Evolution of radiotherapy and chemotherapy practice in malignant gliomas

Anusheel Munshi, Sayan Paul
Department of Radiation Oncology, Fortis Memorial Research Institute, Gurgaon, Haryana, India

ABSTRACT
Malignant astrocytomas of the brain carry a poor prognosis. This article traces the evolution of radiotherapy and chemotherapy practice including the development of concurrent chemo-radiation schedules in the context of these tumors.

Key words: Chemotherapy, glioma, radiotherapy

INTRODUCTION
Tumors of the central nervous system (CNS) are rare neoplasms constituting 1-2% of all malignancies.[1] Approximately, 85-90% of primary CNS tumors are intracranial tumors, while the rest are in the spine.[1,3] Depending upon the age, histology and site in the CNS, these tumors have varied presentations and contrasting clinical outcomes.[4] Among CNS neoplasms, gliomas are the most common tumors. These tumors have annual incidence of 3.4-1.00,000 population.[1-3] At least, 80% of malignant gliomas are glioblastomas.[3] Treatment options include surgery, radiotherapy (RT) and systemic chemotherapy, in varied schedules and combinations,[6] Glioblastoma multiforme (GBM), the most common intraparenchymal brain tumor in adults, is highly invasive and has a poor prognosis. Long-term survival, even with optimal treatment remains poor. Typical median survival time for patients with GBM and anaplastic astrocytoma ranges from 10 to 12 months and 30 to 40 months, respectively. However, it is well-known that geographical, genetic and phenotype differences in populations can alter the incidence, natural history, behavior and response to treatment of cancers.[7]

MOLECULAR ASPECTS
Primary GBM’s tend to occur in older patients (mean age, 55 years), whereas secondary GBM’s tend to occur in younger adults (45 years of age or less).[6,9] The difference between these two entities can occasionally be recognized radiographically. Regions of non-enhancing tumor are evident in secondary glioblastomas, as well as pathologically, when a surgical specimen contains low-grade disease. The two types of glioblastoma arise through different molecular pathways. Primary glioblastomas are associated with a high rate of overexpression or mutation of the epidermal growth factor receptor, p16 deletions and mutations in the gene for phosphatase and tensin homologs.[9-11] Secondary glioblastomas have genetic alterations involving the p53 gene and overexpression of platelet-derived growth factor A and its receptor, platelet-derived growth factor receptor.[12]

Three molecular markers have redefined the outlook for malignant gliomas: 1p/19q chromosomal codeletion, O (6)-methylguanine methyltransferase (MGMT) promoter methylation and mutations of isocitrate dehydrogenase (IDH) 1 and 2. The assessment of these molecular markers has so far not been implemented in clinical practice because of the lack of precise therapeutic implications. It is considered that these markers are more prognostic than of predictive value, irrespective of whether patients were receiving RT, chemotherapy or both (1p/19q, IDH1/2). Also, with the advent of Temozolomide and lack of a viable alternative, testing was considered of limited value because testing itself has complexity and cost implications. However, in 2012, long-term follow-up of the Radiation Therapy Oncology Group (RTOG) 9402 and European Organization for Research and Treatment of Cancer (EORTC) 26951 trials demonstrated an overall survival benefit from the addition to RT of chemotherapy with procarbazine/
Lomustine/vincristine confined to patients with anaplastic oligodendroglial (AO) tumors with (vs. without) 1p/19q co-deletion.\[13\]

**SURGERY IN MALIGNANT GLIOMAS**

Surgery remains the cornerstone of the management of malignant glioma. However, surgery alone results in a short median survival time of about 4 months. Surgical options in a malignant glioma patient include stereotactic biopsy, open biopsy or debulking procedure and major tumor resection. Optimal debulking surgery using an adequate tissue sample appears to offer the best outcome in eligible patients with good performance status.\[14\] Although the aim is complete or near-complete surgical removal, it has to be within the constraints of preservation of neurologic function and underlying patient health.\[14,15\] An exception to the general recommendation for attempted resection is the case of deep-seated tumors such as pontine gliomas. These tumors are diagnosed on clinical evidence and treated without initial surgery approximately 50% of the time. Two primary goals of surgery in malignant gliomas therefore include (1) establishing a histologic diagnosis (2) reducing intracranial pressure by removing as much tumor as is safely possible while preserving neurological function.\[16\] In view of poor patient outcomes in malignant gliomas after surgery alone, adjuvant treatment is strongly recommended.

**RT**

Radiation therapy has a significant role in the treatment of patients with high-grade gliomas. Use of RT in malignant gliomas is based on two trials in 1970’s, which demonstrated improvement in survival. In the landmark study by Walker et al., a total of 303 patients were randomized. Patients were divided into four random groups and received bis-chloroethylnitrosourea (BCNU) (80 mg/m²/day on 3 successive days every 6-8 weeks) and/or RT (5000-6000 rads to the whole brain through bilateral opposing ports) or best conventional care, but no chemotherapy or RT. Median survival of patients was best conventional care: 14 weeks; BCNU: 18.5 weeks; RT: 35 weeks; and BCNU plus RT: 34.5 weeks.\[17\] A randomized trial compared 60 Gy (in 30 fractions over 6 weeks) with 45 Gy (in 25 fractions over 4 weeks) and showed superior survival in the first group (12 months vs. 9 months median survival; hazard ratio [HR] =0.81; 95% confidence interval (CI): 0.66-0.99). This trial made 60 Gy as the accepted standard dose of RT for malignant gliomas.\[18\] A statistically significant survival advantage was found comparing post-operative radiation therapy with no radiation therapy in a systematic review and meta-analysis of five randomized trials (risk ratio=0.81; 95% CI: 0.74-0.88).\[19\]

On the other hand, there have been some approaches in radiation therapy that have failed to deliver in the context of malignant gliomas. These include stereotactic radiosurgery and brachytherapy. A randomized trial tested radiosurgery as a boost added to standard external beam radiotherapy (EBRT), but found no improvement in survival, quality-of-life or patterns of relapse compared with EBRT without the boost.\[20,21\] Similarly, brachytherapy has been used to deliver high doses of radiation locally to the tumor while sparing normal brain tissue. A randomized study was undertaken to assess the role of brachytherapy as a boost (using I 125 seeds) to external beam radiation therapy in the initial management of patients with malignant astrocytomas. This study did not find any benefit of using brachytherapy.\[22\] This approach fell out of favor in view of the technical challenges and no proven benefit over external RT.

Conformal external beam radiation is the most commonly used approach.\[21\] EBRT using either 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy is considered an acceptable technique in radiation therapy delivery. In general, 2-3 cm margins on the magnetic resonance imaging-based volumes (T1-weighted and fluid attenuated inversion recovery to create the planning target volume are used. Dose escalation using radiosurgery has not improved outcomes.\[23\]

**CHEMOTHERAPY**

Traditionally, chemotherapy was considered to have little or no benefit in the management of brain tumor. This perception is changing in recent years. The first agents to make some breakthrough in malignant gliomas were nitrosoureas. For many years, the nitrosourea carmustine (BCNU) was the standard chemotherapy added to surgery and radiation for malignant gliomas. The use of this agent was based upon a randomized trial (RTOG -8302) of 467 patients conducted by the brain tumor study group that compared four regimens after initial resection.\[24\] This study used the arms of semustine (methyl-CCNU), radiation therapy, radiation therapy plus carmustine and radiation therapy plus semustine. The radiation therapy plus carmustine arm had the best survival rate.

More recent randomized trials evaluated various chemotherapy regimens as alternatives to nitrosourea, different RT techniques and pre-irradiation multi-agent...
chemotherapy. Several observations in the late 1980s led to the development of independent research strategies for patients with GBM tumors, anaplastic astrocytoma lesions and patients with anaplastic oligodendroglioma (AO), including selective use of brachytherapy, various radiosensitizing agents and the development of a novel statistical approach to patient grouping by prognostic characteristics and survival (recursive partitioning analysis classes). In 2002, a patient-level meta-analysis of 12 randomized trials was published. It suggested modest impact on survival using nitrosourea containing chemotherapy regimens for malignant gliomas (combined HR death=0.85; 95% CI: 0.78-0.91).[25]

In 2005, a large multicenter trial of glioblastoma patients conducted by the EORTC National Cancer Institute of Canada that showed a survival advantage.[26,27] In this landmark study, 573 patients with glioblastoma were randomly assigned to receive standard radiation to the tumor volume with a 2-3 cm margin (60 Gy, 2 Gy per fraction, over 6 weeks) alone or with temozolomide (75 mg/m^2 orally per day during radiation therapy for up to 49 days, followed by a 4-week break and then up to six cycles of five daily doses every 28 days at a dose of 150 mg/m^2 increasing to 200 mg/m^2 after the first cycle). Patients in the combined therapy group were given prophylactic therapy for pneumocystis carinii during the period of concomitant radiation therapy and temozolomide. Overall survival (OS) was statistically significantly better in the combined radiation therapy/temozolomide group (HR for death=0.6; 95% CI: 0.5-0.7; survival at 3 years was 16.0% vs. 4.4%). The oral agent, temozolomide, has since replaced the nitrosoureas as the standard systemic chemotherapy for malignant gliomas. Studies are to determine whether it is the concurrent component or the sequential component of Temozolamide, which is more crucial during the concurrent component or the sequential component of radiation.

Ependymoma is the third most common primary brain tumor in children. Tumors are classified according to the WHO pathological grading system. Prior studies have shown pathological grades are important prognostic factor. Regardless of tumor location or pathological grade, gross total resection (GTR) is associated with a better outcome than subtotal resection (STR). GTR is associated with the lowest rates of mortality, the best overall survival and the longest progression free survival (PFS). However, pathological classification, tumor location and method of treatment play a role in outcomes. Cage et al. in a study showed that GTR is associated with the best overall and PFS rates. Patients with WHO Grade II tumors had better overall survival after GTR + EBRT and better PFS after GTR alone. Patients with WHO Grade III tumors had better overall survival after STR + EBRT. Patients with infratentorial tumors had improved overall survival compared with those with supratentorial tumors. Progression-free survival was best in those patients with infratentorial tumors following STR + EBRT. Consideration of all of these factors is important when counseling families on treatment options.[38]

**LOCALIZED TUMOUR BED CHEMOTHERAPY**

Because malignant glioma-related deaths are nearly always the result of an inability to control intracranial disease (rather than the result of distant metastases), the concept of delivering high doses of chemotherapy while avoiding systemic toxicity is attractive. A biodegradable Carmustine wafer has been developed for that purpose. The wafers contain 3.85% Carmustine and are implanted into the tumor bed lining at the time of open resection. There have been two randomized placebo-controlled trials of this focal drug delivery method both showed a trend towards OS advantage associated with the Carmustine wafers. The first was a small trial closed because of a lack of continued availability of the Carmustine wafers after 32 patients with high-grade gliomas had been entered.[39] Although OS was better in the Carmustine wafer group (median 58.1 vs. 39.9 weeks; P=0.012), there was an imbalance in the study arms (only 11 of the 16 patients in the Carmustine wafer group vs. 16 of the 16 patients in the placebo-wafer group had Grade IV
The second study was a multicenter study of 240 patients with primary malignant gliomas, 207 of whom had glioblastoma. At initial surgery, they received the carmustine versus placebo waters, followed
by radiation therapy (55-60 Gy). Systemic therapy was not allowed until recurrence, except in the case of AO, of which there were nine patients. Unlike the initial trial, patient characteristics were well-balanced between the study arms. Median survival in the two groups was 13.8 months versus 11.6 months; \( P=0.017 \) (HR=0.73; 95% CI: 0.56-0.96). A systematic review combining both studies estimated a HR for overall mortality of 0.65; 95% CI: 0.48-0.86; \( P=0.003 \). However, both these trials had drawbacks including inferior control arms and non-use of temozolomide. These issues and the cost implications of therapy have prevented placement of wafers from becoming standard therapy in GBM’s.

**SURVIVAL TRENDS FOR HIGH-GRADE GLIOMA OVER THE PAST YEARS IN GENERAL POPULATION**

There is some evidence that the survival benefits seen in clinical trials have translated into benefits seen in population-based registries as well. In a relevant study, patients diagnosed between 2000 and 2006 with a GBM who underwent surgery and post-operative RT were selected from the Surveillance, Epidemiology and End Results database. Patients were grouped into time periods: 2000-2001, 2002-2003, 2004 and 2005-2006 (which represented those treated after the EORTC/NCIC trial presentation in 2004). Relative survival (RS) was estimated by the Kaplan-Meier method and Cox multivariable regression modeling was used to estimate proportional HR. Over time, there was improvement in median and 2 year RS of 12 months and 15% for 2000-2001, 13 months and 19% for 2002-2003, 14 months and 24% for 2004 and 15 months and 26% for 2005-2006 (\( P<0.0001 \) compared with 2000-2001 and 2002-2003; \( P=0.07 \) compared with 2004). Table 2 highlights the trials that led to increments in survival.

**ELDERLY PATIENT WITH MALIGNANT GLIAL TUMOURS**

Most patients with glioblastoma are older than 60 years. Paradoxically, most studies and treatment guidelines are based on trials in patients aged only up to 70 years. Some work addressing elderly patients with high-grade gliomas has been published recently. Of note is a randomized study assessed Temozolomide versus standard 6 week RT versus hypofractionated RT in patients older than 60 years with glioblastoma. Patients treated with temozolomide who had tumor MGMT promoter methylation had significantly longer survival than those without MGMT promoter methylation (9.7 months [95% CI: 8.0-11.4] vs. 6.8 months [5.9-7.7]; HR: 0.56 [95% CI: 0.34-0.93], \( P=0.02 \)), but no difference was noted between those with methylated and unmethylated MGMT promoter treated with RT (HR: 0.97 [95% CI: 0.69-1.38]; \( P=0.81 \)) for all patients who received temozolomide or hypofractionated RT (\( n=242 \)) overall survival was similar (8.4 months [7.3-9.4; \( n=119 \)] vs. 7.4 months [6.4-8.4; \( n=123 \)]; HR: 0.82, 95% CI: 0.63-1.06; \( P=0.12 \)). Another randomized study reconfirmed that temozolomide alone is non-inferior to RT alone in the treatment of elderly patients with malignant astrocytoma. MGMT promoter methylation seems to be a useful biomarker for outcomes by treatment and could aid decision-making.

**TREATMENT OPTIONS PRESENTLY UNDER CLINICAL EVALUATION**

In view of the overall dismal outcome of high-grade gliomas, further research in developing RT and chemotherapy practices is needed. Heavy particle
radiation, such as proton beam therapy, carries the theoretical advantage of delivering high doses of ionizing radiation to the tumor bed while sparing surrounding brain tissue. The available data for this technique are preliminary. Novel biologic therapies under clinical evaluation for patients with brain tumors include Dendritic cell vaccination, Tyrosine kinase receptor inhibitors, Farnesyltransferase inhibitors, Viral-based gene therapy, Oncolytic viruses, Epidermal growth factor-receptor inhibitors, Vascular endothelial growth factor inhibitors and other anti-angiogenesis agents.[47-49]

To summarize, treatment of malignant gliomas of the brain has evolved from surgery predominant approaches to approaches including radiation and chemotherapy in the adjuvant treatment.

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