HGG who also have medically intractable seizures should be considered for a palliative

resection guided by electrocorticography and functional mapping. Antiepileptic drugs remain the mainstay of seizure treatment in HGG, and antiepileptic medication should be started after a tumor-related seizure, but should not be used prophylactically in the absence of seizure activity.

Pathology: Commonly Monitored Glioblastoma Markers: EGFR, EGFRvIII, PTEN, and MGMT 237

Joaquin Q. Camara-Quintana, Ryan T. Nitta, and Gordon Li

The purpose of this article is to update the neurosurgical field on current molecular markers important to glioblastoma biology, treatment, and prognosis. The highlighted biologic markers in this article include epidermal growth factor receptor (EGFR), EGFR variant III (EGFRvIII), phosphatase and tensin homolog deleted on chromosome 10 (PTEN), and O6-methylguanine-DNA methyltransferase (MGMT).

The Role of Adjuvant Radiation Therapy in the Management of High-Grade Gliomas 247

Joshua J. Wind, Richard Young, Ashima Saini, and Jonathan H. Sherman

The purpose of this article is to update the neurosurgical community on the role of adjuvant radiation therapy in the management of patients with high-grade glioma. This information guides clinicians in the multidisciplinary management of these patients via a review of the literature describing current treatment paradigms as well as new avenues of investigation.

Radiation Options for High-Grade Gliomas 259

Benedict Beng Teck Taw, Alessandra A. Gorgulho, Michael T. Selch, and Antonio A.F. De Salles

Radiotherapy has become a part of the standard treatment of high-grade gliomas. Studies have shown that high-dose radiation results in more effective tumor control but at the cost of radionecrosis and other radiation-related side effects. Despite advancing techniques in stereotaxy and precise radiotherapy delivery techniques, studies published for stereotactic radiosurgical treatment of high-grade gliomas have not been unanimous, with large trials showing no survival benefit compared with conventional conformal radiotherapy. New imaging modalities have been studied with the hope to improve accuracy in the planning of radiosurgical treatments. However, further large scale studies are needed to confirm these results.

Radiology: Criteria for Determining Response to Treatment and Recurrence of High-Grade Gliomas 269

Joshua Lucas and Gabriel Zada

The development of radiologic criteria for the assessment of response to treatment in high-grade gliomas (HGGs) has evolved considerably over the past few decades since the original response criteria based on computed tomography imaging. Accuracy and objectivity in the assessment of response to treatment of HGGs is necessary for altering treatment regimens, establishing accurate provider communication, and improving the quality of clinical trials. Future studies assessing emerging advanced neuroimaging techniques will facilitate the development of even more accurate evidence-based radiologic response criteria.

Pseudoprogression and Treatment Effect 277

Arman Jahangiri and Manish K. Aghi

The standard of care for newly diagnosed malignant glioblastoma entails postoperative radiotherapy and adjuvant chemotherapy with temozolomide. There has been an increase in the incidence of enhancing and progressive lesions seen on magnetic

resonance imaging (MRI) following treatment. Conventional MRI with gadolinium contrast is unable to distinguish between the effects of treatment and actual tumor recurrence. New modalities have provided additional information for distinguishing treatment effects from tumor progression but are not 100% sensitive or specific in diagnosing progression. Novel radiographic or nonradiographic biomarkers with sensitivity and specificity verified in large randomized clinical trials are needed to detect progression.

The Role of BCNU Polymer Wafers (Gliadel) in the Treatment of Malignant Glioma **289**

Seema Nagpal

The 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; carmustine) polymer wafer (Gliadel) was developed for use in malignant glioma to deliver higher doses of chemotherapy directly to tumor tissue while bypassing systemic side effects. Phase III clinical trials for patients with newly diagnosed malignant gliomas demonstrated a small, but statistically significant, improvement in survival. However, the rate of complications, including an increase in cerebrospinal fluid leaks and intracranial hypertension, has limited their use. This article reviews the current data for use of BCNU wafers in malignant gliomas.

Alternative Chemotherapeutic Agents: Nitrosoureas, Cisplatin, Irinotecan **297**

Jose A. Carrillo and Claudia A. Munoz

Irinotecan, cisplatin, and nitrosoureas have a long history of use in brain tumors, with demonstrated efficacy in the adjuvant treatment of malignant gliomas. In the era of temozolomide with concurrent radiotherapy given as the standard of care, their use has shifted to treatment at progression or recurrence. Now with the widespread use of bevacizumab in the recurrent setting, irinotecan and other chemotherapies are seeing increased use in combination with bevacizumab and alone in the recurrent setting. The activity of these chemotherapeutic agents in brain tumors will likely ensure a place in the armamentarium of neuro-oncologists for many years.

Temozolomide and Other Potential Agents for the Treatment of Glioblastoma Multiforme **307**

Daniel T. Nagasawa, Frances Chow, Andrew Yew, Won Kim, Nicole Cremer, and Isaac Yang

This article provides historical and recent perspectives related to the use of temozolomide for the treatment of glioblastoma multiforme. Temozolomide has quickly become part of the standard of care for the modern treatment of stage IV glioblastoma multiforme since its approval in 2005. Yet despite its improvements from previous therapies, median survival remains approximately 15 months, with a 2-year survival rate of 8% to 26%. The mechanism of action of this chemotherapeutic agent, conferred advantages and limitations, treatment resistance and rescue, and potential targets of future research are discussed.

Supersensitive Intra-Arterial Cerebral Infusion of Novel Agents After Blood–Brain Disruption for the Treatment of Recurrent Glioblastoma Multiforme: A Technical Case Series **323**

Benjamin J. Shin, Jan-Karl Burkhardt, Howard A. Riina, and John A. Boockvar

Glioblastoma multiforme constitutes the most common primary brain tumor and carries a grim prognosis for patients treated with conventional therapy including surgery, radiation therapy, and chemotherapy. There has been a recent revival of

selective intra-arterial delivery of targeted agents for the treatment of glioblastoma multiforme. Because these agents are less toxic and their delivery leads to a higher tumor–drug concentration, this combination may provide a better outcome in patients with high-grade glioma. This article discusses early experiences in patients who received superselective intra-arterial cerebral infusion of bevacizumab, cetuximab, and temozolamide after blood–brain barrier disruption with mannitol.

The Role of Avastin in the Management of Recurrent Glioblastoma **331**

Jennifer A. Sweet, Michelle L. Feinberg, and Jonathan H. Sherman

Glioblastoma multiforme is a malignant primary brain tumor for which no cure has been developed. However, with aggressive surgical resection, radiation, and the advent of temozolomide, the overall survival of patients with glioblastomas has improved significantly. Despite this multimodal treatment, glioblastoma invariably recurs. Although treatment options for glioblastoma recurrence are limited, one promising therapy is bevacizumab (Avastin). The role of Avastin in the management of recurrent glioblastomas is reviewed.

Management of Multifocal and Multicentric Gliomas **343**

Chirag G. Patil, Paula Eboli, and Jethro Hu

The diffuse nature of gliomas has long confounded attempts at achieving a definitive cure. The advent of computed tomography and magnetic resonance imaging made it increasingly apparent that gliomas could have a multifocal or multicentric appearance. Treating these tumors is the summit of an already daunting challenge, because the obstacles that must be surmounted to treat gliomas in general, namely, their heterogeneity, diffuse nature, and ability to insidiously invade normal brain, are more conspicuous in this subset of tumors.

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