

Perspectives In Neuroscience



A Quarterly Publication for Continuing Medical Education

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Neuro-Oncologic Management of Malignant Gliomas

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This quarterly publication is designed for primary care physicians, neurosurgeons, neurologists, neuroradiologists, and other practitioners. The purpose of this publication is to provide these physicians with current management strategies for dealing with a variety of disorders and conditions in the neurosciences, and to provide up-to-date diagnostic and prognostic information written by specialists in the field. It is estimated that it will take the physician 1 hour to complete the activity. The 10 questions at the end of each lesson are designed to test and evaluate the participants' comprehension of the topic. This CME program is sponsored by the Central Illinois Neuroscience Foundation and funded by grants and donations. This CME activity was planned in accordance with the essentials for Continuing Medical Education set forth by the Illinois State Medical Society. The Central Illinois Neuroscience Foundation is accredited by the Illinois State Medical Society to sponsor continuing medical education for physicians. The Central Illinois Neuroscience Foundation designates this activity for a maximum of 1 hour of Category I credit towards the American Medical Association's Physician Recognition Award. It is the intent of the Central Illinois Neuroscience Foundation to assure that its educational mission, and Continuing Medical Education activities in particular, is not influenced by the special interests of individuals associated with its program.

Dr. Raul A. Rodas is a Clinical investigator and member of the speaker's bureau for Scherring Plough and Guilford Pharmaceuticals.

OBJECTIVES

At the conclusion of this CME Activity, the participant should be able to:

1. Recognize the development and advancements in the field of Neuro-Oncology.
2. Describe evolving trends in the management of malignant gliomas.
3. Discuss advancements in neuroradiology and neuropathology which have provided non-invasive formats for distinguishing neoplastic lesions and have modified the subsequent histological classification of brain tumors.

Table 1. Prognostic Factors

	Good	Poor
Age	< 60 y.o.	> 60 y.o.
Performance Status	KPS > 70	KPS < 70
Degree of Tumor Resection	GTR Gross Total Resection	Partial resection or biopsy
Histologic	Grading Grade III (anaplastic) oligodendroglioma, astrocytoma, mixed glioma	Grade IV (glioblastoma) astrocytoma

Neuro-oncology as a discipline

The birth of neuro-oncology dates back to 1884, from the collaboration between a neurologist and a neurosurgeon who shared an interest in the study (clinical-cerebral localization) and treatment (surgical resection) of a brain tumor at a time when radiology was not available and neuropathology was in its infancy. Neuro-oncology has evolved since then and has grown to encompass the talents of other medical/surgical specialties in what is now truly a multidisciplinary field. Advancements in the fields of diagnostic neuro-radiology, neuropathology, neurology, neurosurgery and radiation medicine have supported this specialty, which focuses on the special needs of the brain tumor patient. The management of the patient with a brain tumor requires the expertise of a physician who has first hand knowledge of the brain, spinal cord and peripheral nerve structures.

INTRODUCTION

Each year more than 17,000 people are affected by a primary brain tumor in the United States. Primary brain tumors constitute only 2% of all cancers. Glial cell tumors ("gliomas") are the most common of the primary brain tumors in the adult, with an annual incidence of 5 per 100,000 population. Glioblastoma Multiforme (GBM) is the most common type of glial tumor and the most malignant, having one of



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Table 2.
Developments in the Management
of Malignant Gliomas

Advances in neuroimaging
a. MRI, MRA, MRS
b. SPECT, PET
Advances in neuroanesthesia
Refinements in neuropathology
Image guided neurosurgical techniques
Advances in radiation therapy
a. Fractionated radiotherapy/optimal radiation schedules
b. Brachytherapy
c. Stereotactic radiosurgery
d. Radiation sensitizers
New approaches to chemotherapy
a. New agents
b. High dose/dose-intensive chemotherapy
c. Pre-radiation chemotherapy/chemo-radiation synergism
d. Novel delivery systems
Biological therapeutics/immunotherapy
Advances in the molecular genetics and cell biology of cancer
Evolution of gene therapy

the highest annual case-mortality ratios of any form of cancer. For this reason, malignant gliomas have historically been looked upon with despair by most of the medical and lay communities. The original Brain Tumor Study Group trial (1969-1974) reported a median length of survival of 34 weeks for patients with malignant gliomas who underwent surgery. The Brain Tumor Cooperative Group (1980-1984) found that the median length of patient survival had extended to 54 weeks when radiation therapy and chemotherapy supplemented a gross total removal of the tumor.

Clinical trials over the last 20 years have identified certain critical factors, such as age, performance status, histologic grade of the glial tumor and degree of surgical

resection as independent predictors of long-term survival. (Table 1) These factors also directly influence treatment decisions, particularly in regards to limiting potential toxic therapies in patients with poor performance status or advanced age. Conversely, these same factors support aggressive therapies (including investigational therapies) for younger patients with very good performance status.

The armamentarium available to treat malignant gliomas has rapidly evolved over the last two decades (Table 2). Although these developments have not resulted in substantial increases in long-term survival, they have significantly minimized some of the major iatrogenic morbidities associated with earlier diagnostic and therapeutic efforts, and have propagated the evolution of neuro-oncology into an active subspecialty.

This lesson will focus on the current management of the patient with a GBM, emphasizing a multidisciplinary approach towards optimizing the evaluation and therapeutic components of the patient's care plan.

DIAGNOSIS

Neuro-imaging

The technical armaments utilized this past century to diagnose brain tumors pre-operatively have included plain Xrays, pneumoencephalography, cerebral angiography, electroencephalogram, nuclear-isotope brain scan, CT scan and MR imaging. MRI with contrast enhancement is the most sensitive, least invasive and most reliable test to date for identifying infiltrating glial tumors. MRI is superior to CT scanning in distinguishing the tumor mass from surrounding vasogenic edema and usually suggests the grade of the tumor (degree of malignancy) by virtue of the degree of tumor enhancement.

As a complement to MRI, MR angiography identifies the relationship of the tumor to large arterial and venous structures, while functional MRI (fMRI) readily depicts motor, sensory and language areas of the brain in relation to the tumor. The information gained from both MRA and fMRI can allow the surgeon a safer approach to, and subsequent resection of the tumor by avoiding highly functional cortical areas adja-

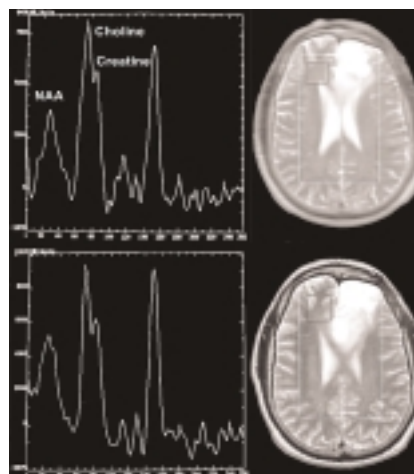


Figure 1A. (Above right) Voxel sampling of normal brain at initial diagnosis shows choline/creatine levels within normal range.

Figure 1B. (Above bottom) Voxel sampling of normal brain at six-month post-resection shows stable choline/creatine levels.

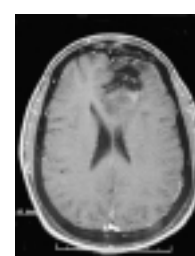


Figure 1C. (Above) MRI, six-month post-resection follow-up, shows no evidence of tumor progression.

cent to or within the tumor as well as identifying vessels encased by the tumor.

Magnetic resonance spectroscopy (MRS) quantitatively analyzes the biochemical nature of a suspected glial tumor non-invasively,

and has the capacity to distinguish an advanced neoplastic lesion from an inflammatory or a demyelinating lesion (Figure 1A&E). MRS can be used to guide both the biopsy and the resection of a brain tumor by identifying the area of greatest malignancy within the tumor's region of brain infiltration.

Neuropathology

Despite the unprecedented advancements in neuroimaging, the definitive diagnosis of a brain tumor still depends on the histological examination of the tissue. Astrocytic glial tumors are graded according to the World Health Organization (WHO), by their degree of malignancy, whereby more differentiated tumors are given a lower grade (grade I, II), less differentiated forms with vascular proliferation are given an intermediate grade (III) and the least differentiated forms that possess necrosis (glioblastoma multiforme) are given the highest grade of IV.

Neuropathologists are in the process of refining the current classification of gliomas. The use of immunohistochemical staining has helped differentiate the various types of brain tumors to their underlying cell of origin as well as providing reliable and reproducible methods of assessing how quickly a tumor cell divides (proliferation index).

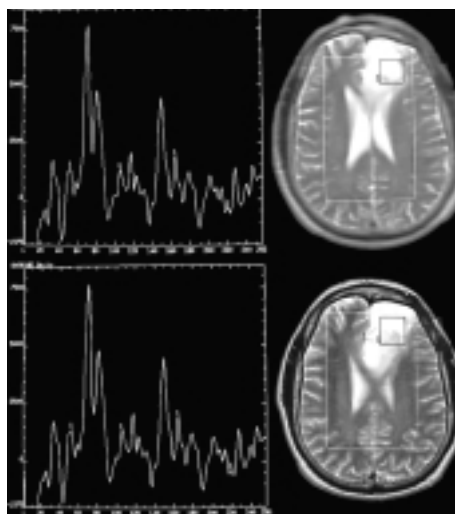


Figure 1D. (Left top) Voxel sampling of tumor bed at initial diagnosis shows abnormal choline/creatine levels of 4500-7500.

Figure 1E. (Left bottom) Voxel sampling of tumor bed six-months post-resection shows choline/creatine levels increased two-fold to 7000-14000 indicating tumor progression towards malignancy. Routine MR imaging failed to demonstrate progression. (1C).

The field of molecular neuropathology is creating a new chapter that will expose the molecular fingerprint of each type of brain tumor, which will then lead to a focused way of treatment.

Therapy

Three therapeutic modalities are currently available to treat malignant gliomas: surgery, radiation therapy and chemotherapy. The progress made in each respective modality over the last 20 years have minimized the degree of iatrogenic induced morbidity. Although the combination of all three have increased survival, they have not provided a cure for gliomas.

Surgery

For treatment of malignant gliomas, a gross total resection verified by a post-operative CT or MRI scan leads to better outcomes. There is ample literature to support the view that a gross total resection of a malignant glioma affords the patient with the best chances of longest survival, improved quality of survival, and less dependency on corticosteroids as compared to patients who only have a partial resection or biopsy.

The mechanical removal of tumor and necrotic debris from the lymphatic-deficient brain can ameliorate the general symptoms of raised intracranial pressure as well as palliate the more focal symptoms related to mass effect caused by the tumor. Removal of the necrotic material and hypoxic cells that are believed to be resistant to radiation and chemotherapy will enhance the effect of adjuvant therapy.

In those patients who develop a progression/recurrence of their malignant glioma, reoperation appears to offer diagnostic (ie: differentiate tumor progression from radiation induced necrosis) and therapeutic benefits. An aggressive cytoreductive surgery at the time of recurrence prolongs the survival and the quality of survival in patients younger than 60, those with good performance status and in those patients who have deteriorated neurologically from tumor growth no less than 6 months from their first surgery.

Radiation Therapy

Standard radiation schemes applied to patients diagnosed with GBM include the delivery of ionizing external beam radiation based on 3-D treatment planning that encompasses the tumor, as seen on pre-operative contrast-enhanced MRI, plus a 2-3 cm margin. Although many radiation oncology clinical trials have looked at a variety of radiation schedules, the combination of an aggressive resection of all visible tumor followed by the delivery of 60 Gy of external beam radiation therapy has provided the best survival (median of 54 weeks). This radiation plan is usually carried through by daily treatments (of 180-200 cGy) that generally last less than an hour delivered over a 6 to 7 week period of time. This treatment regimen has demonstrated the least amount of focal toxicity ("sun burn" type of irritation to the skin, slight decline in hearing if ports involve the ear-temporal bone region, change in taste/appetite) and general toxicity (malaise/fatigue/tiredness).

The trend of employing stereotactic radiosurgery (SRS) for GBM, where a high dose of radiation is focused/contoured to fit the shape of the tumor by computerized techniques and delivered in one single session, has been supported by certain radiation oncology programs. Alternatively, one can deliver a carefully calculated high "boost" of radiation to the tumor at the completion of standard radiation and the time of recurrence. The use of stereotactic radiosurgery (SRS) techniques for GBMs, as supported by certain programs, is currently under clinical investigation.

Table 3.
Chemotherapeutic Agents Demonstrating
Anti-Angiogenic Activity Against Malignant Gliomas

BCNU	Temozolomide
Procarbazine	Tamoxifen
Cyclophosphamide	Crisnatol
Cisplatin	Camphotecans: topotecan, irinotecan
Carboplatin	RMP 7 – carboplatin
PCV	Cis-Retinoic Acid
CTX / VP-16	O-6 Benzylguanine
Cisplatin / VP-16	Fenretinide
Carbo / VP-16	Sodium Phenylbutyrate
BCNU / Cisplatin	
BCNU / Cisplatin / Etoposide	

Chemotherapy

Since the 1970's, the Brain Tumor Study Group and later, the Brain Tumor Cooperative Group chose the nitrosoureas as the most commonly used chemotherapy agent for malignant gliomas. Carmustine (BCNU: bis-choloroethylnitrosourea), was initially chosen among other chemo agents for its demonstrated activity against this tumor type and its high lipid solubility which allowed good penetration into the brain. BCNU alone was also compared to protocols involving multiple chemotherapy agents during this period. Prior to the wide availability of CT scanning, measurements of response from BCNU chemotherapy relied heavily on clinical assessment. These earlier studies indicated a response of 40-50%, while more contemporary studies based on MRI measurements suggest that the actual response rate of BCNU for GBM is in the range of 15-25%.

None of the earlier trials demonstrated more than a slight increase in median survival for GBM patients as a whole group when comparing radiation plus BCNU with radiation alone. Although, there was a fourfold increase in the percentage of patients surviving beyond 18 months in the subgroup of patients who received BCNU. These studies suggested the presence of a subgroup of GBM patients with chemosensitive tumors and provided the basis for our current standard therapy for GBM that includes the use of BCNU following surgery and radiation therapy.

Unlike microbiologic studies of resistance and sensitivity, in vitro chemosensitivity studies using cell cultures of human brain tumors have been difficult to standardize. Recommendations regarding treatment management are strongly influenced by their toxicities. The toxicity of intravenously administered BCNU at standard doses (150-200 mg/m²) are generally modest. BCNU chemotherapy is given at regularly scheduled cycles (every 6-8 weeks) so long as there is no objective clinical and radiologic progression of the tumor and no severe systemic adverse effects. Generally no more than 9 cycles are given sequentially. Of the potential side effects, nausea and vomiting are infrequent. Hematologic toxicities tend to be mild to moderate and somewhat delayed. Transfusion of blood products required in approximately 5% of cases at standard doses, and the use of hematopoietic growth factors are seldom needed. The toxicity of intravenously administered BCNU to solid organs tend to be cumulative. Pulmonary fibrosis can occur in up to 20% of patients who have received > 1200mg/m². Periodic pulmonary function tests should be carried out in patients exposed to these cumulative doses or in smokers receiving systemic BCNU. Renal, hepatic, persistent anorexia and central nervous system toxicities have been reported, but are uncommon. These latter effects are generally delayed. Neutropenic (WBC count less than 2.0) fevers should always be clinically and radiographically investigated. Although they can occur at any time, they seldom do at the beginning of therapy.

For otherwise healthy individuals, the risk of serious complications from systemic BCNU is small, and the negative impact on the overall quality of life of patients with malignant gliomas is only slight to moderate. Since there exist a subgroup of patients who will benefit from BCNU, in terms of a modest increase in time to progression and overall length of survival, the current recommendation of adjuvant therapy with this agent is still supported. In addition to nitrosoureas, a number of other chemotherapeutic agents have demonstrated activity against malignant gliomas (Table 3).

Alternative/novel chemotherapy agents

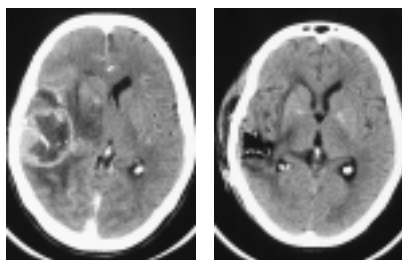


Figure 2A. (Above left) CT scan showing a large inhomogeneously enhancing, aggressive appearing mass of the right temporal lobe.

Figure 2B. (Above right) CT scan, post-resection, of the right temporal lobe GBM with implanted BCNU wafers.

The development of techniques that increases the delivery of chemotherapy agents to the tumor have recently include RMP-7 (a bradykinin analog that selectively and temporarily disrupts the blood brain barrier surrounding the glial tumor) followed by carboplatin.

The BCNU impregnated polymer wafer, is FDA approved for use in recurrent malignant glioma, and support for its use at first resection is growing. The surgical cavity created from the gross total resection of the glial tumor is lined with BCNU

wafers, slowly releasing the BCNU chemo agent into the tumor-infiltrated margins surrounding the cavity (Figure 2A & 2B). This "intracavitary" method of delivering BCNU produces a chemo-concentration that is over 100 times the amount that the tumor will see if a comparable dose of BCNU were given by intravenous method. A negligible amount of BCNU from this delivery method escapes into the systemic circulation. Subsequently, systemic side effects from intra-cavitary BCNU wafer implantation is rare. However, because of its focally high dose, the margins of the surgical cavity can be irritated, producing an additional amount of cerebral edema. This is generally well controlled by the use of perioperative steroid medication. Post-operative seizures are slightly increased by BCNU wafer placement, but this is also controlled by the proper and judicious use of anticonvulsants. Although there is a slight increase in the rate of wound infection with the use of the BCNU wafer, proper closure techniques (water tight closure of the dura sealing off the edges of bone flap with "gelfoam-like" material, and layered closure of the skin without the use of drains) have minimized this problem.

Agents that are currently under investigation which have promising anti-glioma activity include angiogenesis inhibitors thalidomide (Celgene), TNP-470 (TAP Pharmaceuticals), endostatin (EntreMed) and SU6668 (Sugen); differentiation inducing agents (phenylacetate and phenylbutyrate); growth factor antagonists (suramin); inhibitors of intracellular signaling (lovastatin); inhibitors of cellular invasion [matrix metalloproteinases: marimastat (British Biotech)].

Immuno-chemosensitization is an approach which genetically induces the glioma tumor cell to produce a chemical that activates the cytotoxic effect of a chemo agent, or allow the tumor to become selectively antigenic to the body's own immune system. This strategy targets the glioma tumor cell and spares adjacent normal brain cells from the toxic effects of the chemo agent.

CONCLUSIONS

Despite aggressive combination therapies, the vast majority of patients with malignant gliomas will recur focally and will prove fatal. For this reason, currently available strategies, such as high-energy boost radiation therapy (stereotactic radiosurgery), intracavitary radiation (I^{125} Gliasite), and intracavitary chemotherapy (BCNU impregnated wafer) at first resection are attractive.

New technological developments on the horizon are accelerating clinical trials utilizing novel surgical techniques, immuno-chemo-sensitization and targeted molecular therapies. Temporary control of tumor progression can be achieved for the large majority of patients with malignant gliomas. Patients less than 60 years of age who function at a high level and have undergone an image-verified gross total resection have the longest survival with adjunct radiation therapy and chemotherapy. In those patients who have achieved a substantial cytoreductive treatment from surgery and radiation, a significant reduction of symptoms and/or stabilization of neurologic deficits is common.

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Continuing Medical Education Questions

- MR Spectroscopy in patients with brain masses is a reliable, non-invasive procedure that can be used to distinguish tumor from non tumor masses as well as detecting the progression towards malignancy.
☐ True ☐ False
- The mean survival for GBM at the present time is longer than for a patient with newly diagnosed HIV.
☐ True ☐ False
- The variables of age, performance status, degree of surgical resection and tumor grade/histology can reliably predict the prognosis of patients with glioma type of brain tumors.
☐ True ☐ False
- Contemporary radiation techniques and chemotherapy agents seldom improve the quality of survival of glioblastoma patients.
☐ True ☐ False
- Immunohistochemical and molecular analysis of brain tumors are unlikely to add any useful diagnostic and therapeutic targeting information than routine histology.
☐ True ☐ False
- Patients with malignant gliomas who are functional, but fail standard radiation and chemotherapy options seldom benefit from further surgical resection of the tumor that has progressed.
☐ True ☐ False
- Immunochemosensitization is a promising option for malignant brain tumors. Although investigational, this and other forms of therapy which focus on the inherent fingerprints of the brain tumor will further limit iatrogenic injury to normal brain cells.
☐ True ☐ False

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Mission Statement

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