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Review Article

The Role of Radiation Therapy in the Treatment of High Grade Gliomas

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Abstract

High grade gliomas (HGG) account for the majority of primary central nervous system tumors and are infiltrative tumors with microscopic disease extending into the adjacent brain paranchyma, characterized by aggressive growth and poor prognosis. Patients are managed in a multidisciplinary team setting in order to ensure their care is guided by the most current evidenced based treatments. Currently accepted adjuvant management includes maximal surgical resection or biopsy followed by concomitant Temozolamide and radiation (a total dose of 60 Gy administered in 30 fractions) followed by 6 cycles of adjuvant Temozolamide. The outcome in patients with HGG is still poor, tumors recur in the majority of patients and the disease is most often fatal. Therefore there is a need to develop new treatment regimens and technological innovations to improve overall survival in patients with HGG. Since most the recurrences occurring within the previous irradiation field new regimes designed to deliver higher dose. Several studies used hyperfractionated or accelerated regimens as a means to escalate dose; however there is insufficient data regarding hyperfractionation/accelerated radiation versus conventionally fractionated radiation. Recently, the role of novel radiation techniques such as stereotactic radio surgery (SRS) or stereotactic radiotherapy (SRT) investigated in HGG patients both in newly diagnosed patients as well as the recurrent setting; however there is insufficient evidence in terms of the benefits/harms of using SRS/SRT. This review discusses the role of the RT in the treatment of HGG by the light of current standards, new concepts, and innovations in RT.

ABBREVIATIONS

AA: Anaplastic Astrocytoma; AG: Anaplastic Glioma; AO: Anaplastic Oligodendroglioma; AOA: Anaplastic Oligoastrocytoma BRT: Brachytherapy; BTSG: Brain Tumor Study Group; CGE: ^{60}Co Gray Equivalent; CT: Computerized Tomography; CTV: Clinical Target Volume; EORTC: European Organization for Research and Treatment of Cancer; FLAIR: Fluid Attenuation Inversion Recovery; GBM: Glioblastome; GTV: Gross Tumor Volume; Gy: Gray; HGG: High-Grade Gliomas; IMRT: Intensity Modulated Radiotherapy; MRI: Magnetic Resonance Imaging; NCCTG: North Central Cancer Treatment Group; NCIC: National Cancer Institute of Canada Clinical Trials Group; OAR: Organ at Risk; OS: Overall Survival; PTV: Planning Target Volume; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group; SRS: Stereotactic Radio surgery; SRT: Stereotactic Radiotherapy; Three-Dimensional: 3D; WBRT: Whole Brain Radiotherapy; WHO: World Health Organization

INTRODUCTION

High-grade gliomas (HGG) are malignant, often rapidly progressive brain tumors that are divided into anaplastic gliomas including anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma; and glioblastoma (GBM) based upon their histopathologic features [1]. A better prognosis is associated with grade III tumors (according to World Health Organization (WHO) classification: anaplastic gliomas) when compared to grade IV tumors (WHO grade IV: i.e., GBM) and for oligodendroglial tumors when compared to astrocytic tumors [2]. Despite the advances in new treatment options, due to the aggressive behaviour of HGG, the prognosis of HGG is still poor. Treatment is determined by a number of different prognostic factors including age of the patient, performance status, tumor location and histological grade. The standard care for the definitive treatment of newly diagnosed HGG under 70-year-old is the delivery of approximately 60 Gray (Gy) of fractionated partial brain radiotherapy (RT) with concurrent Temozolamide after maximal safe surgical debulking. Adjuvant Temozolamide also should be administered for at least 6 months following the end of the RT unless disease progression occurs [2]. Despite this multimodal treatment, most patients will die within 1-2 years. Median progression-free survival from diagnosis of 6.2-7.5 months and median overall survival from diagnosis of 14.6-16.7 months have been reported in clinical trials [3-5]. The reported 2- and 5-year survival rates are 27% and 10%, respectively [3-5]. RT is the cornerstone of the treatment in patients with HGG. The current review focuses the role of the RT in the treatment of HGG

by the light of current standards, new concepts, and innovations in RT.

Rationale for using adjuvant radiotherapy in high-grade gliomas

Newly diagnosed HGG patients should firstly undergone maximal surgical resection consistent with preservation of neurologic function, whenever possible. Although gross total resection is preferred, subtotal resection or stereotactic biopsy may be required depending upon the location and extent of the tumor. Surgery provides tissue to establish the diagnosis and is used to relieve symptoms due to mass effects in patients with HGG. There are no randomized trials evaluating the benefit of maximal surgical resection compared with more limited resection, and such studies are unlikely to be conducted [6,7]. However there are some retrospective studies supporting a positive association between a more extensive resection and prolonged survival [8,9]. One of the largest studies evaluating the survival benefit of extent of surgical resection in patients with HGG is conducted in M. D. Anderson Cancer Center [8,9]. This study demonstrated that improved median survival (13 months vs 8.8 moths, $p<0.0001$) following at least 98% resection, as defined by postoperative Magnetic Resonance Imaging (MRI) scans [10]. High-grade gliomas are infiltrative tumors with microscopic disease extending into the adjacent brain parenchyma to the gross tumor. Adjuvant RT directed to residual microscopic and gross disease improves local control and survival after resection. Several lines of evidence have influenced the trend to treat the gross tumor volume along with a margin approximately 2 cm during radiation treatment [2]. In a study conducted by Hochberg and Pruitt it was shown that nearly %90 of recurrences occurred within 2 cm of the primary tumor site [11]. Therefore the adjuvant RT is standard component of therapy for HGG patients and that has been shown to improve local control and survival after resection [12,13].

Radiotherapy target volume definitions

The effect of RT on survival in patients with HGG was initially demonstrated with whole brain RT (WBRT). In a representative trial from the Brain Tumor Study Group (BTSG), the addition of adjuvant WBRT to surgical resection increased median survival from 14 to 36 weeks [12]. Other data from the BTSG demonstrated the superiority of adjuvant RT compared to adjuvant chemotherapy alone as a postoperative therapy [13]. Subsequent advances in RT technique have utilized improved imaging of the tumor and focused on RT techniques that maximize treatment to the tumor while minimizing radiation exposure to the healthy brain tissue. In 1989, Shapiro et al published data from Brain Tumor Cooperative Group trial 80-01, in which the randomization was altered during the trial to compare partial brain irradiation with WBRT [14]. This study suggested that there was no difference in terms of the overall survival (OS). Moreover the pattern of treatment failure was not changed. Therefore the inclusion of all radiographic evidence of tumor and associated edema with generous margins is the rule in design of treatment portals in HGG patients. The introduction of computerized tomography (CT) and MRI has contributed substantially to improve the accuracy of tumor delineation in HGG patients [15]. The three-dimensional (3D) conformal RT technique makes partial-brain irradiation easier and more accurate [16]. The radiation oncologists use pre-and-post operative MR images of the tumor and co-register these MR images with planning CT images in order to better define the treatment volumes. T1 contrast enhanced sequences of the preoperative MRI are used to define the gross tumor volume (GTV). GTV should be surrounded with a margin that encompassing the microscopic extends of the disease that is called as clinical target volume (CTV). T2 Fluid attenuation inversion recovery (FLAIR) sequences plus a margin define CTV, which reflects the bulk of the microscopic infiltration. CTV is surrounded by planning target volume (PTV) that encompasses both organ motion and set-up errors. The PTV may be further modified to exclude normal tissue in the treatment field where gliomas are unlikely to infiltrate [2].

Halperin et al., studied the CT scans and pathologic sections of 15 brains of patients with Glioblastoma who received minimal or no RT. If RT portals had been designed to cover the contrast-enhancing volume and peritumoral edema with a 1 cm margin, the portals would have covered histologically identified tumor in only 6/11 cases [17]. If the treatment volume was contrast enhancing areas plus all surrounding edema with a 3 cm margin around the edema, the portals would have covered histologically identified tumor in all cases. Therefore the general rule in the treatment of HGG patients is that the inclusion of all radiographic evidence of tumor and associated edema with generous margins [18]. However, the optimal treatment volume for HGG patients remains a controversial issue and varies among cooperative groups [19]. Table 1 summarizes the partial brain volumes advocated by several cooperative groups for the successive phases of delineation of HGG patient's treatment volumes. It is clear from the Table 1 that the margins of the planned target volume vary quite significantly among institutions. The guidelines of the Radiation Therapy Oncology Group (RTOG) states that the initial field is defined as the peritumoral edema (defined with T2 or FLAIR images of MRI) +2 cm and prescribed to 46 Gy. The boost field is defined as GTV (T1-enhancing GTV) + 2.5 cm and prescribed to 60 Gy (as per RTOG 0525 and RTOG 0825 trials) [20]. The rationale for including peritumoral edema is that such areas are believed to contain high concentrations of tumor cells [17,21,22]. On the other hand, the European Organization for Research and Treatment of Cancer (EORTC) describes a single-phase treatment pattern with 2–3 cm dosimetric margins around the tumor (as evaluated by MRI), because 80%–90% of treatment failures occur within this margin [3]. The University of Texas MD Anderson Cancer Center uses a 2 cm margin around the gross tumor volume (GTV), which consists of the resection cavity and any residual contrast enhancing tumor, but ignoring any edema, and a PTV as CTV+0.5 cm. The PTV prescribed to a dose of 50 Gy. The boost PTV, which was an expansion of the GTV by 0.5 cm, was taken to a dose of 60 Gy [22].

The target volume delineation for WHO grade III gliomas is also conflicting. Table 2 summarizes the target volume definitions for grade III gliomas from different studies. There is an ongoing phase III trial, the CATNON Intergroup Trial, which is conducted on grade 3 gliomas [23]. In this study the GTV is defined as the entire region of high signal intensity on the T2-weighted MRI images or FLAIR sequences plus the region of

Table 1: The definition of radiation treatment volumes during the delineation of high-grade gliomas patients.

Clinical Trial	Block Edge Dosimetry Margin	RT dose
RTOG	T2+ 2cm T1+2.5 cm	46 Gy 14 Gy
EORTC	T1+2-3 cm	60 Gy
NCCTG	T2+2cm T1+2cm	50 Gy 10 Gy

Abbreviations: EORTC: European Organization for Research and Treatment of Cancer; Gy: Gray; NCCTG: North Central Cancer Treatment Group; RT: Irradiation Dose; RTOG: Radiation Therapy Oncology Group [2].

Table 2: The target volume definitions for grade III gliomas.

Clinical Trial	Histology	Target Volume (GTV)	CTV	PTV	RT dose
RTOG 9402	AOA, AO	Surgical cavity and T2 abnormality	-	PTV initial: GTV+ 2cm PTV boost: GTV+1 cm	50.4 Gy +boost 9 Gy
EORTC 26951	AOA, AO	The hyper-intensity area on preoperative T2-MRI	-	PTV initial: GTV+ 2.5 cm PTV boost: GTV + 1.5 cm	45 Gy+ boost 14.4 Gy
CATNON EORTC 26053/22054	AG	Surgical cavity+contrast-enhancing T1 abnormality+T2 FLAIR abnormality	GTV+1.5-2 cm	CTV+5-7 mm	59.4 Gy
NOA 4	AA, AOA, AO	Preoperative imaging (MRI or CT)	-	GTV+ 2cm	59.4-60 Gy

Abbreviations: AA: Anaplastic Astrocytoma; AG: Anaplastic Glioma; AO: Anaplastic Oligodendroglioma; AOA: Anaplastic Oligoastrocytoma; CTV: Clinical Target Volume; GTV: Gross Tumor Volume; EORTC: European Organization for Research and Treatment of Cancer; Gy: Gray; PTV: Planning Target Volume; RT: Irradiation Dose; RTOG: Radiation Therapy Oncology Group

enhancement on postoperative CT/MRI if available, or as the region of enhancement on preoperative CT/MRI if postoperative imaging is not available, plus the tumor resection margin. In some cases, no enhancement can be seen, and GTV is defined according to the T2 abnormality. The CTV is defined as a 1.5 to 2.0 cm volumetric expansion of the GTV, and the PTV will add 0.5 to 0.7 cm, depending on the centers. A total dose of 59.4 Gy in 33 fractions of 1.8 Gy is recommended [23,24].

Radiotherapy dose

Standard therapy for HGG patients is a total dose of 60 Gy in 30-33 fractions [18]. Adequate doses of RT are required to maximize the survival benefit [6,25,26]. Coffey et al conducted a retrospective review of 91 patients with high-grade glioma who had a stereotactic biopsy followed by RT [25]. Their results suggested that regardless of extent of resection, patients who had RT doses of 50 to 60 Gy had a longer median survival than those who received lower postoperative RT doses (19 versus 11 weeks for patients with GBM and 27 versus 11 weeks for AA).Walker et al. evaluated the relationship between increasing survival and increasing doses of RT in 621 malign gliomas patients who were entered into three successive Brain Tumor Study Group protocols [26]. Doses ranged from < 45 Gy to 60 Gy, using daily fractions 0f 1.7-2 Gy. They showed that there was a significant improvement in median survival from 28 to 42 weeks in the groups treated with doses of 50 to 60 Gy.

A benefit for dose escalation > 60 Gy has not been shown. In two randomized trials, there were no significant differences in tumor control or survival in patients treated with 60 Gy of WBRT or 60 Gy followed by a 10 Gy tumor boost [28,29]. It was shown that dose escalation using 3D conformal RT or Intensity modulated radiotherapy (IMRT) also has not consistently shown to improve clinical outcome. Lee et al. analyzed the failure patterns for patients with high-grade astrocytomas treated with high-dose conformal radiotherapy using a quantitative technique to calculate the dose received by the CT- or MR-defined recurrence volume [29]. Their results suggested that the treatment of patients at the 70- and 80-Gy dose levels results in failure patterns were nearly always within the high-dose volume and the marginal failure was rare. The authors concluded that further dose escalation to 90 Gy thus seemed reasonable, based on the same target volume definition criteria. On the basis of this analysis, from the same clinic, Chan et al. Evaluated 34 patients with HGG treated using 3D conformal IMRT to a dose of 90 Gy [30]. The GTV was defined based on postoperative gadolinium-enhanced T1-weighted images. Surrounding edema was not included in the defined GTV. They defined three separate PTVs. The GTV was expanded in three dimensions by 0.5 cm to make PTV1, 1.5 cm to make PTV2, and 2.5 cm to make PTV3. At median follow-up of 11.7 months, median survival was found to be 11.7 months, and 1- and 2-year survivals were 47.1% and 12.9%, respectively. The authors concluded that despite dose escalation to 90 Gy, the predominant failure pattern in HGG remained local. This suggested that close margins used in highly conformal treatments did not increase the risk of marginal or distant recurrences.

Since the majority of tumor recurrences were seen within the previous radiation therapy fields and the poor outcomes associated with standard regimen, the new therapy strategies were evaluated to deliver higher doses to the tumor bed. Higher doses for HGG have been attempted with a variety of methods,

including altered fractionation [31,32], stereotactic radio surgery [33], and brachytherapy [34].

The term "conventional RT" refers giving daily radiation of 180 to 200 cGy per day. "HypofractionatedRT" refers to the use of a higher daily dose of radiation (> 200 cGy per day) which typically reduces the overall number of fractions and therefore the overall treatment time. "Hyperfractionated RT" defined as to the use of a lower daily dose of radiation (< 180 cGy per day), a greater number of fractions and multiple fractions delivered per day in order to deliver a total dose at least equivalent to external beam daily conventionally fractionated RT in the same time frame. The aim with this approach is to reduce the potential for late toxicity. "Accelerated RT" refers to the delivery of multiple fractions per day using daily doses of radiation consistent with external beam daily conventionally fractionated RT doses. The aim is to reduce the overall treatment time; typically, two or three fractions per day may be delivered with a six to eight hour gap between fractions [35].

Khan et al., reviewed five studies that randomised participants to hypofractionated radiation therapy versus conventionally fractionated RT [35]. Their results suggested that hypofractionatedRT has similar efficacy for survival as compared to conventional radiotherapy, particularly for individuals aged 60 and older with HGG.

Although many studies have used hyperfractionation or accelerated regimens as a means to escalate dose; only the study of Shin et al showed an improvement in survival using daily fractionation [36,37]. In this study, the authors compared hyperfractionated RT (with or without chemotherapy) versus conventionally fractionated RT (without chemotherapy). The trial included 81 HGG patients randomized to conventional fractionation (5800 cGy in 30 daily fractions) or hyperfractionation (6141 cGy in 89 cGy fractions given three times a day every 2 to 4 hours for 4.5 weeks). Median survival in two groups was 39 and 27 weeks, respectively, and the 1-year survival rates were 41% and 20% respectively. Others have failed to confirm these results. Therefore there is insufficient data regarding hyperfractionation versus conventionally fractionated radiation (without chemotherapy) and insufficient data regarding accelerated radiation versus conventionally fractionated radiation (without chemotherapy) [35].

There are no data comparing optimal dose and schedule in grade III gliomas versus GBM. However, many radiation oncologists use a dose of 59.4 Gy in 1.8 Gy fractions for grade III tumors versus 60 Gy in 2 Gy fractions for grade IV tumors with the expectation that the 10 percent dose reduction per fraction may lead to reduced late normal tissue effects for patients with projected longer term survival [2].

TECHNIQUES OF RADIOTHERAPY

3D Conformal RT

Three-dimensional conformal RT utilizes CT-based treatment planning with dosimetric software to create composite treatment plans. Fusion of planning CT with MRI is extremely helpful in assisting with target definition [38]. The incorporation of PET or MR spectroscopy data is still largely investigational and most commonly used to define boost volumes rather than primary target volumes [6,39,40]. Photons of 6 to 8 megavolts (MV) are most commonly used with three to four angled radiation fields. When compared to 2D techniques, 3D treatment planning has decreased the amount of brain irradiated which means to decreased radiation-related toxicity[6,38]; however no benefit in progression-free or OS has been demonstrated [6,39,40].

Intensity-modulated RT

Intensity-modulated RT (IMRT) is a technique that relies upon software and modification of standard linear accelerator output to vary the radiation intensity across each treatment field. IMRT provides particular advantages when the target is juxtaposed to radiation-sensitive structures [6]. IMRT is one form of 3D conformal RT that is optimized to protect adjacent normal tissues from high doses of radiation while still delivering adequate doses to the target volume. Although conventional 3D conformal RT can achieve similar results, the dose fall-off at the edge of the treatment volume with IMRT can be much more pronounced when compared with that of conventional 3D conformal RT, which is especially important when the treatment volume abuts an important structure [41].

Adjuvant RT is standard component of therapy for HGG patients and that has been shown to improve local control and survival after resection [12,13]. However, considering that GBM may lie in close proximity or surrounding several radiosensitive normal tissues (such as optic pathways, ocular globes and brainstem), radiation treatment planning can be challenging. In fact, any effort to spare normal structures may translate into sub-optimal target coverage as pointed out by the quality assurance article regarding the randomized phase III EORTC/NCIC trial [42]. In European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group (NCIC) study, > 50% of patients had tumors in close proximity of optical pathways and/or brainstem. In 19% of the cases field size was reduced in the effort to decrease the dose to adjacent critical structures and 39% of the participating centers registered PTV under-dosage [42]. Given that most recurrences are local and that the outcome with partial brain RT is not inferior in terms of tumor control or OS, the field arrangement for gliomas has evolved from opposed lateral fields encompassing the whole brain to conformal RT, and has now culminated with IMRT [41].There are many studies in the literature evaluating to role of IMRT in gliomas [42-46]. Most of them suggested that IMRT technique lead to a reduction of doses to organ at risk (OAR) and to the healthy brain tissue, surrounding PTV, while maintaining target coverage without significant variations [46].

In conclusion the most appropriate application of IMRT in the brain will likely be when the radiation target abuts radiation-sensitive structures such as the eyes, optic nerves, optic chiasm, or brainstem. The disadvantages of IMRT include increased radiation scattering to surrounding non-target tissues and the complexity of radiation planning, which requires adaptation of the hardware of linear accelerators and skilled medical support [6].

Stereotactic radiotherapy/radio surgery

Stereotactic radio surgery (SRS) uses three-dimensional

planning techniques to precisely deliver narrowly collimated beams of ionizing radiation in a single high-dose fraction to small (<4 cm) intracranial targets. When this approach is divided into several factions it is called stereotactic radiotherapy (SRT) [6]. SRS utilizes highly precise radiation techniques to allow dose escalation and delivery of ablative radiation doses to the tumor while minimizing dose to the adjacent normal structures.

A radio-surgical boost was reported as an effective treatment modality in newly diagnosed HGG patients in a retrospective analysis [47]. The actuarial 2-year and median survival for all patients was 45% and 96 weeks, respectively. When this result was compared with three RTOG external beam RT results from 1974-1989, patients treated with radio surgery had significantly improved 2-year and median survival. This improvement in survival was seen particularly for the worse prognostic classes. Therefore patient selection may in part account for the outcome.

RTOG 9305 study evaluated the efficacy of SRS in patients with newly diagnosed GBM [48]. In this study203 patients with supratentorially GBM measuring less than 4 cm randomized to external beam radiation therapy (60 Gy), plus bis-chloroethylnitrosourea (BCNU) chemotherapy with or without an upfront SRS boost The SRS radiation doses were dependent on the tumor size but ranged from 15 to 24 Gy delivered in a single fraction. There was no difference in median overall survival, two and three-year overall survival rates, or in the pattern of failure between the two treatment groups. In addition, quality of life and cognitive outcomes were comparable between the two groups.

In phase II multi-institutional RTOG 002 study, 76 patients with newly diagnosed GBM with < 6 cm of residual contrast-enhancing tumor were evaluated [49]. In this trial, the Treatment was composed of 50 Gy conventional RT and four SRT boost fractions of either 5 or 7 Gy. SRT was administered once weekly during the final four weeks of therapy. The results suggested that while the regimen was safe, there was no survival benefit compared to the historical RTOG database for the entire cohort. However, the patient subset undergoing complete or near-complete resection, in fact, did appear to have improved survival with this boost approach, suggesting that perhaps minimal to no residual disease might represent an important selection parameter.

SRS may be used in patients with recurrent HGG that have progressed following the standard of care fractionated RT, plus Temozolamide. A number of small prospective and retrospective series suggest that SRS may prolong survival in this setting, either alone or in combination with chemotherapy [50]. However it is really difficult to interpret these data, since many studies did not report the details of the previous treatments including initial radiation dose, the extent of initial and second surgical resections, tumor volume at the time of SRS, timing and use of chemotherapy, and the time between initial radiation therapy and retreatment have clear implications on patient outcomes but are variably reported [50,51]. Nevertheless, in spite of all of these limitations, carefully selected patients do live longer than expected and careful evaluation of the role of SRS in the recurrent setting is warranted [50].

In conclusion, for patients newly diagnosed or progressive/recurrent malignant gliomas, there is insufficient evidence in terms of the benefits/harms of using SRS/SRT. The use of radiosurgery boost is associated with increased toxicity. There is also insufficient evidence regarding the benefits/harms in the use of SRS/SRT at the time progression or recurrence.

Interstitial brachytherapy

Interstitial brachytherapy uses the intraoperative placement of radioisotope seeds (most commonly iodine-125) into the tumor or resection cavity. Brachytherapy permits the delivery of a large radiation dose to the tumor volume, with rapid fall-off in surrounding tissues. Continuous rather than intermittent dose delivery decreases repair of sublethal damage and increases tumor susceptibility as cells progress into a sensitive phase of the cell cycle [6].

Laperriere et al., conducted a study to assess the role of brachytherapy as a boost to external beam radiation therapy in the initial management of patients with malignant astrocytomas. [52]. Patients were randomized as external RT alone (50 Gy) or external RT plus a temporary stereotactic iodine-125 implant delivering a minimum peripheral tumor dose of 60 Gy. The authors concluded that stereotactic radiation implants have not demonstrated a statistically significant improvement in survival in the initial management of patients with HGG.

The largest study was the Brain Tumor Cooperative Group NIH Trial 87-01 trial, and reported by Selker et al [53]. The authors investigated the effect of additional implanted RT, with iodine-125, in newly diagnosed patients with pathologically confirmed malignant gliomas. They found that there was no long-term survival advantage of increased radiation dose with iodine-125 seeds in newly diagnosed glioma patients.

In conclusion despite the theoretical and radiobiologic advantages, in patients with HGG, brachytherapy application did not have any survival advantage over conventional technique both in newly diagnosed patients and in recurrent setting. Due to the several technical difficulties and clinical limitations of brachytherapy, interest in brachytherapy has waned with the use of 3D-conformal RT and stereotactic RT techniques to deliver a radiation boost, both of which offer dosimetric advantages similar to that of brachytherapy.

Heavy particle RT

Charged heavy particles (helium and neon ions), protons, and neutrons have been used alone and as a boost to conventional RT. The rationale for heavy particle RT is that these techniques may work better in the hypoxic microenvironment of HGG. Moreover, heavy particle RT induces damage at more DNA sites, and tumor cells are less able to repair multiple damaged sites compared to the more sparse damage following photon RT [6,54,55].

The only randomized trial about the use of heavy particles in HGG patients was conducted with proton beam RT. In this phase II study, 23 patients with newly diagnosed HGG treated with proton RT [56]. The median survival was found as 20 months following surgery+proton RT. Recurrence was observed in regions treated to 60-70 ^{60}Co gray equivalent (CGE) regions. There was only one recurrence in 90 CGE regions. However this dose escalation was associated with high rate of brain necrosis that resulted in neurological symptoms. Given its limited availability and high

cost proton therapy requires further prospective, randomized trials to validate superiority over photon therapy.

Reirradiation in recurrent high-grade gliomas

Despite several therapeutic options, the tumor recurrence is inevitable in HGG patients. Progressive disease can be difficult to distinguish from radiation necrosis or other radiation-induced imaging changes, and this distinction has important implications for further treatment. Treatment decisions for patients with recurrent or progressive HGG must be individualized, since therapy is not curative and there are no randomized trials that directly compare active intervention versus supportive care. For recurrent disease, reoperation is an important treatment modality and may involve either biopsy (for diagnostic purposes) or repeat debulking of tumor. However, only 20-30% of recurrent HGG patients are candidates for a second surgery [57].

Focal RT approaches are often employed with limited volume recurrences; however the role of reirradiation in patients with recurrent HGG is uncertain, and there is a lack of prospective data. Based on retrospective series, selected patients with small recurrent tumors and a good performance status may benefit from repeat radiation using modern high-precision techniques [58]. In a retrospective analysis of 101 patients with recurrent HGG, the median survival was found as 12 months for patients with grade III tumors and 8 months for those with grade IV lesions. In this study fractionated SRT was performed with a median dose of 36 Gy (range 15-62) in a median fractionation of 5 x 2 Gy/wk. The one-year survival rates were 65 and 23 percent for patients with grade III and IV lesions, respectively [59].

Beside SRS, interstitial brachytherapy is widely used in recurrent HGG patients, and a survival benefit was reported in many studies [60-62]. Scharfen et al., reported the largest series on interstitial brachytherapy application in recurrent gliomas patients [62]. They used high-activity removable iodine-125 interstitial brain implants. Median survival measured from the date of implant for recurrent glioblastoma multiforme and high grade non glioblastoma glioma was 49 weeks and 52 weeks, respectively.

An alternate form of brachytherapy uses an inflatable balloon catheter containing a liquid I-125 radioisotope (Glia Site) inserted at the time of surgical resection [63]. This approach allows delivery of a quantifiable dose of radiation to the tissue at highest risk for tumor recurrence. No randomized clinical trials have been reported comparing this form of brachytherapy to other approaches.

Toxicities of radiation therapy

The complications of RT are usually divided into acute effects that can occur during radiation or up to three months afterwards, early-delayed effects that appear up to six months after radiation, and late effects that can develop six months or more after the completion of radiation. Unlike acute and early-delayed reactions that are usually reversible, late reactions are generally irreversible.

Acute radiation morbidity during cranial irradiation includes fatigue, erythema, alopecia, headache, and rarely, nausea with or without vomiting; these are usually not severe and are self-limiting [2]. The primary factors influencing the likelihood of developing complications include the volume of normal brain tissue treated, the total radiation dose, and the fractionation schedule.

Fatigue is one of the most common side effects of cranial irradiation. In a prospective study of 68 evaluable patients treated for primary brain tumors, fatigue was scored according to the Littman somnolence scale [64]. In this study 70 consecutive patients receiving radical cranial irradiation were prospectively assessed for somnolence at baseline, during and up to 10 weeks following RT. Most of the patients were treated for GBM and received 55 Gy partial brain irradiation in 30 fractions. Their results suggested that 90% of patients experienced $\geqslant$ grade 1 symptoms (disturbance with some tiredness, but activity not curtailed), and approximately half experienced mild to moderate symptoms (decreased activity and increased tiredness, sleeping much of the day, most activities curtailed). The symptoms typically began within two weeks of the start of RT, peaked at approximately six to eight weeks, and then slowly resolved over the next several months.

Nausea and vomiting may occur occasionally as a side effect of cranial radiation. Antiemetics or corticosteroids are used to prevent or mitigate symptoms.

Late effects of cranial irradiation including cognitive impairments and radiation necrosis are worrisome and may become manifest many years after RT [65]. Cranial irradiation can result in a spectrum of neurocognitive deficits in the years following treatment in children and in adults. The data of radiation-induced cognitive impairment mostly learned from Studies that are conducted in low-grade glioma patients. Changes in cognitive functioning were affected by antiepileptic drug use, the extent of surgery, tumor lateralization, and age [65].

Radiation necrosis is a serious and uncommon late toxicity that typically develops one to three years after radiation, although the range is quite broad and cases have been reported more than ten years after radiation [66].The dose that causes a higher than 5 percent risk of focal radiation necrosis using conventional 2 Gy fractionation is usually estimated to be 72 Gy, but this may be an oversimplification, and the dose that causes necrosis may vary by region of the brain as well [67]. The risk of radiation necrosis probably increases with concurrent chemotherapy or radio sensitizers [68]. The risk of radiation necrosis after stereotactic radiosurgery has been reported to be higher, with a steep dose-response relationship [69].

CONCLUSIONS

- The standard of care for HGG adults, up to age 70 with WHO performance status 0 to 2, who have no contraindication to radiotherapy or Temozolamide chemotherapy, is conventionally fractionated radiotherapy (6000 cGy in 30 daily fractions) with the addition of concurrent and adjuvant Temozolamide chemotherapy following maximal safe debulking of the tumor.
- There are no data comparing optimal dose and schedule in grade III gliomas versus GBM. However, many radiation oncologists use a dose of 59.4 Gy in 1.8 Gy fractions for

grade III tumors versus 60 Gy in 2 Gy fractions for grade IV tumors.

- The optimal treatment volume for HGG patients' remains a controversial issue and varies among cooperative groups.
- Dose escalation > 60 Gy has not been shown any survival benefit.
- There is insufficient data regarding different fractionation regimes versus conventionally fractionated radiation (with/without chemotherapy).
- IMRT may be beneficial in tumors when the radiation target abuts radiation-sensitive structures such as the eyes, optic nerves, optic chiasm, or brainstem.
- Treatment decisions for patients with recurrent or progressive HGG must be individualized, when the reirradiation is chosen as treatment option, SRT, SRS, interstitial brachytherapy or an inflatable balloon catheter containing a liquid I-125 radioisotope may be used.

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