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

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KEYWORDS

• Radiation therapy • Radiosurgery • Glioma • Glioblastoma

High-grade gliomas (HGGs) encompass the most malignant and the most commonly encountered primary brain neoplasms in clinical neuro-oncology practice, with an incidence of 5 cases per 100,000 people.[1] They are commonly defined to include World Health Organization grade III and IV glial-based neoplasms, most frequently glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas. A multidisciplinary approach to the management of these tumors includes surgical resection when feasible, chemotherapy, and radiation therapy. Each of these treatment components has contributed to increased survival in patients with HGGs, with an improvement in mean survival of 8 to 15 months over the past 40 years.[2]

Radiation therapy has become a standard component of the management of HGGs since the 1970s.[3,4] Advances in the understanding of radiobiology have led to refinements in the delivery methods of radiation, resulting in optimization of radiation therapy in terms of dosage, fractionation schedule, conformality, and treatment modalities. Further development of new radiation technologies such as stereotactic targeting and delivery has allowed physicians to investigate whether focal radiation treatment may improve patient outcomes as well.

RADIOBIOLOGY

The primary physiologic mechanism of radiation therapy is through DNA damage; however, recent advances in the understanding of radiobiology have shown that ionizing radiation triggers a variety of complex and dynamic responses in both normal and neoplastic cells, leading to the concept of the cell damage response.[5] There are 5 core concepts of radiobiology within this concept of the cell damage response (the 5 Rs of radiation): repair, repopulation, reoxygenation, redistribution, and radiosensitivity. These 5 concepts are being further refined at the tissue, cellular and molecular level as our understanding of radiobiology advances.[6]

Repair

The molecular biology of repair includes responses to various different types of cell death, including mitotic death (within 1 to 2 cell cycles), interphase death (death of sensitive cells within hours), apoptotic death (programmed cell death), necrotic death (caused by a pathologic rather than physiologic process), and autophagy. Current studies support that in response to DNA damage, cells trigger elaborate signaling pathways to repair the most lethal DNA damage, including double-stranded DNA breaks and the induction of

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apoptosis. Complicated mechanisms of repair include base excision repair, single-strand repair, homologous and nonhomologous recombination of double-strand DNA breaks, and chromatin remodeling.[6,7] Additional cell death pathways and modulators are manipulated to increase repair, including the p53-dependent apoptosis pathway, survival proteins such as survivin,[7] and epidermal growth factor receptor (EGFR)-mediated signaling for increased repair.[8,9]

Repopulation

Repopulation refers to the ability of neoplastic cells to repopulate after radiation treatment. This repopulation shows a lag period after radiation treatment followed by the triggering of an enhanced regenerative process or accelerated and aggressive repopulation.[10] The onset time of this repopulation is variable, but growth factor signaling has been found to play an important role in accelerated regeneration of cancer stem cells (CSCs) after radiation.

Reoxygenation

Oxygenated neoplastic cells are more sensitive to radiation treatment secondary to the availability of oxygen to participate in the generation of DNA damage via the generation of free radicals. Reoxygenation of hypoxic tumor cell populations is arrested via the cell damage response, with hypoxia-induced genes, EGFR signaling, vascular endothelial growth factor (VEGF) upregulation, and neovascularization. Hypoxia inducible factor 1 also functions in a variety of pathways to create enhanced neoplastic cell survival mechanisms and radioresistance.[11–13]

Redistribution

Redistribution of cells refers to the transition of cells through their natural cell cycle, with differences in their sensitivity to radiation at different points within the cycle. Cells within the mitotic phase are most sensitive to radiation damage, thus conveying radiosensitivity to dividing neoplastic cells over normal cell populations in other phases of the cell cycle. However, ionizing radiation has been shown to trigger cyclin-dependent kinase and EGFR signaling, which interferes with cell cycle progression and results in the arrest of neoplastic cells in relatively radioresistant phases.[7]

Radiosensitivity

Radiosensitivity reflects how cells have different intrinsic genetic sensitivities to radiation and usually reflects the shoulder in cell survival curves that can be manipulated by various radioresistance pathways.[7] The principles of radiobiology described earlier can all be manipulated to convey radioresistance, via enhanced DNA repair, increased repopulation responses, hypoxia, and inhibition of cell cycle redistribution.

Advances in Understanding Radioresistance: The Perivascular Niche, CSCs, and Linear-Quadratic Modeling

The tumor microenvironment, with its heterogeneous cell populations of fibroblasts, endothelial cells, reactive inflammatory cells and microvascular proliferating structures, is crucial to tumor expansion and response to radiation.[14] Ionizing radiation induces a series of events that can lead to a microenvironment favorable to neoplastic growth and radiation resistance. These pathways include a composite of cell loss and damage, gene alteration, induced gene products,[15] immunosuppression, and hypoxia.[8] Recent evidence suggests that the glial microenvironment, also termed the perivascular niche, facilitates expansion and differentiation of brain tumor stem cells.[16] Cell types, such as those listed earlier, are present in the perivascular niche and promote cell damage response and signaling pathways that initiate repair mechanisms resulting in radioresistance. The presence of hypoxia promotes the persistence of stem cells and induces the upregulation of proangiogenic factors such as VEGF. Complex immunosuppressive pathways are activated, including transforming growth factor β 1, which acts to suppress antitumor immune responses, enhance extracellular matrix production, and augment angiogenesis, making neoplastic cells more radioresistant.[17]

The concept of the neural stem cell has also further refined concepts of radiobiology and resistance.[18–20] Recent insights into tumor biology suggest that in many cancers only a small subset of cells, defined as CSCs, have the potential to survive and proliferate indefinitely. This small subpopulation of cells resists the exponential cell kill that is generated during fractionated radiation therapy. Consequently, these CSCs are believed to be a primary reason that HGGs recur and are resistant to known forms of therapy.[21] Research has shown that CD133+ CSCs increase after tumor radiation, conveying radioresistance secondary to increased activation of DNA damage response.[5] Further identification and research of these CSCs is required to determine their role in glioma pathophysiology.

The cumulative impact of the classic concepts of radiobiology as well as new concepts of the

perivascular niche and the CSC collectively form the unique response profile of a tumor to radiation as well as the response of normal surrounding tissues. Advances in mathematical modeling of the radiation responses of HGGs have led to the application of the linear-quadratic (LQ) model. The LQ model is used to calculate biologically effective doses (BEDs) to compare various treatment modalities or fractionation schedules.

$$BED = \frac{E}{\alpha} = nd\left(1+\frac{d}{\alpha/\beta}\right) - \frac{\gamma(T - T_k)}{\alpha}$$

This model can be used to extract BEDs from historical treatment cohorts to compare across radiation modalities and fractionation schemes. In addition, the LQ model can also be used to gain understanding about how specific tumor types respond to radiation and to predict how this response might vary with alterations in fractionation and dosage.[22,23]

[Tags: Radiobiology, repair, repopulation, redistribution, reoxygenation, radioresistance, CSCs, perivascular niche, linear-quadratic model].

DEVELOPMENT OF THE CURRENT RADIATION TREATMENT PARADIGM

Initial Studies and Proof of Efficacy

Radiation therapy was initially observed to provide survival benefit in patients with gliomas in a clinical trial performed in 1967.[24] Subsequently, a randomized controlled trial in 1978 confirmed this survival benefit. In this trial, patients who received treatment with BCNU chemotherapy and radiotherapy displayed a 16-week survival advantage over patients receiving chemotherapy alone (34.5 weeks vs 18.5 weeks, $P = .001$). This trial established the efficacy of radiation treatment in the multimodal therapy for gliomas, with a treatment model of 50 to 60 Gy delivered to the entire brain via 5 fractions per week for 5 to 7 weeks.[4] Subsequent randomized controlled trials have confirmed the survival benefit conveyed by radiation therapy.[25–29]

Effect of Cumulative Radiation Dose on Efficacy

With the knowledge that adjuvant radiation is efficacious, additional studies aimed to address the effect of cumulative radiation dose on survival. These studies displayed an increase in overall survival as the cumulative dose is increased up to 60 Gy.[30,31] As the cumulative dose is increased past 60 Gy to doses up to 70 Gy, no additional survival benefit is identified.[32] In addition, analysis of patient outcomes treated with dose escalation as high as 90 Gy has shown that recurrence still occurs locally, within radiation delivery.[33] Because of these negative studies, 60-Gy radiation therapy for HGG has remained the standard cumulative dosage.

Effect of Hyperfractionation on Efficacy

Fractionation of radiation therapy represents another variable that has been manipulated in the attempt to optimize outcomes in patients treated with radiation. Hyperfractionation is the use of a larger number of smaller-dosed radiation fractions and can be performed on a standard or accelerated schedule. Hyperfractionation has the positive effects of allowing repair of radiation damage in normal nonneoplastic tissues, redistribution of neoplastic cells to radiosensitive portions of the cell cycle, and reoxygenation of tumor cell populations that renders them more radiosensitive. Hyperfractionation also carries the negative effect of allowing time for the neoplastic cells to repopulate. Standard conventional radiation therapy is currently delivered in a hyperfractionated format, with 30 fractions delivered over 6 weeks.

With the goal of combating fraction-related neoplastic cell repopulation, multiple trials have analyzed the survival outcomes with hyperfractionated radiotherapy into even smaller and more frequent fractions, with most as well as pooled meta-analyses showing no survival advantages (1 smaller trial reported a 10-week survival benefit with further hyperfractionation).[3,34–38] A follow-up Radiation Therapy Oncology Group (RTOG) phase III trial also showed no efficacy from hyperfractionation of 72 Gy delivered in 2 daily fractions of 1.2 Gy over 6 weeks.[39,40]

Effect of Radiation Volume on Efficacy

Analysis of failures from radiation therapy has shown that recurrence occurs locally, within 2 cm of enhancing tumor.[33,41,42] This finding is in contrast to many other malignancies that spread via metastasis or cerebrospinal fluid dissemination. The pattern of local failure has led to investigations of varying radiation volumes, which have guided the transition from whole brain radiation therapy to more regionally focused treatment plans with the goal of maximizing radiation delivery to tumor cells while limiting delivery to normal tissue. A randomized controlled trial reported no survival difference between patients receiving 6020 cGy of whole brain radiation and those receiving 4300 cGy of whole brain radiation plus 1720 cGy delivered to enhancing tumor volume plus a margin of 2 cm.[43] The results of this trial have formed the standard regional delivery of radiation in patients with HGG, as opposed to whole brain radiation that was previously delivered. A

recent RTOG phase I study used dose escalation with conformal radiation therapy ranging between 66 and 84 Gy and reported no increase in rates of radiation injury.[44]

[Tags: Glioma, glioblastoma, radiation, whole brain radiation, radiotherapy, dose escalation, fractionation, hyperfractionation].

RADIATION SENSITIZERS

As discussed earlier in relation to radiobiology, there are multiple factors that contribute to the resistance of a neoplasm to radiation treatment. Therefore, multiple radiation sensitizing methods have been investigated as to whether they can increase efficacy of radiation and decrease radiation damage to viable normal brain tissue. The 2 largest radioresistance pathways commonly targeted are DNA repair mechanisms and hypoxia-induced radioresistance.

DNA Damage and Repair-mediated Radiosensitization

Ineffective mismatch repair has been postulated as a mechanism by which radiation may be more effective in treating various neoplasms, and this was confirmed with in vitro and in vivo models.[45–48] In 2005 Stupp and colleagues[49] performed a randomized controlled trial comparing radiotherapy alone against radiotherapy with concomitant temozolomide therapy. Temozolomide depletes the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT), resulting in mismatched base-pairing, failed DNA replication, and cell death.[50] This trial reported a significant survival benefit of temozolomide, extending median survival by 2.5 months, with minimal toxicity. Additional studies have also shown this survival benefit for temozolomide as part of the standard treatment regimen for HGGs.[49,51,52] The investigators propose the interplay of radiation-induced DNA damage and impaired DNA repair secondary to temozolomide therapy as a synergistic effect leading to the increased survival.[49]

In contrast to limiting innate DNA repair mechanisms, investigators have also studied whether compounds that enhance DNA base-pair damage with radiation might have efficacy as adjuvants to standard therapy. One class of studied agents are the halogenated pyrimidines, such as bromodeoxyuridine, which are substituted for thymidine in dividing cell DNA replication, leading to increased lethality from radiation treatment. However, 2 phase III RTOG trials failed to show any efficacy with bromodeoxyuridine treatment.[53,54]

Oxygen-mediated Radiosensitization

HGGs are known to have regions of hypoxia within the tumor environment, which decreases effectiveness of radiation therapy.[55] Methods for overcoming tumor-related hypoxia include extracorporeal treatments such as hyperbaric oxygen, as well as systemically administered pharmacologic agents.

The concept of hyperbaric oxygenation (HBO) as a method of radiosensitization was initially studied in the 1950s.[56] Studies in HBO have been performed primarily on head and neck cancer and cervical cancer, showing some efficacy with increased rates of radiation injury.[57,58] Khoshi and colleagues[59] published initial results on HBO treatment in HGGs, followed by a nonrandomized trial that reported increased survival in patients treated with adjunct HBO.[60] Other studies have shown the feasibility of HBO therapy in conjunction with radiation therapy.[59,61–64] Despite these results, there are no randomized controlled trials reporting HBO therapy as an efficacious adjunct to radiation therapy. HBO is generally well tolerated; however, it must be delivered in a strict time frame with respect to radiation therapy, making its application difficult in many clinical scenarios. Further investigation is required to assess its efficacy.

Nitroimidazoles such as metronidazole and misonidazole combat hypoxia via oxygen-mimetic mechanisms.[65] They have been investigated as radiosensitizers, with initial increased survival reported in 1976[66]; however, further randomized trials and meta-analyses have failed to show any survival benefit.[3,67,68] Trans-sodium crocetinate (TSC) is an investigational compound that increases blood and tissue oxygenation by its interactions with water and oxygen molecules. This increase in oxygen concentration is proposed as a further mechanism for combating the hypoxic and radioresistant milieu of HGGs. In vivo studies have reported increased oxygen concentrations selectively in tumor tissue via Licox probes (Integra Life Sciences, Plainsboro, NJ) and functional neuroimaging of hypoxia.[69,70] These and other studies have reported radiosensitization of glioblastoma cell lines by treatment with TSC, with an increased mean survival in this animal model.[71,72] Clinical evaluation of TSC is ongoing.

[Tags: Radiosensitizers, hyperbaric oxygen, temozolamide, trans-sodium crocetinate, nitroimidazoles, halogenated pyrimidines].

PREDICTORS OF RESPONSE TO RADIATION THERAPY

Tumor Factors

In an effort to determine whether any factors may be predictive of response to radiation therapy,

resected glioma specimens were analyzed via genetic and immunohistochemical studies. This information provides prognostic information to patients as well as helping tailor therapy toward unique tumor populations. Molecular immunology borstel-1 (MIB-1) did not predict survival or response to radiation therapy.[73] Upregulation of EGFR showed equivocal accuracy in predicting prognosis for patients with high-grade glioma,[74] whereas deletion of nuclear factor kappa-B inhibitor alpha (NFKBIA)[75] and an unmethylated MGMT promotor[76,77] were associated with poorer prognosis in patients with high-grade glioma. EGFR pathway manipulation has been implicated in radioresistance in vitro,[78] whereas MGMT promoter methylation status has been shown to be predictive of radiation response in a recent clinical study.[79] Further research is required to stratify HGGs into tumor subsets with clinically significant prognostic and radiation response profiles.

Patient Factors

Recursive partitioning analysis (RPA) of pooled data from several HGG RTOG trials was introduced in 1993, allowing stratification of patients in these trials with significantly different survival curves. The variables in the initial RTOG model with an effect on outcome included age, histology, Karnofsky Performance Status (KPS), mental status and neurologic function, duration of symptoms, extent of resection, and cumulative radiation dose (**Table 1**).[80] A simplified RPA scheme was introduced in 2010 for patients with glioblastoma, which resulted in 3 classes of patients based on age, KPS, extent of resection, and neurologic function. This simplified model has been validated and shown to provide prognostic information.[81] This newer classification scheme can be seen in **Table 2**. Median survival for RPA class III (the lowest class for a patient with glioblastoma) was 17.1 months, whereas it was 11.2 months for RPA class IV, and 7.5 months for RPA class V + VI. The patient factors identified in RPA analysis show that pretreatment factors have a significant prognostic significance.

[Tags: MGMT, EGFR, RPA, KPS].

MODIFICATION OF RADIATION DELIVERY TYPES

Methods of Delivering Standard Fractionated Radiotherapy

Before modern imaging techniques, whole brain irradiation was used to deliver radiation to the target tissue as well as all surrounding tissue. Imaging advancements have led to an increased ability to refine tumor shape and volume, thus allowing the evolution of radiation delivery techniques from whole brain irradiation to two-dimensional regional irradiation, to three-dimensional conformal radiotherapy (**Fig. 1**). The reduction of radiation delivery from whole brain irradiation to regional field delivery is supported by studies reporting no difference in survival with improved performance status.[43,82] Intensity-modulated radiotherapy (IMRT) uses a multileaf collimator to divide the radiation delivery beam into many smaller portions that can be modulated into a desired shape. This strategy allows further

Table 1
RTOG RPA stratification of patients with HGGs

Class	Definition
I	Age <50 y, anaplastic astrocytoma, and normal mental status
II	Age ≥50 y, KPS 70–100, anaplastic astrocytoma, and at least 3 months from time of first symptoms to initiation treatment
III	Age <50 y, Anaplastic astrocytoma and abnormal mental status Age <50 y, Glioblastoma multiforme and KPS 90–100
IV	Age <50 y, Glioblastoma multiforme, KPS <90 Age ≥50 y, KPS 70–100, anaplastic astrocytoma and 3 months or less from time of first symptoms to start of treatment Age <50 y, glioblastoma multiforme, surgical resection, and good neurologic function
V	Age ≥50 y, KPS 70–100, glioblastoma multiforme, either surgical resection and neurologic function that inhibits the ability to work or biopsy only followed by at least 54.4 Gy of RT Age ≥50 y, KPS <70, normal mental status
VI	Age ≥50 y, KPS <70, abnormal mental status Age ≥50 y, KPS 70–100, glioblastoma multiforme, biopsy only, receiving less than 54.4 Gy of RT

Abbreviation: RT, radiotherapy.

Table 2
Simplified RTOG RPA stratification of glioblastomas

Class	Definition
III	Age <50 y, KPS ≥90
IV	Age <50 y, KPS <90
	Age ≥50 y, KPS ≥70, surgical removal with good neurologic function
V + VI	Age ≥50 y, KPS ≥70, surgical removal with poor neurologic function
	Age ≥50 y, KPS ≥70, no surgical removal
	Age ≥50 y, KPS <70

restriction of the desired conformal radiation target and minimization of radiation delivery to surrounding tissues.[83] IMRT may decrease rates of radiation toxicity because of improved dose conformality, as reported in a dosimetric study that showed significant reductions in cumulative dose delivery to surrounding sensitive structures such as the spinal cord, optic nerves, eyes, and brainstem.[84]

Stereotactic Radiation Techniques

Stereotactic delivery of radiation allows single or multisession delivery of high doses of radiation, with less radiation delivered to surrounding tissue. Stereotactic radiosurgery (SRS) refers to single-session radiation delivery, whereas stereotactic radiotherapy (SRT) refers to radiation delivery in up to 5 sessions.[85] These delivery methods offer the benefits of shorter or even single-session radiation delivery with decreased risk of radiation injury to surrounding tissue, similar to the highly conformal radiotherapy techniques listed earlier. These techniques are also focal radiation treatments that do not address tumor extending into surrounding tissue outside the radiation treatment field. However, as discussed earlier, most recurrences after radiation therapy occur at the previously treated tumor margin, and less frequently at distant sites.

An RTOG phase II trial studied the use of SRT as a boost of radiation after conventional radiation treatment in patients with residual tumor after surgery. These patients received 4 additional SRT sessions (1 per week) of 5 to 7 Gy per session. This boost therapy was well tolerated, but did not show any survival benefit.[86] Retrospective studies have reported varied survival advantages with this treatment strategy after standard radiotherapy.[87–98] These retrospective studies prompted an RTOG phase III randomized controlled trial with standard treatment compared with patients receiving SRS boost treatment before conventional radiotherapy. This trial reported no benefit in survival or patient quality of life.[99] Although no large phase III trial has examined the application of stereotactic radiation boost therapy after conventional radiotherapy, this RTOG trial led the American Society for the Therapeutic Radiology and Oncology to issue a review that radiosurgery boost followed by conventional radiotherapy does not confer a benefit and is associated with increased toxicity. The investigators further concluded that there was insufficient evidence to support the use of SRS or SRT for patients with malignant glioma at either diagnosis or recurrence.[100]

Charged Particle Therapy

Charged particle therapy (ie, proton beam therapy) offers further evolution on the goals of stereotactic techniques using photons. The Bragg-Peak effect of proton beam treatment creates a sharp fall-off

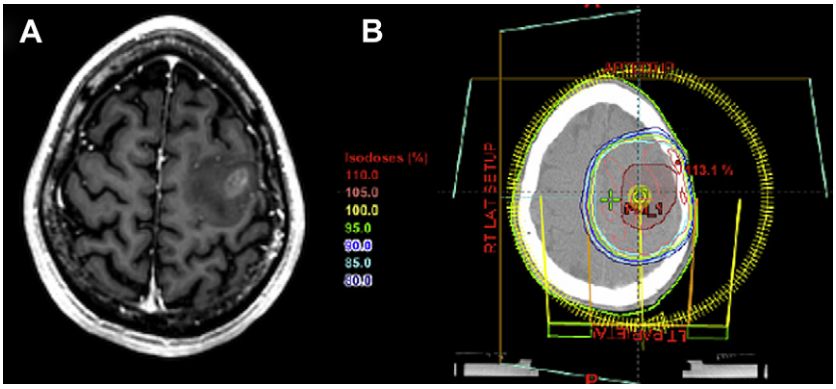

Fig. 1. (*A*) A preoperative axial T1-weighted magnetic resonance sequence after gadolinium administration in a patient with a left frontal glioblastoma. (*B*) The postoperative conformal radiation delivery plan after gross total resection.

of radiation after target delivery, allowing even further refinement in conformality with radiation doses of at least 90 cobalt-Gray-equivalent.[101] However, photon-based therapy has shown local failure at dose escalation up to 90 Gy.[33] Therefore, further research is required to evaluate the efficacy of proton beam therapy clinically compared with conventional photon radiation therapy for high-grade gliomas.

[Tags: Radiosurgery, stereotactic, IMRT, conformal radiotherapy, proton beam].

RADIATION THERAPY IN SPECIAL CIRCUMSTANCES

Further Radiation Treatment in Recurrence

High-grade gliomas recur almost universally, and as described earlier the recurrence patterns show that nearly all tumors recur within 2 cm of the primary tumor location. Salvage therapies include repeat surgery, continued or altered systemic chemotherapy administration, or further radiation therapy. Repeat surgical resection has been reported to offer survival benefit in certain selected patients[102]; however, surgery without additional adjuvant therapy may not be effective.[103]

The administration of repeat radiation therapy has been limited by concerns over fear of radiation-related complications associated with increasing radiation doses. Reexamination of radiation toxicity after the advancements of increasing conformal radiation delivery techniques have shown rare cases of radiation necrosis, occurring at doses of more than 100 Gy to normal tissue.[104] Maximum tolerances of critical structures such as the brainstem and optic apparatus are controversial.

The delivery method of repeat radiation therapy can include conformal or IMRT techniques or stereotactic methods. As described earlier, increasing conformality limits the cumulative normal tissue radiation dose and toxicity, suggesting a possible role for stereotactic techniques to minimize toxicity. Studies have reported survival benefit compared with historical controls in SRS,[105] and have attempted to delineate rates of radiation toxicity associated with this type of salvage treatment.[106] On the other hand, fractionated SRT may convey decreased toxicity compared with single-session SRS.[107] Further research is required to determine the optimum method of radiation delivery in recurrent HGGs.

Palliative Radiation Treatment

As described earlier, certain patient characteristics are strongly associated with prognosis and response to various therapies in patients with HGGs. Specifically, older patients tend to have more aggressive disease and poorer outcomes.[108–110] In addition, the combination of chemotherapy and radiation therapy in elderly patients is associated with significant morbidity.[111] Consequently, patients older than 70 years are generally excluded from randomized trials and are often not treated as aggressively as higher-functioning, younger patients. This more conservative treatment strategy is also true for patients with a poor KPS at the time of presentation. Despite the tendency to treat these patients less aggressively, there is a clear survival benefit to treating patients with radiotherapy as opposed to supportive care.[112] In these specific subsets of patients, some groups have advocated a short course of radiation therapy without concomitant chemotherapy to a total of 40 Gy delivered in 15 fractions over 3 weeks. This treatment modality has shown similar survival to standard radiotherapy schema without a decrease in quality of life.[113]

[Tags: Recurrent glioma, palliative radiation, reirradiation].

SUMMARY

Radiation therapy is an integral part of the multimodality treatment of patients with HGG. An understanding of the radiobiology and mechanisms of radioresistance is critical for clinicians involved in the management of these complex patients. Advances in molecular biology are prompting further investigation into methods to improve the efficacy of chemoradiation in HGGs. Further research in the use of radiation sensitizers may assist clinicians in this regard.

Current radiation therapy schemas for HGGs are supported by multiple clinical trials reporting efficacy in increasing patient survival. Manipulation of radiation delivery in terms of dose escalation, hyperfractionation, and the radiation delivery modality have allowed clinicians to give high doses of radiation to neoplastic cells and progressively limit the cumulative radiation dose to surrounding normal tissues. Despite this situation, treatment of HGGs is a palliative therapy, with local failure being the near universal mode of recurrence and progression. Further investigation is needed to refine the role that radiation plays in the treatment of these patients as understanding of the molecular and genetic mechanisms of gliomas evolves.

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