Chapter 6
Principles of Radiation Therapy for Glioblastoma Patients

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Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor in adults. GBMs are aggressive tumors with diffusely infiltrating microscopic disease that extends into the brain parenchyma and, despite years of ongoing research, the prognosis remains poor. With both diagnostic and therapeutic implications, surgical resection is the primary treatment modality for GBM and the extent of resection has been shown to be related to patient prognosis [1]. However, complete surgical resection of GBM is uncommon due to the diffuse, infiltrative nature of the disease and maximal safe resection alone results in high rates of local recurrence [2]. Post-operative radiation therapy (60 Gy in 30 daily fractions) is essential in controlling this unresectable microscopic disease and has been shown to significantly increase median survival compared to surgery alone [2–5].

In 2004, a randomized phase III trial by the European Organization for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) established the widely adopted current standard of care for GBM. This landmark study showed a survival benefit with the addition of concurrent and adjuvant temozolomide (TMZ), an oral alkylating chemotherapy, to maximal safe resection and post-operative radiation therapy. Indeed, overall survival increased to 9.8% at 5 years with the addition of TMZ to radiation therapy compared to 1.9% OS at 5 years with radiotherapy alone [6, 7]. Moreover, patients in the chemotherapy arm had an increased median survival of 14.6 months compared to 12.1 months for the radiation alone arm [7]. Since this landmark study

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in 2004, the standard of care for the management of GBM remains maximal safe resection followed by concurrent chemoradiation and adjuvant chemotherapy.

In contrast to other malignancies, GBM tend to recur locally rather than at distant areas of the central nervous system (CNS) [2]. Indeed, the majority of recurrences occur within the previous high dose radiation field, further emphasizing the need for improving the efficacy of radiation therapy. While the standard of care for treatment of GBM has not significantly changed since the landmark EORTC/NCIC CTG study [7], radiation therapy techniques have evolved over the past 15 years with the hopes of increasing local control and survival in these patients. In this chapter, we will explore the principles of radiation therapy, radiation techniques that have been studied as potential approaches for increasing the efficacy of radiation as well as a more recent focus toward identifying molecular biomarkers that may help radiosensitize glioblastoma cells and predict response to radiation.

Basics of Radiation Therapy

External beam radiation therapy has long been an essential part of treatment for GBM patients. Therapeutic X-rays (photons) are produced by linear accelerators and form the basis of external beam radiation therapy. The biologic effects of X-rays may be caused by direct action (by directly ionizing the target molecule) or by indirect action (by interacting with water to produce free radicals that in turn interact with the target molecule). In most cases, X-rays are indirectly ionizing by transferring their energy to free radicals that in turn damage DNA. When the DNA damage is unrepairable, radiation leads to death of the cancer cell [8]. TMZ chemotherapy is believed to facilitate this process by producing cytotoxic lesions, such as methylation of O^6-methylguanine, that stabilize and further delay repair of RT-induced double strand breaks [9–11].

Radiation Planning Techniques

Involved field radiation therapy is the current standard approach for adjuvant RT in patients with GBMs and the involved area is defined by radiographic MRI abnormalities. In order to precisely locate the area of interest to be covered and minimize errors in daily setup, computed tomography (CT) simulation for radiation planning is necessary. The patient is immobilized in supine treatment position with a custom-fitted thermoplastic mask (Fig. 6.1a). A CT scan of the head is done once the patient is immobilized in treatment position. This planning CT scan is used for radiation planning and registered with the post-operative MRI brain (both T1 contrast enhancing and T2-weighted MRI on a fluid-attenuated inversion recover (FLAIR) series are helpful for defining targets). As shown in Fig. 6.1b, c, the radiation oncologist will use both the CT and MRI to define and delineate volumes for tumor targets and

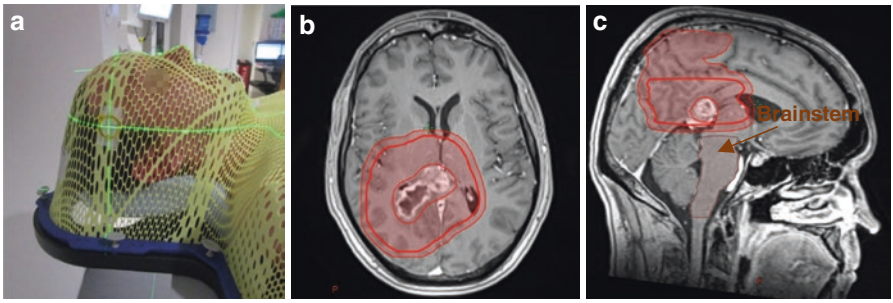

Fig. 6.1 (**a**) A thermoplastic mask conforms to the patient's head for immobilization during the CT simulation for radiation planning. (**b**) Axial T1-enhancing MRI is fused to the planning CT scan in order to delineate tumor volumes and critical surrounding structures. (**c**) Brainstem, in close proximity to tumor volumes, is shown on the sagittal view

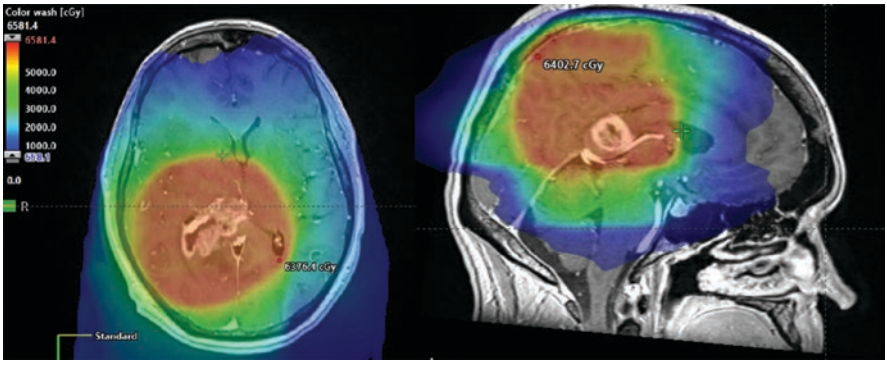

Fig. 6.2 A 3-arc VMAT radiation plan for glioblastoma. The 60 Gy treatment volume shown in red includes the glioblastoma resection cavity with a margin on both axial and sagittal views

surrounding normal structures (such as the optic chiasm, optic nerves, retina, lens and brainstem).

Intensity-modulated radiation therapy (IMRT) and Volumetric modulation arc therapy (VMAT) are commonly used in the treatment of GBM. IMRT is an advanced technology that allows several photon radiation beams from different angles to be manipulated in order to conform to the shape of the GBM target. The shape and dose intensity of the beams can be varied across the treatment field in order to better target the tumor and at the same time avoid critical structures. This is especially important in radiation planning for patients in which tumors are in close proximity to critical structures. Typically IMRT utilizes five, seven or nine stationary radiation beams, each from different angles. VMAT is a type of IMRT in which the head of the linear accelerator continues to move in an arc around the patient while delivering the radiation treatment (Fig. 6.2).

Radiation Toxicity

The toxicity of radiation depends on multiple factors, including the volume of brain treated, radiation dose, fractionation schedule, as well as any chemotherapies or targeted agents being delivered concurrently with radiation. Toxicity following radiation can be grouped into three phases, including early toxicity (days to weeks), early delayed toxicity (1–6 months) and late toxicity (>6 months to years).

Acute toxicities of intracranial radiation may occur days to weeks after radiation and are often managed with supportive care. General symptoms include fatigue, headache, nausea, vomiting, dermatitis and alopecia. Transient worsening of pretreatment neurologic symptoms and seizures may also occur due to radiation-related edema, which often responds to dexamethasone steroids [12]. In contrast, late toxicities can develop months to years after radiation and are often progressive and irreversible. There can be a risk of cognitive decline and memory impairment depending on the location and size of the radiation field. Treatment of lesions near the optic pathways, cochlea, sensory or motor cortex may cause focal neurologic deficits if radiation dose constraints are not respected. Radiation necrosis is a complication of radiation that may cause mass effect and/or neurologic symptoms. Radiation necrosis is a complex process that may be related to vascular endothelial cell injury, white matter damage and immune mechanisms [13]. Differentiating progressive or recurrent tumor from radiation necrosis by imaging is often challenging.

The Evolution of Radiation Therapy for GBMs

As we previously discussed, GBM recur locally rather than at distant CNS sites, therefore emphasizing the importance of increasing local control by optimizing radiation therapy [2]. Since the landmark EORTC/NCIC CTG study in 2004 [6, 7], extensive research has explored different approaches for increasing radiation dose and efficacy against the tumor as well as minimizing radiation toxicity.

Dose Escalation Studies

In a disease where distant spread is uncommon and most recurrences occur within the previous radiation field, dose intensification clinical studies were conducted to better understand the radiation dose that provides the best local control with minimal toxicity [14]. The Brain Tumor Study group examined adjuvant radiation doses among 621 patients with malignant gliomas after surgery and found that patients with 50 Gy adjuvant radiation had a median survival of 36 weeks compared to the median survival of 42 weeks of those patients with 60 Gy of adjuvant radiation [15]. Therefore, the median survival significantly improved by approximately 1.3 times

when increasing the dose from 50 to 60 Gy [15]. Another randomized trial by the Medical Research Council also concluded that increasing the radiation dose to 60 Gy improved survival outcomes when two common GBM radiation dose regimens of 45 Gy in 20 fractions and 60 Gy in 30 fractions were compared [16]. While these initial dose-escalation studies showed promise for improving outcomes in GBM patients, a subsequent study showed that further dose escalation from 70 to 90 Gy increased toxicity with no survival benefit [17]. Together, these studies confirmed 60 Gy in 30 daily fractions to be the standard radiation dosing for GBM.

Multiple studies have also examined dose escalation with a stereotactic boost as another approach for increasing radiation dose and local control with minimal toxicity. Stereotactic radiosurgery is a highly precise technique in which ablative doses of radiation are delivered focally within a single fraction with a very sharp dose fall off such that critical structures are avoided at the same time. Initially, Loeffler et al. (1992) reported benefit to stereotactic radiosurgery (SRS) as part of the initial treatment of malignant gliomas [18]. Moreover, Sarkaria et al. (1995) found a median survival benefit and an increase in 2-year overall survival with stereotactic treatment of newly diagnosed GBMs in addition to conventional radiation and surgery [19]. However, the Phase III randomized Radiation Oncology Therapy Group (RTOG) 9305 later evaluated dose escalation with an upfront SRS boost in addition to conventional radiation therapy and BCNU in newly diagnosed GBMs. Unfortunately, there was no survival benefit (median survival of 13.5 months in the SRS arm versus 13.6 months in the standard arm), no changes in local failure and no changes in quality of life with the addition of an SRS boost compared to conventional radiation and BCNU alone [20]. Currently, there is no strong evidence for using SRS in the management of newly diagnosed GBMs, although it is often used in the recurrent glioblastoma setting.

Hyperfractionation, also studied as a method for increasing radiation dose, refers to the more frequent administration of smaller than standard radiation therapy doses. This often involves two doses of radiation daily, each dose occurring at least 6 hours apart. Hyperfractionation was believed to offer increased local control by preventing tumor cells from repopulating between radiation treatments and at the same time reducing late radiation injury. RTOG 8302 initially evaluated 64.8 Gy vs. 72 Gy hyperfractionated twice per day radiation in the presence of BCNU and found no significant difference in survival or toxicity with conventional radiation [21]. RTOG 9006 was a Phase III randomized study comparing a hyperfractionated radiation regimen of 72 Gy in 60 fractions given twice per day with the standard regimen of 60 Gy in 30 daily fractions (both arms receiving concurrent BCNU) and found no benefit to survival or toxicity outcomes with hyperfractionation [22].

Protons have also been studied as a way to get more dose to the tumor tissue but at the same time spare surrounding normal structures. Protons are charged particles that have the ability to concentrate the majority of their dose at the end of their finite path length (Bragg peak), thus resulting in a sharper dose fall off and better ability to avoid surrounding normal tissue [8]. Fitzek conducted a Phase II trial treating GBM with a photon-proton mixture to a 90 gray cobalt equivalent (CBE) in order to minimize toxicity with escalated dosing and found that survival was increased to

20 months [23]. Mizomuto et al. conducted a Phase II trial in which patients with GBM were treated with conventional photon radiation followed by an evening (>6 hours later) proton boost to a prescribed dose of 96.6 Gy in 56 twice daily fractions with concurrent nimustine chemotherapy [24]. Median survival was 22 months and 2-year survival was 45% [24], suggesting that more clinical trials with proton treatment of GBM are warranted due to these promising results. There is an ongoing Phase II clinical trial, NRG BN001, comparing dose-escalated protons and IMRT photons to conventional photon radiation (NCT02179086), which is estimated to be completed by 2026.

Decreasing Radiation Volumes to Minimize Toxicity

Before CT and MRI imaging, radiation therapy for GBMs was delivered as whole brain radiation therapy [25], in which large, opposed lateral fields were utilized to cover the entire brain volume. However, now involved-field partial brain radiation is the standard of care as studies have demonstrated that radiation field volumes can be decreased from whole brain radiation and still provide disease control with less toxicity. In fact, Ramsey and Brand (1973) found that GBM patients treated with limited field radiation therapy compared to whole brain radiation therapy had significantly increased overall survival, which was believed to be due to reduced toxicity of sensitive areas of the brain [26]. Moreover, in the Brain Tumor Cooperative Group Trial (BTCG) 80-01, patients receiving whole brain radiation to 60.2 Gy had no significant survival advantage compared to patients receiving 43 Gy to the whole brain plus an additional 17.2 Gy radiation to the tumor volume [27].

Since these studies, involved field conformal brain radiation has become the standard adjuvant treatment for GBM. Historically, many have delineated the target as gross tumor volume and resection cavity along with a 2 cm margin in the radiation field, which has been influenced by multiple studies. Indeed, after the advent of CT imaging, Hochberg and Pruitt (1980) used CT scans to show that more than 90% of GBM cases recurred within 2 cm of the primary tumor [28]. Wallner et al. reported that 78% of 32 GBMs recurred within 2.0 cm of the initial tumor margin [25]. Kelly et al. (1987) evaluated 40 untreated GBMs by CT and MRI-guided stereotactic biopsies and found that T1 contrast enhancement corresponded to gross GBM tissue and that isolated GBM cells extended at least as far as the edema or T2 FLAIR signal [29]. As a result of these studies, the inclusion of all radiographic MRI evidence of GBM and associated edema with large 2 cm margins became widely adopted.

However, even today there is no consensus regarding optimal radiation volumes for maintaining local control in GBMs yet at the same time avoiding treatment-associated toxicity. In Radiation Oncology, recommended radiation treatment volumes and margins depend on the specific pathology of tumor. For GBM, the gross tumor volume, referred to as GTV, corresponds to any residual gross tumor after surgery and the resection cavity. The clinical target volume (CTV) is a margin on

the GTV that accounts for the estimated extent of microscopic or subclinical disease. The planning treatment volume (PTV) is an additional margin on the CTV that accounts for uncertainties in set up and radiation delivery (Fig. 6.1). While the GTV is more straightforward, there continues to be wide variation in radiation volumes, especially CTV and the inclusion of peri-tumoral edema, included in the radiation field [30–40].

While further investigation is warranted for identifying the best margin for radiation volumes, studies provide evidence that decreased margins may improve survival by minimizing toxicity without compromising recurrence patterns [31]. Kumar et al. (2019) recently reported that while two common contouring consensus guidelines resulted in similar recurrence rates, there was significantly improved survival and quality of life in patients treated with smaller radiation volumes [41]. One hypothesis is that reduced radiation volumes may decrease the incidence of severe lymphopenia in GBM patients, possibly by reducing the irradiated circulating blood volume (reviewed in [31, 42]). Huang et al. showed that increased brain volumes receiving 25 Gy was an independent predictor of severe lymphopenia and those patients developing severe lymphopenia had significantly worse median survival of 12.5 months compared to 20.2 months in those without lymphopenia [43]. While the exact mechanism of lymphopenia-related decreases in overall survival is uncertain, many hypothesize that reduced lymphocyte counts cause the immune system to be less effective at removing malignant GBM cells from the body.

Molecular Biomarkers and Radiation Therapy in GBM

Along with the World Health Organization's (WHO) update on the classification of gliomas to incorporate molecular markers [44], researchers have also evaluated the ability of molecular markers to predict patient response to treatments in order to facilitate clinical decision making. While GBM is associated with poor prognoses, a small subset of patients have been shown to experience longer survival, suggesting some heterogeneity among GBMs. As a tool for predicting prognosis of GBM patients, initial recursive partitioning analyses (RPA) identified clinical non-molecular based prognostic factors, such as age, histology, performance status, mental status, extent of surgery, and radiation dose [45–47]. However, with our improved understanding of molecular pathways involved in GBM pathogenesis, a revised RTOG GBM RPA included both clinical and molecular biomarkers to better stratify GBM patient outcomes. Indeed, Bell et al. [48] evaluated expression of more than 12 proteins by immunohistochemical staining of tissue microarrays from patients enrolled on the RTOG 0525 clinical trial, a phase III randomized trial comparing conventional adjuvant TMZ to dose-dense TMZ [49]. This revised RPA model, including c-MET and MGMT protein levels, resulted in improved outcome stratification in GBM patients treated with radiation and TMZ compared with earlier RPA models [48]. Importantly, their results also reported MGMT protein expression to have better prognostic significance than the more commonly reported

MGMT promoter methylation. As previously mentioned, MGMT protein expression has also been shown to be related to increased radiation response in pre-clinical studies [10]. Future studies on identifying additional molecular biomarkers to predict response to radiation and increase sensitivity to radiation are ongoing.

Hypofractionated Radiation Therapy in Elderly Patients

Almost half of all GBMs occur in patients greater than 65 years old and these patients often have worse outcomes than the younger cohorts [50]. Moreover, patients older than 70 years old were excluded from the EORTC/NCIC CTG study that developed the current standard of care for treatment of patients with GBM [6, 7]. Considering the poor prognosis associated with newly diagnosed GBM in elderly and frail patients, multiple studies have investigated the role for more tolerable treatment regimens in this patient population. Keime-Guibert et al. (2007) reported patients >70 years old and Karnofsky performance status (KPS) >70 with anaplastic astrocytoma/GBM had improved median survival when receiving 50.4 Gy of conventional radiation in 28 fractions compared to supportive care alone (29.1 weeks vs. 16.9 weeks) without a decline in quality of life or cognition [51], providing support for the benefit of radiation therapy in the elderly GBM population. Multiple trials have shown that hypofractionated (shortened) radiation schedules yield the same survival outcomes as conventional radiation, yet also reduce morbidity with shorter treatment times for patients enduring a terminal illness. Hypofractionation of radiation treatments refers to the use of a fewer number of higher dose radiation treatments in order to reduce the overall treatment time. Roa et al. (2004) compared GBM patients >60 years old receiving hypofractionated radiation schedule (40 Gy in 15 fractions) to the conventional fractionation schedule (60 Gy in 30 fractions) without concurrent chemotherapy and found no difference in survival (5.6 months vs. 5.1 months) between the two radiation schedules [52]. Moreover, Roa et al. (2015) reported that a hypofractionated radiation regimen of 25 Gy in 5 fractions had non-inferior overall survival compared to 40 Gy in 15 fractions in elderly and frail patients with newly diagnosed GBM not receiving chemotherapy [53].

The Phase III randomized EORTC 26062 trial later evaluated whether there was benefit to adding TMZ chemotherapy to 40 Gy in 15 fraction hypofractionated radiation in patients >60 years old with newly diagnosed GBM. They reported an overall survival benefit with the addition of TMZ to hypofractionated radiation compared to radiation alone (9.3 vs. 7.6 months) [54]. Moreover, Ammirati et al. (2015) demonstrated that GBM patients receiving hypofractionated radiation (52.5 Gy in 15 fractions) with concurrent TMZ tolerated the treatment well [55]. In summary, these studies generated support for combined modality therapy in older patients, especially those with *MGMT* hypermethylation. However, hypofractionated radiation alone can be an effective treatment in elderly patients with GBM who are not candidates for TMZ due to poor functional status or medical co-morbidities, especially those patients with GBM that are not *MGMT* hypermethylated [56].

Re-irradiation of GBM

Despite standard aggressive therapies, nearly all GBM recur within months to years following initial therapy. Most recurrences are located within or adjacent to the high dose radiation field. Since radiation necrosis and recurrent GBM have similar appearances on MRI imaging, determining the diagnosis of recurrent GBM can be challenging. While there is no standard of care treatment for recurrent GBMs in the United States, potential treatment options include re-resection, re-irradiation, systemic therapy, best supportive care or a combination of these palliative treatment modalities. The treatment plan for each patient should be individualized with close consideration of age, performance status, time since initial treatment, extent of recurrence and tumor location (any involvement of eloquent areas of the brain).

Re-irradiation is increasingly being used in the treatment of recurrent GBMs and is often recommended for patients, especially those who are not candidates for re-resection and have minimal systemic options available to them. The patient's performance status and how the potential toxicities of re-irradiation may impact the patient's quality of life should be heavily weighed before proceeding with re-irradiation. Moreover, radiation dose, fractionation and treatment volume should be carefully planned in order to minimize radiation necrosis and other serious toxicities. Stereotactic radiation has been used for focal recurrent GBMs in order to avoid wide margins that may increase the risk of toxicity [57–60]. However, in cases of multifocal or large recurrent tumors, conventional external beam radiation with smaller dose per fraction may offer local control of larger treatment volumes with less toxicity. Various radiation dose and fractionation regimens for external beam radiation therapy have been reported, however, at this time, there is not enough data to recommend a standard regimen [30]. TMZ, bevacizumab and immune modulators are systemic therapies that have been the most commonly studied in the re-irradiation setting [61–65]. While many retrospective studies have shown encouraging survival outcomes, these studies are difficult to interpret and compare due to inconsistencies in treatment technique, dose, and volumes treated (reviewed in [30, 66, 67]). More prospective clinical trials are warranted for direct comparisons of radiation regimens.

Summary and Conclusions

In summary, GBM is an aggressive tumor that most commonly recurs within or adjacent to the previous high dose radiation field, further emphasizing the need for improving the efficacy of radiation therapy. Radiation therapy techniques have been studied over time in order to increase local control but minimize radiation toxicity with some success. Further pre-clinical and clinical studies are needed to not only improve the efficacy of radiation therapy, but also identify molecular biomarkers that may help predict response to radiation and prognosis in GBM patients.

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