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Current Advances in Radiotherapy for Newly Diagnosed Glioblastoma Multiforme

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Abstract

Glioblastoma multiforme is the most common adult primary brain tumor that is associated with very poor survival. The current standard therapy for newly diagnosed glioblastoma multiforme includes surgical resection and a combination of radiotherapy and chemotherapy with temozolomide. This treatment strategy leads to better overall survival; however, majority of tumor recurrences occur within the irradiated field. To overcome this problem, dose intensification is being tested in the management of glioblastoma multiforme.

In recent years, technological development of radiotherapies, such as intensity-modulated radiation therapy, stereotactic radio surgery, stereotactic radiation therapy, boron neutron capture therapy, and particle beam therapy, has improved dose distribution. Several prospective studies using these radiotherapies have shown that dose escalation is feasible and appears to be effective. Although the number of patients with glioblastoma multiforme in each study was not large, the survival times in these studies tended to be better than in those with standard dosing schedules. Dose escalation radiotherapy could be a hopeful strategy for patients with glioblastoma multiforme. In this review, we review advances in current radiotherapies for patients with newly diagnosed glioblastoma multiforme.

Keywords: Glioblastoma multiforme (GBM); Radiotherapy; Dose escalation; Intensity-modulated radiation therapy (IMRT); Particle beam therapy

Abbreviations: GBM: Glioblastoma Multiforme; TMZ: Temozolomide; MST: Median Survival Time; MGMT: O^6-Methylguanine-DNA Methyltransferase; RTOG: The Radiation Therapy Oncology Group; PET: Positron Emission Tomography; IGRT: Image-Guided Radiotherapy; 3D-CRT: Three-Dimensional Conformal Radiation Therapy; IMRT: Intensity-Modulated Radiation Therapy; SRS: Stereotactic Radio Surgery; SRT: Stereotactic Radiation Therapy; BNCT: Boron Neutron Capture Therapy

Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults, which accounts for approximately 70% of high-grade gliomas [1]. The prognosis of patients with GBM has been poor, with a median survival time (MST) of only approximately 15 months. Pretreatment patient characteristics such as age at diagnosis and Karnofsky performance status are the best predictors of survival [2]. The standard treatment for patients with GBM consists of maximal surgical resection followed by adjuvant chemoradiotherapy. A recent randomized trial showed that standard radiotherapy was associated with poor outcomes comparing short-course radiotherapy, especially in patients older than 70 years [3]. Both temozolomide (TMZ) alone and short-course radiotherapy alone would be considered as standard treatment options in elderly patients with GBM [3]. However, the efficacy of TMZ depends on the DNA-repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) promoter status [3,4]. Thus, postoperative radiotherapy is considered for all patients with GBM.

The standard care is 60 Gy in 30-33 fractions with concurrent TMZ for postoperative with newly diagnosed GBM except elderly or fragile patients [3,4]. Although the addition of TMZ has prolonged survival of these patients, the MST is approximately 15 months. To further improve overall survival, dose escalation to the target volume by innovations in radiotherapy is being tested. This review highlights dose escalation studies using modalities that deliver excellent dose distribution, which is expected to improve clinical outcomes.

Advances in Radiotherapy

Historical context

Historically, clinical studies of GBM have shown a dose-effect relationship with postoperative radiotherapy. In the 1970s, Walker et al. from the Brain Tumor Study Group discovered a radiation dose-effect relationship, and a dose of 60 Gy was established as the standard care [5]. Further dose intensification using higher radiation doses and altered fractionation was pursued but failed to provide a clear clinical benefit [6,7]. The Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group randomized 253 patients to either whole-brain irradiation with 60 Gy or 60 Gy plus a 10-Gy boost to limited volume. The MSTs were 9.3 months and 8.2 months, respectively, with no additional benefit for the group receiving the higher irradiated doses [7]. Given these results, 60 Gy has been regarded as the standard dose in postoperative radiotherapy for patients with GBM and has been adopted in most clinical trials. However, with the majority of tumor recurrences occurring within the irradiated field and poor outcome being associated with standard therapy [8], the role of radiation dose intensification in the management of GBM has been undergoing further exploration.

Advances in diagnostic imaging and radiotherapy techniques

Diagnostic imaging plays key roles in radiotherapy for patients with GBM. Besides technological improvements in x-ray imaging

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including computed tomography scans, recent advances in magnetic resonance imaging (MRI) and positron emission tomography (PET) have made possible the routine acquisition of physiological data [9]. Glioma cells are known to migrate along myelinated fibre tracts of the white matter and penetrate to the peritumoral edema [10]. In a pattern of failure study, Wallner et al. noted that 78% of unifocal recurrences occurred within 2-cm of the initial tumor volume, defined as the enhancing edge of the tumor on computed tomography (CT) scan [11]. Pitzkall et al. showed metabolically active tumors extending outside the region defined on T2-weighted MRI in 88% patients with high-grade gliomas [12]. Recent studies have demonstrated the possibility that the ^{11}C-methionine PET could distinguish infiltrative tumors from non-tumor lesions [13]. These advances have contributed to establishing an appropriate definition for target volume, although their role in the noninvasive grading of the tumors is limited.

To date, there is no consensus on what volume constitutes the optimal target of radiotherapy. However, several studies have attempted to define the optimal target definition for GBM. The Canadian GBM committee established guidelines have been suggested that the clinical target volume (CTV) should be identified with T1 gadolinium-contrast-enhanced MRI with a margin of 2-3 cm [14]. Also, the current RTOG 0825 phase III trial recommends that the initial gross tumor volume (GTV) should be defined by either the T2 or the fluid-attenuated inversion recovery abnormality on the postoperative MRI. The initial CTV is defined as the GTV plus a margin of 2 cm. In addition, they recommend that preoperative imaging should be used for correlation and improved identification [15]. In principle, inclusion of all radiographic data of tumor and peritumoral edema with generous margin while considering of dose limitation to critical structures is the rule in design of treatment plans.

Advances in radiation techniques include image-guided radiotherapy (IGRT), which makes it possible to verify the positions of the target volume and organs at risk during the treatment sessions. Using IGRT, the position of the target volume is known throughout movement and irradiation can be precisely targeted to the actual position of the tumor. This precise targeting results in a substantial decrease of planning target volume margins leading to reduction in the volume of normal tissue to which irradiation is prescribed. These advances in diagnostic imaging and radiotherapy techniques have contributed to researchers' attempts to intensify the radiation dose to the target volume.

Patient management decisions require an assessment of both initial responses to treatment as well as subsequent evidence of progressive disease. Previously, the most widely used criteria for assessing response to therapy in high-grade gliomas, the Macdonald Criteria, are based on two-dimensional tumor measurements on CT or MRI, in conjunction with clinical assessment and corticosteroid dose [16]. However, there are significant limitations to these criteria, which only address the contrast-enhancing component of the tumor. For example, chemoradiotherapy for newly diagnosed GBM in transient increase in tumor enhancement (pseudo-progression) in 20% to 30% of patients after the treatment, which is difficult to differentiate from true tumor progression [17]. In addition, pseudo-progression can develop during TMZ combination chemoradiotherapy in patients with malignant glioma [18]. Furthermore, antiangiogenic agents produce high radiographic response rates, as defined by a rapid decrease in contrast enhancement on CT/MRI that occurs within days of initiation of treatment and that is partly a result of reduced vascular permeability to contrast agents rather than a true antitumor effect [19]. Recently, new criteria have been proposed by the Response Assessment in Neuro-Oncology working group to address problems in assessing patients with pseudo-progression or in assessing progressive disease in patients with non-enhancing lesions [20].

Potential of dose escalation in radiotherapy

Nakagawa et al. showed a potential benefit of dose escalation in postoperative radiotherapy for patients with GBM by using three-dimensional conformal radiation therapy (3D-CRT) (Table 1). They noted that postoperative radiotherapy with 90 Gy in 45 fractions in patients with GBM resulted in significantly fewer local failures than in those who received postoperative radiotherapy with 60-80 Gy in 30-40 fractions; the local failure rates were 31% and 80% in the high-dose and low-dose groups, respectively [21]. Furthermore, Tanaka et al. demonstrated that patients who received high-dose radiotherapy had significantly longer MSTs compared with those who received conventional radiotherapy. In this study, MST was 16.2 months for patients who received 80-90 Gy in 40-45 fractions and 12.4 months for patients who received 60 Gy in 30 fractions [22]. These results suggest that dose escalation to the target volume can achieve better local control and longer survival of patients with GBM.

In contrast, as expected, radiation-induced white matter abnormalities with shorter onset were observed more frequently when high-dose radiotherapy was employed [22]. In their study, nine patients in the high-dose group developed radiation-induced necrosis, compared with none in the 60-Gy group: necrosis was confirmed pathologically from surgical samples in five patients and diagnosed clinically by PET in four patients. In addition, optic chiasm and nerve injury may manifest at 54-60 Gy, while onset of hormone insufficiency from irradiation of the hypothalamic-pituitary axis is variable but may be observed with doses as low as 20 Gy [23]. Therefore, an ingenious method is needed to decrease the risk of radiation-induced toxicity while maintaining a high dose to the target volume. The candidate modalities are intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), stereotactic radiation therapy (SRT), boron neutron capture therapy (BNCT), and particle beam therapy.

Intensity modulated radiation therapy

IMRT is an ingenious method for treatment of central nervous system malignancies [24]. Comparison of IMRT with 3D-CRT has clearly shown that IMRT improves target dose conformity, reduces doses to organs at risk (e.g., the brainstem, optic chiasm, lens, optic nerves, and cerebral cortex), and achieves comparable target coverage [25] (Figures 1a and 1b). Recently, dose escalation studies using IMRT showed prolongation of survival in patients with GBM with no increase in incidence of severe toxicity. Tsien et al. compared the efficacy of dose escalation using IMRT with concurrent TMZ [26]. They found that doses of 66-81 Gy over 30 fractions delivered by IMRT resulted in an MST of 20.1 months, and a lower in-field recurrence rate was observed in groups that received higher doses. In their study, late Grade 3radiation-induced necrosis was observed at 78 Gy (2 of 7 patients) and 81 Gy (1 of 9 patients). No case of radiation-induced necrosis was observed at or below 75 Gy. Median time to RT necrosis was 7 months (range: 5.4-8.9). The authors concluded that 75 Gy in 30 fractions could be safely delivered to patients with GBM using IMRT with concurrent TMZ. Iuchi et al. evaluated dose escalation using hypofractionated IMRT [27]. They found that the 1- and 2-year progression-free survival rates were and 71.4% and 53.6%, respectively. Dose escalation showed significant improvement in both local control and patient survival. Although massive radiation-induced necrosis required a second

Author	Treatment	Fraction Size	Chemotherapy Agents	No. of patients	Survival	Adverse events
Nakagawa K et al. (21)	3D-CRT	60-80 Gy/30-40 fr. versus 90 Gy/45 fr.	Nimustine 1 mg/m^2 plus vincristine 80 mg/m^2 on Days 1 and 28, and nimustine	38	The 1-year, 2-year, 5-year, and 10-year overall survival rates were 75%, 42%, 20%, and 15%, respectively.	Two among 16 patients of the higher dose group developed radiation necrosis. One patient died of radiation necrosis.
Tanaka M et al. (22)	3D-CRT	80-90 Gy/40-45 fr.	Nimustine or carmustine with or without vincristine	90	16.2 months in MST	Nine patients developed radiation necrosis,
Tsien CI et al. (26)	IMRT	66-81 Gy/30 fr.	Concomitant temozolomide 75 mg/m^2 daily for 6 weeks	38	20.1 months in MST	Three among 16 patients received 78 Gy or higher dose developed radiation necrosis.
Iuchi T et al. (27)	IMRT	48-68 Gy/8 fr.	(not described in detail)	25	The 1-year and 2-year overall survival rates were 71.4% and 55.6%, respectively.	Three among 25 patients developedmassive radiation necrosis and required secondsurgery.
Souhami L et al. (32)	3D-CRT+SRS	60 Gy/30 fr. with 3D-CRT plus 15-24 Gy with	Carmustine 80 mg/m^2 in days 1-3 every 8 weeks for six	89	13.5 months in MST	Four patients who received a 15-Gy boost developed radiation necrosis.
Fitzek MM et al. (42)	3D-CRT+proton radiotherapy	45 Gy/25 fr. with 3D-CRT plus 45 GyE/25 fr. with protons,	(unused)	23	20.0 months in MST	Seven patients developed radiation necrosis,
Mizumoto M et al. (43)	3D-CRT+proton	50.4 Gy/28fr. with 3D-CRT plus 46.2 GyE/28 fr. with protons	Nimustine hydrochloride 80 mg/m^2 during the first and fourth weeks	20	21.6 months in MST	Late radiation-induced necrosis and leukoencephalopathy were each seen in only one among 20 patients.
Mizoe JE et al. (47)	3D-CRT+Carbon ion	50 Gy/25 fr. with 3D-CRT plus 16.8-24.8/8 fr. with carbon ions	Nimustine hydrochloride on the 1st and 4th or 5th weeks of the x-ray at a dose of 100 mg/m2	32	26.0 months in MST	Four patients developed Grade 2 brain toxicity.No case of Grade 3 or higher brain toxicity was observed.

Abbreviations:
3D-CRT, 3-dimensional conformal radiotherapy; fr, fractions; MST, median survival time; IMRT, intensity modulated radiation therapy; SRS, stereotactic radiosurgery; CNS, central nervous system; CGE, cobalt gray equivalent

Table 1: Results of recent dose escalation studies with external beam radiotherapy.

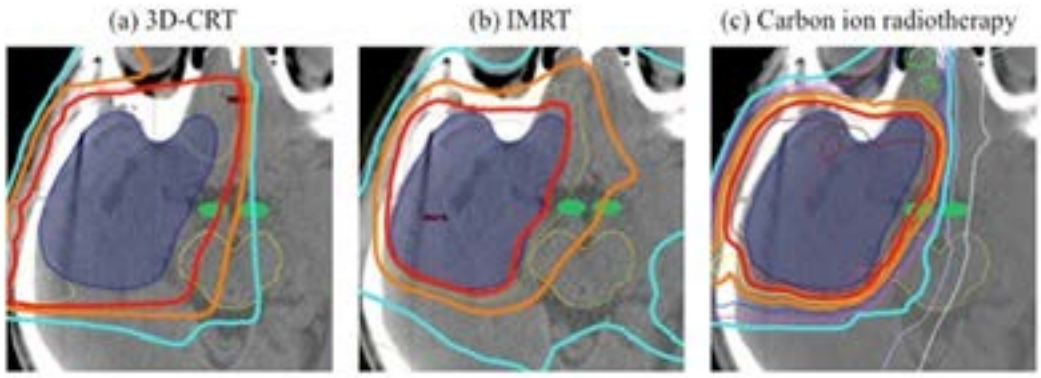

Figure 1: (a) 3D-CRT, (b) IMRT, and (c) Carbon ion radiotherapy. Representative axial dose distribution for three-dimensional conformal radiation therapy (3D-CRT) plan (4 ports), intensity-modulated radiation therapy (IMRT) plan (9 ports), and carbon ion radiotherapy (4 ports) plan. The cyan-, orange-, and red-colors show 50%, 80%, and 95% isodose lines, respectively. The dark blue-, green-, and yellow-colors show the target volume, optic nerves, and brain stem, respectively.

surgery in 3 of 25 cases in this study, dose escalation using IMRT may contribute to better survival in patients with GBM.

Stereotactic radiosurgery and Stereotactic radiation therapy

SRS and SRT are forms of hypofractionated high-precision radiotherapy delivery [28]. To date, several clinical studies on SRS and SRT have been conducted in patients newly diagnosed with GBM [29-31]. RTOG 93-05, the only randomized controlled trial on this topic, tested the benefits of administering SRS before conformal radiotherapy with bis-chloroethylnitrosourea (BCNU) in 186 patients with GBM [32]. These patients were randomized into the following two groups: 97 patients received conformal radiotherapy and BCNU and 89 patients received SRS 1 week prior to conformal radiotherapy and BCNU. The tumor dose delivered was volume-dependent, ranging from 15 to 24 Gy in compliance with the established maximum safely tolerated doses [33]. This randomized trial showed no significant difference in MST or patterns of failure with the addition of SRS in patients with GBM. Although this study provides Level I evidence against the use of SRS prior to conformal radiotherapy with BCNU, it raises several important issues with respect to study applicability, including timing of SRS, type of chemotherapy (BCNU vs. TMZ), and extent of surgical resection. Further clinical trials to test these issues are warranted.

Boron neutron capture therapy

BNCT is a two-step technique. First, compounds labeled with ^{10}boron are injected into the patient and, depending on the tumor

entity, the injected compounds are selectively enriched in tumor cells [34]. Second, patients are irradiated with low-energy neutrons from a nuclear reactor or fast neutrons from cyclotron. The ^{10}boron in the tumor cells and the thermal neutrons react [boron neutron capture reaction: ^{10}B (n, alpha) ^{7}Li] and release high linear-transfer alpha particles and ^{7}lithium [35]. Because the alpha particles have a limited range of 5-9μm, the therapeutic irradiation is limited to the cells with a high concentration of boron.

Several hundred patients with GBM have been treated with BNCT in phase I and II studies in Europe, the United States, and Japan; the survival period in these studies was comparable with those obtained with standard radiotherapy [34-38]. These studies resulted in an MST of 13.0-17.6 months, which was equal to or better than that of concurrent chemoradiotherapy [4]. However, no randomized trials comparing BNCT with standard therapy have been undertaken. Toxicities are typically acute and related to a temporal increase in intracranial pressure. A residual tumor volume of greater than or equal to 60 cm^3 led to a greater incidence of acute central nervous system toxicity [35,37].

Considerable efforts over the past 20 years to design and synthesize boron-containing compounds capable of selectively achieving sufficient boron concentrations in tumor cells have been unsuccessful. Moreover, methods for transport and delivery of boronated pharmacophores to the hypovascular region or G0 phase cells of the tumor are needed. The relatively high costs associated with the construction of the neutron beam appear to have been the main factor inhibiting the evolution of a technique. Despite these obstacles, considerable improvements in the efficiency and specificity of the delivery of boronated agents may provide the driving force that will bring the technique into the main stream of treatments for patients with GBM.

Particle beam therapy

Charged particle beams consisting of protons and carbon ions have the Bragg peak and allow highly localized deposition of energy that can be used for increasing radiation doses to targets while minimizing irradiation to adjacent normal tissues [39]. Proton radiotherapy has been carried out in the United States, Europe, and Japan. Carbon ion radiotherapy has been carried out in five institutions, and most clinical data have been provided by the National Institute of Radiological Science, Japan [40,41].

Proton radiotherapy

Clinical trials with proton radiotherapy have been conducted for patients with GBM. Fitzek et al. conducted a phase II study of 23 patients with GBM treated with 90 GyE utilizing protons and x-rays in the hyper fractionated radiotherapy [42]. All patients developed new areas of gadolinium enhancement within the high radiation dose regions during the follow-up period. While tissues obtained at biopsy, resection, or autopsy were histologically examined in 15 of 23 patients, radiation necrosis was confirmed only in seven patients. The MST of all the patients was 20.0 months, and the survival of the patients who developed radiation necrosis was significantly longer than that of the other patients. Recently, Mizumoto et al. conducted a phase I/II study of postoperative hyperfractionated concomitant boost proton beam therapy with nimustine hydrochloride in patients with GBM [43]. In their study, the MST was 21.6 months while acute toxicity was mainly hematologic and controllable. Late radiation-induced necrosis and leukoencephalopathy were each seen in only one of 20 patients. These studies showed the clinical usefulness of proton radiotherapy and suggested the possibility of doseescalation in the treatment of patients with GBM using proton radiotherapy.

Carbon ion radiotherapy

Carbon ion radiotherapy can offer better dose conformity to a target volume than other modalities [44]. In addition, high linear energy transfer (LET) radiation, such as carbon ion beams, has greater biological effectiveness than low LET radiation, such as x-rays and proton beams. Because of its better dose distribution and cell-killing potency, carbon ion radiotherapy is a promising modality in the treatment of patients with GBM [45,46] (Figure 1c).

Mizoe et al. reported a phase I/II study of 32 patients with GBM and 16 patients with anaplastic astrocytoma treated with surgery and postoperative concurrent chemoradiotherapy with x-rays followed by carbon ion radiotherapy [47]. The treatment consisted of 50 Gy of x-ray radiotherapy in 25 fractions with concurrent administration of nimustine hydrochloride and carbon ion radiotherapy with the doses increased from 16.8 to 24.8 GyE in 10% incremental steps. There was no Grade 3 or higher acute toxicity in the brain. The late reactions included four cases of Grade 2 brain toxicity among 48 cases. TMZ was not administered in this study.

Evaluation of the efficacy of concurrent chemo-carbon ion radiotherapy using TMZ is warranted. Combs et al. conducted a randomized phase II study in patients with GBM, in which they compared carbon ion radiotherapy and proton radiotherapy as a boost following 50 Gy of x-ray radiotherapy with concurrent TMZ [48]. In a report of early treatment results of this study, little toxicity was associated with the treatment [49]. This study by Rieken is expected to evaluate the efficacy of dose escalation using particle beam therapy.

Radiation-induced toxicities

Dose-related toxicities for surrounding normal structures should be considered when we postulate dose escalation strategy. A necrosis is one of the most bothersome radiation-induced toxicities. As we described above, even with modalities which deliver excellent dose distribution, dose escalation strategy can develop radiation-induced necrosis because that the surrounding normal tissue adjacent to the fatal lesion is usually included in the target volume. Thus, dose escalation strategy for patients with GBM not only has the therapeutic potential but also provides a difficult challenge in practice.

Recently, new evidences support a role of antiangiogenic therapy, such as bevacizumab, for the treatment of radiation necrosis [50,51]. This antiangiogenic therapy may be effective in patients with radiation necrosis after dose-escalation radiotherapy. In addition, a recent study in which bevacizumab was added to a hypofractionated course of re-irradiation in recurrent gliomas showed that no radiation-induced necrosis was observedin 25 patients who were studied [52]. The addition of bevacizumab to chemoradiation may increase the therapeutic ratio through possible antitumor effects and may also allow safe escalation of radiotherapy by reducing the risk of radiation-induced necrosis.

Conclusions

Despite state-of-the-art oncological therapy that includes maximum safe surgical resection and radiotherapy, the prognosis of patients with GBM remains poor. Several prospective studies using modalities that deliver excellent dose distribution of radiotherapy have shown that dose escalation is feasible and appears to be effective. It is remarkable that the dose escalation strategy can change the pattern of failure. Thus, doses of radiotherapy higher than 60 Gy are needed

within irradiated field to control GBM. However, the strategy could come with limitations that include severe toxicities, such as radiation necrosis in the fatal region. Patients with GBM being treated with dose escalation radiotherapy need to be studied to identify the suitable target volume, dose fractionation. Further prospective trials with large numbers of patients are warranted to establish the efficacy of these advanced radiotherapy treatments for patients with GBM.

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