Radiation-Associated Toxicities in the Treatment of High-Grade Gliomas

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This article gives a brief historical overview of the development of standard management for high-grade gliomas (HGGs). The current standard of care, trimodality therapy with maximal safe resection followed by involved-field radiotherapy (RT) with concomitant/adjuvant temozolomide, confers median survival of 14.6 months, and a modest but measurable proportion (9.8%) of patients survives 5 or more years. We review the toxicities associated with irradiation of the central nervous system for patients with HGG, with focus on the pathophysiology, clinical manifestations, and potential preventative strategies for long-term neurocognitive dysfunction, which remains a pervasive, progressive, and clinically devastating sequela of trimodality therapy. Treatment of cognitive decline after RT is limited, and strategies for preventing this complication are being investigated.
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In 2014, the American Cancer Society estimates that 23,380 new cases of primary brain cancer will develop in the United States and that 14,320 deaths will result from the disease.[1] High-grade gliomas (HGGs) comprise up to 70% of malignant primary brain tumors. Radiation therapy (RT) plays a central role in the treatment of HGG. Radiation effects on the CNS limit both the dose and volume irradiated. The tolerance thresholds of different parts of the CNS dictate the maximum dose of radiation delivered to these radio-resistant tumors. Exceeding the RT dose/volume thresholds can unnecessarily lead to permanent neurologic sequelae that can seriously degrade the quality of life (QOL) in these patients who often have limited life expectancies.

STANDARD RADIATION TREATMENT FOR HGG: HOW DID WE GET HERE?

The current standard of care for HGG patients comprises maximal safe tumor resection followed by concurrent external-beam RT and temozolomide (TMZ), and adjuvant TMZ for approximately 6–12 months.[2] Despite the aggressive trimodality regimen, the prognosis for patients with HGG, particularly those with glioblastoma multiforme (GBM), remains grim.

The essential role of RT was established by the Brain Tumor Study Group (BTSG) in the late 1970s. In a seminal BTSG study, Walker et al found that adjuvant therapy with whole-brain irradiation (WBI) conferred a survival benefit compared to best supportive care (median survival [MS] 37.5 weeks *v* 17 weeks, 1-year overall survival [OS] 24% *v* 3%).[3] Other studies have examined the value of adjuvant radiotherapy versus supportive care alone with similar results.[4]

Standard RT has evolved from treating the whole brain to treating partial brain volumes. Based on classic studies, standard RT today involves treating a volume encompassing the surgical cavity and the edema (microscopic disease) seen on magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) or T2 sequences to 46 Gy plus a margin, followed by a boost to the surgical cavity and MRI T1 post-gadolinium-enhancing residual disease plus a margin to a total dose of 60 Gy.

WBI was the standard radiation technique for HGG until the mid 1980s. When computed tomography (CT) and MRI came into routine use, involved-field RT (IFRT) replaced WBI. Though there are no randomized data available directly comparing the two strategies, there have been seminal studies that

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have led radiation oncologists away from WBI, including a BTSG trial published by Shapiro et al.[5] This trial asked both chemotherapy and RT questions. The RT question asked whether WBI to the full dose of 60 Gy was necessary, knowing that the treatment produced significant toxicity and that CT scans could help improve target volume definition, or if partial brain IFRT could suffice. The standard RT tested was WBI to 60.2 Gy compared to WBI to 43 Gy followed by a coned-down IFRT boost to the tumor plus a 2-cm margin. At a median follow-up of 52 months, survival analysis showed no significant difference by type of RT given. The authors concluded that delivering RT to an involved field, at least for part of the course, is reasonable, and that WBI is only indicated for multifocal disease.

The optimal IFRT target volume to be irradiated has developed based on a number of studies that have correlated imaging and pathological findings for HGG. One of the most elegant of these studies was performed by Kelly et al at the Mayo Clinic.[6] The investigators analyzed biopsy histology with respect to location within CT- and MRI-defined abnormalities in patients with previously untreated gliomas. They stereotactically biopsied regions of the brain, defined by digital angiography, CT scanning, and MRI as having abnormalities that presaged a high risk for harboring tumor. Correlation of histology and imaging showed that viable tumor tissue was found in contrast-enhancing regions, and isolated tumor cells were present in all regions of imaging abnormality, even in CT-normal, but MRI T2-enhancing regions. This study showed convincing evidence that tumor cells infiltrate at least as far as T2 abnormalities, and, as such, current RT fields include those MRI-defined volumes at risk for harboring disease.

The current standard dose of 60 Gy was established by Walker et al based on a retrospective review of three BTSG studies from 1966–1975.[7] In this review, they found that patients who did not receive RT had MS of 18 weeks, whereas patients receiving 60 Gy survived a median of 42 weeks. Patients receiving less than 60 Gy had worse survival. Of note, patients receiving less than 45 Gy had a worse survival than patients who did not receive any RT. Based on this, 60 Gy became the standard radiation dose used in the management of most HGG patients. Dose escalation with modern radiation techniques is feasible as demonstrated by Radiation Therapy Oncology Group (RTOG) 9803.[8] This was the first prospective multi-institutional study to evaluate the feasibility and toxicity of radiation dose escalation using three-dimensional conformal RT (3D-CRT) delivered concurrently with chemotherapy in patients with GBM. The study demonstrated that the use of highly conformal 3D-CRT with smaller treatment margins permitted safe dose escalation without increasing CNS toxicity, but the study was not powered to detect a survival advantage.[8,9] Other studies have tested dose escalation using various techniques such as intensity-modulated radiotherapy (IMRT), hyperfractionated RT, accelerated fractionation RT, ^{125}I brachytherapy with or without hyperthermia, stereotactic radiosurgery (SRS), fast-neutron RT, boron neutron-capture therapy, and protons but these have been largely negative, so 60 Gy using partial brain volume irradiation with photons remains the standard of care.[4,9–18]

Multiple systemic and intratumoral agents (chemotherapeutic, hypoxic cell radiosensitizers, viral agents, and immunotherapies) have been tested over the decades, and none was better than the nitrosureas, until the seminal European Organization for Research and Treatment of Cancer (EORTC)-National Cancer Institute of Canada (NCIC) study by Stupp et al, which demonstrated a significant survival benefit with the addition of TMZ to RT (MS 14.6 *v* 12.1 months, 5-year OS 10% *v* 2%).[2,4] The strongest predictor of response to TMZ and outcomes was O(6)-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation status.[19]

REVIEW OF NEUROTOXICITIES FROM CRANIAL IRRADIATION

Trimodality therapy has been shown to prolong survival and provide effective palliation for HGG patients. Unfortunately, high-dose irradiation to the brain is associated with a number of adverse sequelae, particularly late effects including radionecrosis, cognitive dysfunction, endocrine abnormalities, visual loss, hearing loss, and vasculopathies. In addition, even at lower doses, other untoward effects may be found.

Based on the time of clinical expression, RT-associated brain injury is described in terms of acute, early delayed, and late delayed injury[20] (Figure 1). Acute, subacute, and late effects of RT on the CNS are summarized.

Radiation-Associated Brain Injury

The acute side effects of RT are reversible and occur during the first few weeks of radiation. They are commonly characterized by drowsiness, headache, nausea, vomiting, and worsening of preexisting focal neurologic symptoms. Increased vasogenic edema after disruption of the blood-brain barrier is believed to be the cause of these symptoms, and treatment with corticosteroids such as dexamethasone results in rapid symptomatic improvement.[21,22]