

Gliomas: Quo Vadis

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INTRODUCTION

The pessimist would say that there has been little advancement in the management of malignant gliomas in the past 30 years. However, recent basic science research discoveries and published studies in high-impact scientific journals these past few years provide more than enough optimism for patients and treating-physicians alike. We are on the threshold of considerable, significant change in the way in which we care for patients with gliomas, both from a neurosurgical and an oncological standpoint. However, before we illustrate how the field of glioma management has changed, it is prudent to take stock of our past and where we were less than 100 years ago.

GLIOMAS: THE PAST

There were many early pioneers who had more than passing interests in the field of human brain tumors. Sir William Osler (1849–1919), Sir David Ferrier (1843–1928), Sir Byrom Bramwell (1847–1931), Sir William Macewen (1848–1924), and Carl Wernicke (1848–1904) are names of giants in the fields of early contemporary neurology and neurosurgery.¹ Sir William Macewen is credited with the first successful removal of a human brain tumor in 1879 in Glasgow, Scotland. His case entailed the care of a 15-year-old girl with “obscuration of intelligence, slowness of comprehension, and want of mental vigour.” Macewen was able to localize the tumor in this child to the left motor cortex some 16 years before the invention of x-rays by Roentgen. With a large trephine, the fungous tumor of the dura, most likely a meningioma, was removed and the child recovered well.

Before Cushing, the approach to patients with brain tumors was largely nihilistic. The problems of tumor localization, intraoperative hemorrhage, and postoperative infection led most surgeons to the abandonment of neurosurgical procedures. In the words of Ernst von Bergmann in 1888, “It is only after opening the skull that the surgeon can be certain whether the new growth is really accessible; and if this be the case, whether its removal is not contraindicated by its size, its relations to neighboring parts, and its infiltration into these.”¹

GLIOMAS: ADVANCES IN NEUROSURGICAL APPROACHES—1900–1930

Unquestionably, the major advances in glioma surgery stemmed from Cushing’s approach to intracranial tumors. The keys to Cushing’s success included tumor decompression, a separate closure of the galea with silk sutures, local anesthesia, tumor localization with ventriculography, a motor driven suction apparatus, and improved methods of hemostasis.

Cushing recognized the relative neurosurgical impotence with malignant gliomas. He and his colleagues devised the “radium bomb” as a mode of interstitial irradiation for patients with gliomas (*Fig. 8.1*).² In his words, “The type of bomb we have used is made up of a central core of radium needles enclosed in a rubber sponge and wrapped in thin rubber tissue, the size corresponding to the size of the cavity.” Cushing eventually gave up on this approach as there were some issues with infection, and overall patient survival was not dramatically enhanced.

GLIOMAS: THE PRESENT

If we now fast-forward to the present, we can definitively state that there have been several advances in treatment strategies for patients with gliomas even though correlations with improved patient survival have, until recently, been difficult to attain. Perhaps one of the single most important advances to glioma surgery has been the advent of neuronavigation technologies, which have enabled neurosurgeons to accurately plan craniotomy flaps, localize deep-seated tumors, and choose pathways to gliomas which minimize morbidity by avoiding regions of functional brain tissue (*Fig. 8.2*).^{3–5} As one of the limitations of neuronavigation is brain shift occurring after craniotomy, which can limit the neurosurgeon’s ability to gauge extent of resection, the advent of intraoperative magnetic resonance imaging (MRI) has provided instantaneous feedback to the neurosurgeon wishing to perform as complete a resection as possible.^{6–8}

There are many different techniques used today to perform cortical mapping, including awake craniotomy and direct cortical stimulation, electrocorticography, phase reversals by somatosensory evoked potential monitoring, functional MRI and magnetoencephalography (MEG) linked to neuronavigation devices (*Fig. 8.3*).^{4,5} The rationale behind

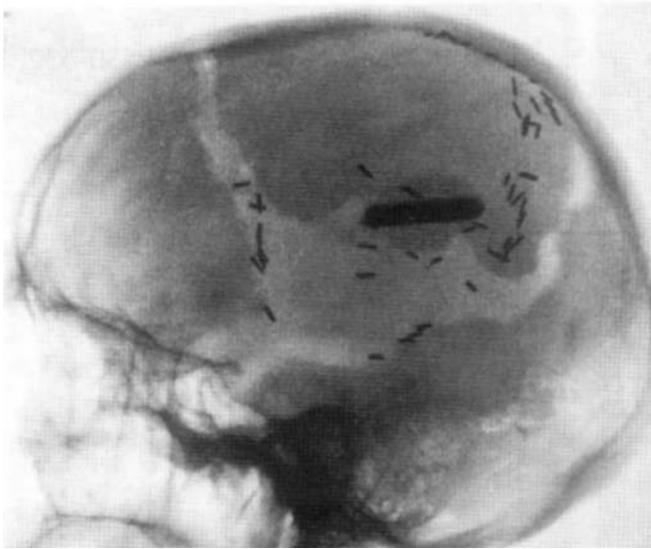


FIGURE 8.1. Lateral skull film from one of Cushing’s patients showing implantation of the “radium bomb” as a form of treatment for malignant gliomas. This treatment represents one of the first attempts at interstitial therapy for human brain tumors. Note the surrounding neurosurgical hemoclips used to promote hemostasis in Cushing’s cases.

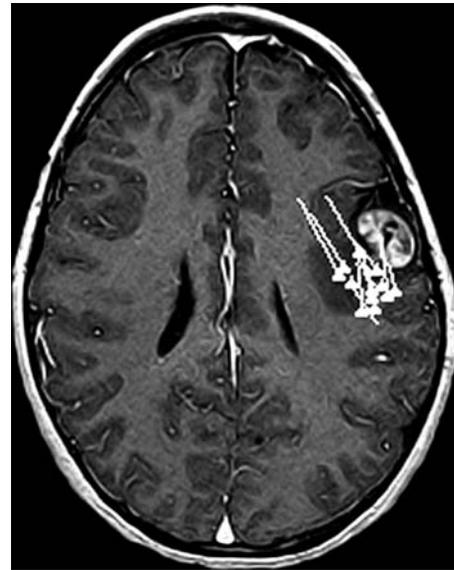


FIGURE 8.3. Axial contrast-enhanced T1-weighted MRI/MEG showing spike waves directly posterior to a contrast-enhancing tumor in a 12-year-old girl with seizures and NF-1. The lesion proved to be a ganglioglioma on resection.

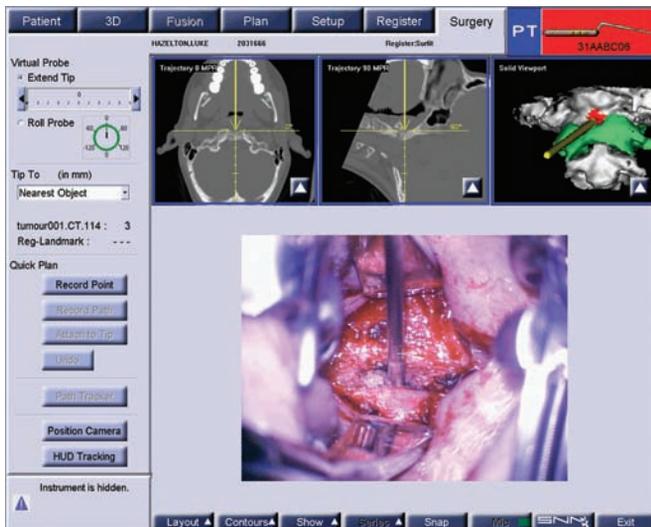


FIGURE 8.2. Intraoperative neuronavigation screen save taken during transoral resection of a clival osteoid osteoma in a 7-year-old boy. Neuronavigation has become a widely disseminated technology, assisting neurosurgeons with the resection of complex lesions, such as this, while minimizing morbidity.

cortical mapping is to preserve functional brain tissue while performing glioma resection so as to maintain a patient’s quality of life.

Much has been written previously on the role of extent of resection and malignant gliomas. Although much of this

literature suffers from the same problems of patient selection, retrospective series, and different histopathology, the work by Lacroix et al.⁹ is perhaps the most definitive in establishing a link between extent of resection and survival after glioblastoma surgery. In this study of more than 400 patients, it was shown that a greater than 94% resection of a glioblastoma multiforme (GBM) is required for a significant survival advantage to exist.

What has evolved quite rapidly in the past decade are new strategies for the neurosurgical delivery of chemotherapeutics, targeted toxins, and genetic and viral therapies in neuro-oncology.¹⁰ The neurosurgeon has thus been thrust into the position of local neuro-oncologist. One of the most exciting and promising delivery strategies of chemotherapeutics and active agents against gliomas is convection enhanced delivery (CED) (Fig. 8.4). Pioneered by Ed Oldfield as a means by which the blood-brain barrier can be obviated, CED is being used in a number of clinical trials to determine its efficacy.^{11,12} As one example, the agent TP-38, a recombinant chimeric comprised of transforming growth factor α (TGF- α) covalently linked to the pseudomonas endotoxin (PE38) is being delivered by CED intraparenchymally to patients with recurrent malignant gliomas.¹³ TP-38 works on the principle that the PE38 molecule bound to TGF- α binds to the ubiquitous epidermal growth factor receptor (EGFR) on malignant gliomas. The receptor:ligand interaction leads to the internalization of TP-38 by endocytosis, and subsequent targeting of the molecule to the lysosomes where the toxin is released resulting in apoptotic cell death (Fig. 8.5).

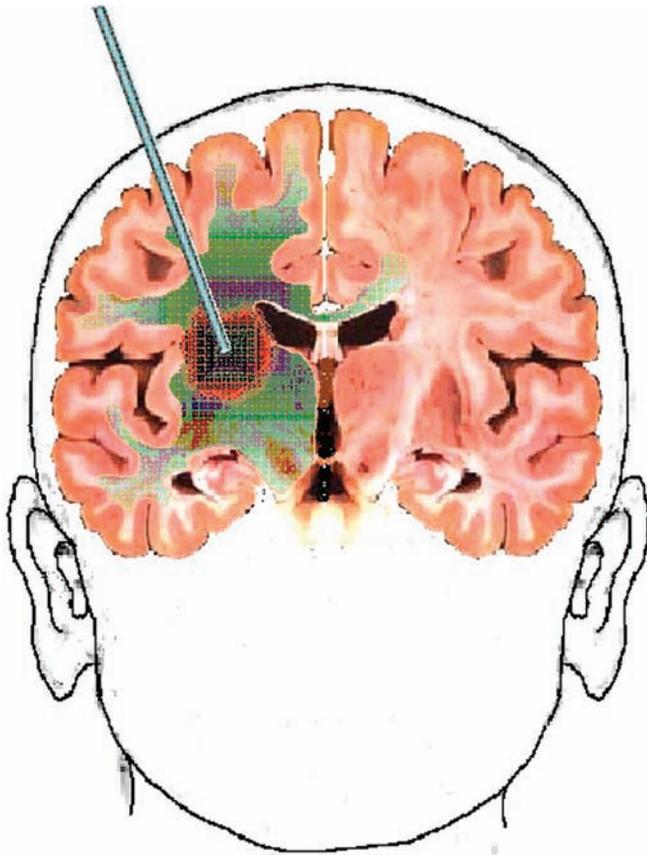


FIGURE 8.4. Schematic depiction of the concept of convection enhance delivery (CED). A catheter is inserted into the cerebral hemisphere, and a slow continuous infusion of a biological agent active against gliomas is distributed widely. Such a delivery strategy is now being examined across numerous Phase I to III clinical trials for patients with malignant gliomas.

GLIOMAS: GENETIC SIGNATURES AND PREDICTING PATIENT OUTCOME

The classic example of a molecular genetic signature which predicts patient outcome after chemotherapy is the loss of 1p and 19q in human anaplastic oligodendroglioma.^{14,15} Patients with anaplastic oligodendroglioma and losses of 1p and 19q have been shown to respond extremely well to procarbazine, cyclohexylchloroethylnitrosurea (CCNU), and vincristine (PCV) chemotherapy or, more recently, to temozolomide. But what about glioblastoma multiforme? Is there a molecular signature for it that predicts for responsiveness to chemotherapy?

In the past year, a clinical trial was conducted across numerous centers in Europe and Canada which showed that the radiation therapy and concomitant and adjuvant temozolomide was effective in extending patient survival on the order of 3 months compared to controls.¹⁶ It turns out that patients whose MGMT gene, a gene responsible for repair of

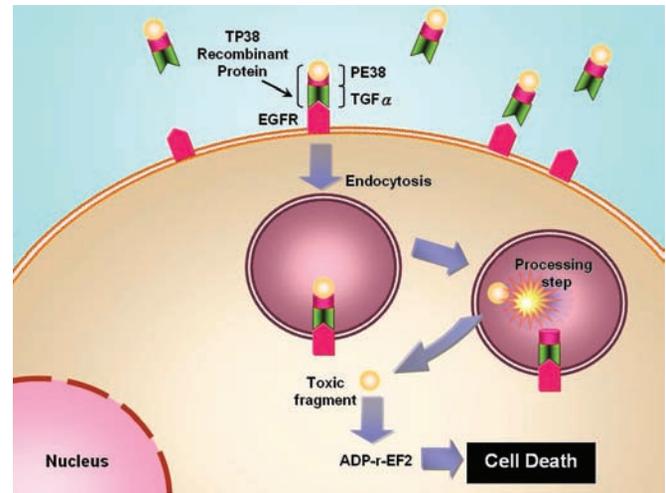


FIGURE 8.5. Schematic representation of Pseudomonas Endotoxin PE38 fused to the transforming growth factor TGF- α protein creating the TP38 recombinant protein, which targets the epidermal growth factor receptor (EGFR) on the cell surface of malignant glioma cells. After the binding of TP38 to EGFR, the receptor-ligand complex is internalized through endocytosis, processed in the endosomes, and the toxic fragment of the endotoxin is released resulting in energy failure and cell death.

deoxyribonucleic acid (DNA) damage caused by radiation injury and by alkylating agents, is methylated will survive longer after treatment than those patients whose MGMT gene is not silenced by methylation.¹⁷ These two studies, published in the *New England Journal of Medicine*, prompted Lisa DeAngelis from Memorial Sloan Kettering to write an editorial in the same issue of the journal stating that chemotherapy for brain tumors has reached a “new beginning.”¹⁸ Efforts are now underway to standardize the methods used to analyze MGMT gene methylation status so that laboratories around the world can benefit from this technology and the identification of patients most likely to respond to temozolomide.

MALIGNANT GLIOMAS: THE ENEMY IS WITHIN

In 2005, an important report was published in the literature which called attention to practice plans in the treatment of patients with newly diagnosed malignant gliomas.¹⁹ This study showed that practice patterns vary widely depending on whether patients are seen in comprehensive cancer centers or in small non-academic institutions. The placement of patients on clinical trials involving novel chemotherapeutics was shown to be highly variable and was not performed in more than the majority of cases. As a result, patients may not be getting the care that they deserve, and may be “short-changed.” One of the challenges in the next

decade will be providing appropriate care for patients with malignant gliomas, and overcoming the perception of nihilism when a patient presents with a brain tumor.

GLIOMAS: THE FUTURE

While it is clear that the management of patients with malignant gliomas has changed dramatically these past 30 years, we can predict for some phenomenal changes over the next 30 years with the advancements in surgical robotics, gene expression array datasets, molecular biology, and nanotechnologies.

It is already becoming clear that the diagnosis of glioblastoma multiforme will be made in the future by a skilled neuropathologist and molecular oncologist. Several studies have shown that gene-expression-based classifications of malignant gliomas correlate better with survival than standard histological classification.²⁰ In addition, the proteome is now being used to identify those patients with survival advantages with human gliomas.²¹ Tissue microarray technology is taking hundreds of clinical samples on a single glass slide and linking protein expression by immunohistochemistry to patient survival.²²

A major advancement in the past 10 years has been the creation of numerous genetically engineered animal models of gliomas which recapitulate the human disease.^{23–25} These models are based on typical genetic lesions found in the human glioblastoma multiforme and, as such, have the potential of being treated by several small molecule inhibitors which, if successful, could be translated to treat the human condition. Some examples of such small molecule inhibitors that will enter human trials for brain tumors include Tarceva, Iressa, Gleevec, Zanestra, and Penfosine.

The field of oncogenomics is quickly becoming an area in which new genetic markers and genes will be uncovered in glioblastoma multiforme and other gliomas.²⁶ Transcriptional profiling platforms now can analyze 17,000–30,000 complementary DNAs (cDNA) per experiment for a given tumor type. Affymetrix has a 100,000 single nucleotide polymorphism (SNP) chip which provides 8500 bp resolution on the human genome for uncovering losses or gains of genetic material in tumors. A 500,000 SNP chip is now available in experimental settings with a 2000 bp resolution. Identifying gene loci with these SNP chips will obviate the need to do huge amounts of sequence analysis since the resolution on the genome is so high. Inherent in such experiments, however, is the need for advanced bioinformatics platforms.²⁷ It is predicted that several studies on genome-wide SNP microarray mapping experiments will be found in the neurosurgery literature in the next 2–5 years, as they have started to appear in other tumor types.

EPENDYMOMA: A GLIAL TUMOR ARISING FROM UNIQUE PRECURSOR CELLS

Ependymomas can occur in the posterior fossa, supratentorial, or spinal compartments in humans. Although these tumors look somewhat indistinguishable under the microscope, a question arose as to whether they could develop from different molecular events. This hypothesis has now proven true. In a recent report by Taylor et al.,²⁸ ependymomas in the different compartments had different molecular genetic signatures. Furthermore, by immunohistochemistry, these tumors were readily distinguishable by their expression of proteins within the Notch signaling pathway. Furthermore, these authors have shown that the radial glial cells are the likely precursor cells in the different compartments that are subject to different tumor generating forces during embryogenesis. A genome-wide scan of ependymomas has now been performed that shows, for example, that the INK4a locus is deleted frequently in supratentorial ependymoma, but not in spinal or posterior fossa ependymomas.

GLIOMAS: ARE STEM CELLS AT THE ROOT OF THE PROBLEM?

In 2003, one of the first reports emerged that described the presence of stem cells in human malignant brain tumors, including glioblastoma multiforme.²⁹ The paradigm of a brain tumor stem cell, similar to the concept of stem cells giving rise to hematogenous malignancies, has now also been established in breast cancer and other solid cancers.^{30,31} One of the most accurate cell surface markers for the brain tumor stem cell is CD133. CD133+ve brain tumor cells have been shown to be the cells endowed with self-renewing properties and are able to grow when serially transplanted into immunocompromised host mice, whereas CD133-ve brain tumor cells do not.³² Targeting the brain tumor stem cell has important implications for future therapy. Chemotherapeutics that target the main tumor mass, but neglect to kill the cancer stem cell, will fail because the surviving stem cells will have an opportunity to repopulate the tumor. However, if drugs are engineered to selectively target the specific properties of stem cells, conventional chemotherapy can be used to induce apoptosis in the differentiated cancer cells and specific stem cell drugs can be used to ensure that the cancer stem cell is eradicated preventing regrowth of the tumor (*Fig. 8.6*).³³

GLIOMAS: BRAVE NEW WORLD

What does the future hold for the treatment of the patient with a malignant glioma? If we think outside traditional paradigms, we can envision a scenario such as the following: A patient with or without neurological symptoms of an intracranial tumor will undergo an imaging study, which will reveal an intracranial mass lesion. The broad category of tumor type will be specified by the advanced

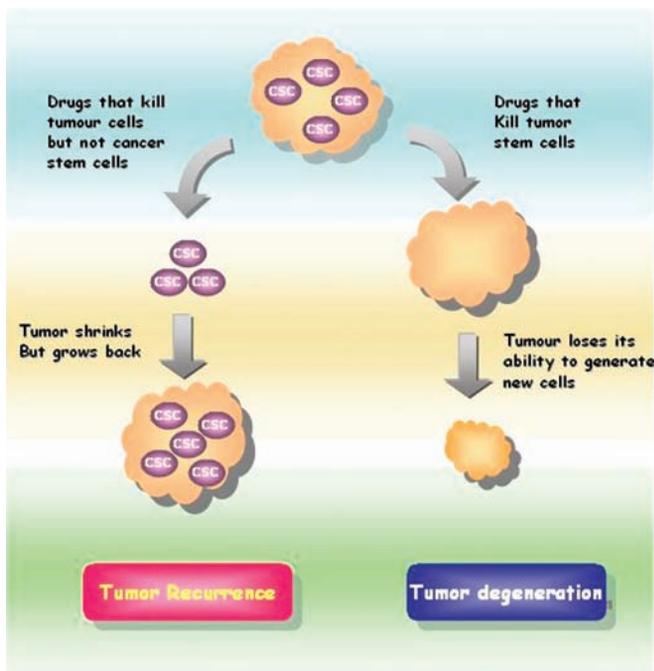


FIGURE 8.6. Stem cell theory of cancer, and implications for therapy. Drugs that are cytotoxic to the differentiated cancer cells will kill the vast majority of the cells in a solid cancer. However, if these drugs do not kill the cancer stem cell, this stem cell has the potential to repopulate the tumor and evade therapy. It is far more preferable to target the cancer stem cell with novel therapeutics, and to treat the differentiated cancer cells with standard cancer chemotherapeutics.

imaging sequences (e.g., novel magnetic resonance spectroscopic features). On an outpatient basis, the patient will undergo robotic procurement of a brain tumor biopsy and oncogenomic characterization of the lesion using bioinformatics platforms that will be available in every treating physician's office or clinic. Oncogenomic characterization of the glioma stem cell will afford an opportunity to synthesize a novel, implantable microcapsule that specifically attacks the stem cell population and can move within the fluid:mechanic interfaces of a tumor seeking out and destroying all specifically targeted cells. This microcapsule will be injected through robotic means. And, the patient discharged home the same day. Whether or not this scenario seems fanciful, it is our strong belief that the days of large craniotomies for malignant gliomas will be relegated to the past.

GLIOMAS: QUO VADIS?

To whom shall we give the last word? Perhaps there is no one more deserving in the history of glioma surgery than Harvey Cushing who said, "The surgery of brain tumors may be likened without being trivial to a form of major sport which is played against an invisible but utterly relentless

antagonist quick to take advantage of every misplay and faulty move. And when the time comes to make public one's score, it is done somewhat apologetically, but with the expectation that others may profit by it and with the assurance they will come to improve upon it." In this chapter, we have provided some strong evidence that others have improved upon the rather dismal prognosis of patients with malignant gliomas that was observed in the days of Cushing. We are on the threshold of realizing new gains in the prognosis of patients with malignant gliomas. We predict that the next decade will be full of new advances that will shape the field greater than ever before.

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