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TOPIC REVIEW

Management of GBM: a problem of local recurrence

John P. Kirkpatrick[1,2] · Nadia N. Laack[3] · Helen A. Shih[4] · Vinai Gondi[5,6]

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Abstract Forty years ago, adjuvant treatment of patients with GBM using fractionated radiotherapy following surgery was shown to substantially improve survival compared to surgery alone. However, even with the addition of temozolomide to radiotherapy, overall survival is quite limited and local failure remains a fundamental problem, despite multiple attempts to increase dose to the tumor target. This review presents the historical background and clinical rationale leading to the current standard of care consisting of 60 Gy total dose in 2 Gy fractions to the MRI-defined targets in younger, high performance status patients and more hypofractionated regimens in elderly and/or debilitated patients. Particle therapies offer the potential to increase local control while reducing dose and, potentially, long-term neurocognitive toxicity. However, improvements in systemic therapies for GBM will need to be implemented before the full benefits of improved local control can be realized.

✉ John P. Kirkpatrick
john.kirkpatrick@dm.duke.edu

[1] Department of Radiation Oncology, Duke University, Durham, NC 27710, USA

[2] Department of Surgery, Duke University, Durham, NC 27710, USA

[3] Department of Radiation Oncology, Mayo Clinic, Rochester, MN 55905, USA

[4] Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA 02114, USA

[5] Central Dupage Hospital Cancer Center, Warrenville, IL 60555, USA

[6] University of Wisconsin Comprehensive Cancer Center, Madison, WI 53792, USA

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Historical overview

Radiation therapy following surgical resection of malignant gliomas has been a recommended component of the management strategy since the 1970s, as it improves overall survival compared to surgery alone. Walker et al. [1] randomized patients with malignant glioma to one of four arms after surgery: chemotherapy (BCNU) alone, radiotherapy (RT) alone, RT + BCNU and best supportive care. Median overall survival was 14 weeks for best supportive care, 18.5 weeks for BCNU, 35 weeks for RT and 34.5 weeks for RT + BCNU. All modalities using radiotherapy and/or chemotherapy provided statistically superior survival compared to post-operative supportive care alone. A subsequent study [2] randomized 467 patients with malignant glioma to chemotherapy (CCNU) alone, RT alone, RT + CCNU or RT + BCNU. Median overall survival was 6 months in the CCNU alone arm, 9 months with XRT alone, 12.8 months with BCNU + XRT and 10.5 months with CCNU + XRT. A meta-analysis [3] of those and four other randomized trials done revealed a significant survival advantage with the addition of radiotherapy to surgical resection compared to surgery alone (RR 0.81, 95% CI 0.74–0.88, $p < 0.00001$).

With an objective of identifying an optimal dose for treatment of malignant glioma, Walker et al. [4] analyzed the results from a variety of prospective trials with doses ranging from 45 to 60. Median overall survival was 3.1 months without RT, 4.2 months with less than 45 Gy, 7 months for 50 Gy, 9 months for 55 Gy and 10.5 months for 60 Gy. Survival was significantly different between groups receiving 50 versus 60 Gy ($p = 0.004$). A study

[5] of 474 patients with malignant glioma randomized to 60 Gy whole brain in 30 fractions versus 45 Gy in 20 fractions found that median survival was significantly higher in the 60 Gy group (12 versus 9 months, $p = 0.007$).

Trials to improve outcome by dose escalation using conventionally fractionated RT [6], hyperfractionation [7], brachytherapy [8, 9] or a stereotactic radiosurgical [10] boost have not revealed a benefit to increasing dose beyond 60 Gy. For example, in RTOG 9305 203 patients with glioblastoma were randomized to receive stereotactic radiosurgery (SRS) versus no SRS prior to a course of conventional radiotherapy (a total of 60 Gy in 2 Gy daily fractions) and concurrent BCNU. No significant differences in survival (14.1 versus 13.7 months with or without SRS), neurocognition, quality of life or patterns of failure were found, with 90% of failures occurring at the treatment field in both arms. Thus, standard RT typically consists of thirty or thirty-three 2.0 or 1.8 Gy daily fractions to a total dose of 59.4 to 60 Gy delivered over a six to seven-week period.

In the following sections, we critically review the rationale and issues surrounding the current treatment of malignant gliomas with radiotherapy, in detail, particularly in regard to improving local control.

Defining the optimal target volume

While historical series involved irradiating the entire brain, due to the concern about the widespread and infiltrative distribution of tumor cells throughout this organ, various trials showed no significant differences in outcome when the volume of brain irradiated was reduced [11, 12]. Thus, in order to avoid toxicity associated with whole-brain irradiation to 60 Gy, the current standard practice is to irradiate only the part of the brain involved tumor, as confirmed by the recently published ASTRO guidelines [13].

Target delineation for postoperative radiotherapy requires semi-automatic fusion of post-operative MRI including post-contrast T1 and T2/FLAIR sequences to the radiotherapy-planning CT simulation scan. Acceptable approaches to treatment include either (1) 45 to 50 Gy to a clinical target including all surrounding postoperative T2/FLAIR signal plus a 1 to 2-cm margin along continuous white matter tracks within the brain with a boost to a clinical target including the surgical cavity and residual enhancing tumor plus a 1 to 2 cm margin or (2) single target volume including surgical cavity and residual enhancing tumor with wide (2 cm) margins, without specifically targeting surrounding T2/FLAIR signal but with manual modification to include T2/FLAIR regions suspicious for disease [14]. To avoid unnecessary irradiation of the posterior fossa or contralateral brain, both the tentorium and falx should be considered effective barriers to spread of glial tumors and clinical targets should be adjusted along known anatomic white matter tracks.

These approaches are derived from studies of patterns of progression. In one study conducted in the pre-temozolomide era, 78% of GBM recurrences occurred within 2 cm of the margin of the initial tumor bed and 56% occurred within 1 cm or less of the volume outlined by CT scan [15]. A more contemporary series in which patients were treated in the era of concomitant and adjuvant temozolomide demonstrated that 92% of first recurrences developed within the 95% isodose line when using radiotherapy target that accounted for margin around the T2/FLAIR signal [16]. Rationale to include surrounding T2/FLAIR signal in the modest-dose target volume is based on pathologic-radiographic correlative analyses. A study correlating CT scans with pathologic sections of 15 brains of patients with GBM who received minimal or no radiotherapy observed that radiotherapeutic treatment of the contrast-enhancing area and all surrounding edema with a 3-cm margin around the edema would cover histologically identified tumor in all cases [17]. In a similar correlative study of 40 glioma patients who underwent CT- and MRI-guided stereotactic serial biopsies, isolated tumor cell infiltration was observed extending at least as far as T2 changes on MRI [18].

Emerging evidence suggests that irradiating the compartment of self-renewing and pluripotent neural stem cells located in the subventricular zone may be associated with improved therapeutic outcomes [19, 20]. However, these retrospective data have not been validated in the setting of a larger clinical trial and the purposeful irradiation of neural progenitor stem cells may adversely affect neurocognitive development [21].

Selecting the optimal total dose and fractionation

In the landmark Stupp trial [22] comparing outcome in patients with GBM treated with radiotherapy and temozolomide versus radiotherapy alone, 60 Gy was given in two Gray fractions over 6 weeks. Median age of patients enrolled was 57, with 30% of patients age 61 to 70 years. Median overall survival was 10.9 months with radiation alone versus 11.8 months with the addition of temozolomide thus is still felt to be standard treatment for patients <70 with good performance status. Similar improvements in survival were observed with the addition of BCNU-impregnated wafers to the resection cavity followed by standard conventionally fractionated radiotherapy versus radiotherapy alone [23]. In elderly patients, treatment at a slightly higher dose per day for a significantly shorter period (e.g., 40 Gy delivered over 3 weeks) yields reasonable outcome [24].

Hypofractionation has been studied in elderly and poor KPS patients with malignant gliomas who are expected to have more limited survival than those who are younger and more robust [24–30]. Hypofractionation would be expected to be associated with increased risk of long-term cognitive toxicity but in select populations with limited survival, late toxicity is not a significant concern and instead minimizing toxicity and disruption of quality of life may be a higher priority. In two recently completed trials, 40 Gy in 15 fractions has been utilized with temozolomide in adults >65–70 years of age with favorable toxicity profile and median survival of 12–12.5 months [28, 31]. In patients whose functional status may preclude the addition of temozolomide, radiation alone to 40 Gy in 15 fractions [29], 34 Gy in 10 fractions [27] and 25 Gy in 5 fractions have also been evaluated [30]. Median survival in these reports ranges from 5.1 to 7.9 months and was not statistically different from conventional radiation (60 Gy in 10 fractions).

Because the pattern of failure is predominantly within the radiotherapy field, efforts to improve outcomes in expected longer-term survivors utilizing dose escalation have been evaluated [6, 7, 9, 10, 32, 33]. In the whole-brain era, 70 Gy was not associated with improved survival compared to 60 Gy [6]. Radiosurgical [10] and interstitial radiotherapy [9] boosts were also evaluated prospectively prior to the incorporation of temozolomide as standard therapy and were not found to be beneficial. However, with the improvements in outcomes seen with the addition of temozolomide, which is believed to function as a radiosensitizer, and the improvements in advanced imaging such as perfusion MRI and PET [34, 35], interest in dose escalation has been renewed. A dose escalation retrospective analysis [33] with TMZ using conventional MRI to determine target volumes did not show a survival benefit or a reduction of in-field failures, but did show tolerable doses up to 78 Gy with only 8% experiencing RTOG grade 3 acute CNS toxicity and 0% grade 4. Another recent study [32] showed that dose escalation to the MRI contrast-enhancing lesion of up to 75 Gy in 30 fractions decreased central recurrences, and did not cause radiation necrosis or an increase any late CNS toxicities. Confirmatory prospective clinical trials are currently underway (NRG-BN001). In addition, metabolic and biologic imaging is currently being evaluated to guide high-dose radiotherapy in prospective trials (NCT01991977).

Opportunities for particle therapy in GBM

The potential clinical benefit of particle therapies in the management of patients with GBM lies in the physics. The physical properties of charge particle beams that are useful clinically are primarily twofold: (1) charge particle beams have finite path lengths and (2) charge particle beams concentrate the majority of their dose at the end of their path length with little "exit dose" beyond the finite path (Fig. 1). Thus, the majority of the dose in a given charge particle beam can be concentrated into the target more effectively than with photon beams, while at the same time reducing radiation exposure to the surrounding normal tissue, as shown in Fig. 2.

A few specific particles have been investigated over the last several decades for potential utility in the management of glioblastoma. The oldest of these is a complex system known as boron neutron capture therapy (BNCT). This technique utilizes nuclear capture and fission of boron-10 that when irradiated with low energy neutrons will produce high linear energy transfer (LET) alpha particles and recoiling lithium-7 nuclei. The methodology relies upon localization of boron into target tissues such that the cytotoxic product of high LET alpha particles and lithium nuclei will injure only those desired tumor cells [38]. Two significant developments in BNCT have redefined the technique

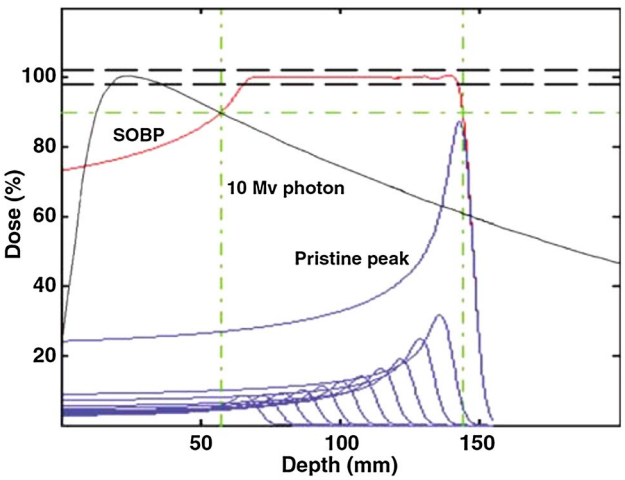

Fig. 1 Depth–dose distributions for a spread-out Bragg peak for a proton beam (SOBP, *red*), its constituent *pristine Bragg peaks* (*blue*), and a 10 MV photon beam (*black*). The SOBP dose distribution is created by adding the contributions of individually modulated *pristine Bragg peaks*. The penetration depth, or range, measured as the depth of the distal 90% of plateau dose, of the SOBP dose distribution is determined by the range of the most distal pristine peak (labeled 'Pristine peak'). The modulation width, measured as the distance between the proximal and distal 90% of plateau dose values, of the SOBP dose distribution is controlled by varying the number and intensity of *pristine Bragg peaks* that are added, relative to the most distal pristine peak, to form the SOBP. The *dashed lines* (*black*) indicate the clinical acceptable variation in the plateau dose of 72%. The *dot–dashed lines* (*green*) indicate the 90% dose and spatial, range and modulation width, intervals. The SOBP dose distribution of even a single field can provide complete target volume coverage in depth and lateral dimensions, in sharp contrast to a single photon dose distribution; only a composite set of photon fields can deliver a clinical target dose distribution. Note the absence of dose beyond the distal fall-off edge of the SOBP. Used with permission from reference [36]

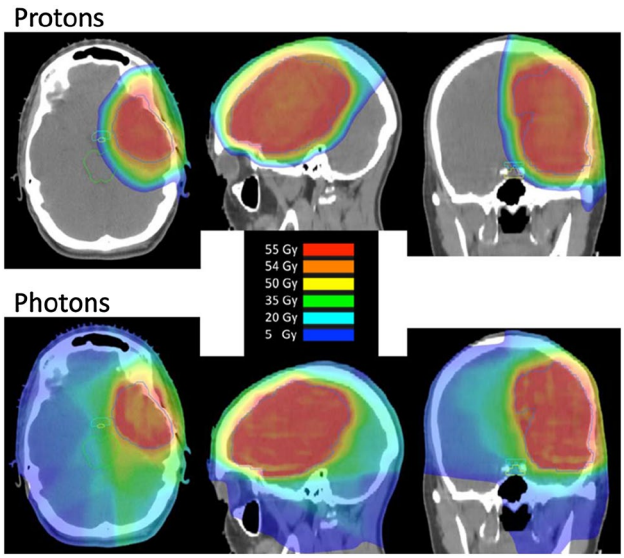

Fig. 2 Radiation dose distributions for proton therapy versus photon therapy for a glioma of the left temporal lobe. While both plans deliver essentially equivalent coverage of the tumor, the proton-based plan yields much lower integral radiation dose to the normal brain. Used with permission from reference [37]

today. One key component is an improved boron compound, boronphenylalanine (BPA), which is more selectively taken up by GBM cells. The second significant evolution has been the transition from use of low energy thermal neutrons that typically required an intraoperative setting to achieve target tissue irradiation to current preference of epithermal neutrons which achieve deeper tissue penetration and thus enable irradiation of more deep seated tumors and in a nonoperative setting. In a contemporary cohort of 23 newly diagnosed glioblastoma patients treated with BNCT in Tokushima, Japan, median overall survival was 19.5 months with failure occurring distantly in 33% of patients [38]. Similar single institutional experiences with BNCT and comparable survival to that seen with standard photon radiation with temozolomide are reported from Sweden [39], Osaka, Japan [40] and Harvard/MIT [41]. Because of the complex resources and expertise to deliver BNCT, the experience remains limited but is steadily growing at multiple centers.

Protons are the particle associated with the greatest clinical experience and development. Photon dose escalation in the management of GBM has established survival benefit up to 60 Gy, as described above. Further dose escalation with incorporation of proton therapy to 90 Gy (radiobiologic effect [RBE]) has improved survival with median survival of 20 months in a small prospective study of 23 patients but at the cost of increased significant normal brain tissue toxicity [42]. Hyperfractionated combined photon and then proton irradiation to 96.6 Gy(RBE) in 20 patients achieved median survival of 21.6 months with acceptable toxicity [43] that with time clearly was associated with radiation necrosis but at least limited to the targeted region, leaving the unaffected part of the brain well preserved [44]. Current investigation underway through the NRG (BN001; ClinicalTrials.gov NCT02179086) incorporates far more advanced imaging, treatment planning and delivery system, including intensity modulated proton therapy with pencil beam scanning technique, with the hypothesis that better tumor definition with far more conformal therapy may offer a survival benefit with a lower toxicity tradeoff. These newly diagnosis GBM patients are randomized between standard of care concurrent temozolomide with 60 Gy fractionated photon radiation therapy versus a dose escalated arm that requires employment of proton therapy in centers with this resource. The dose escalated arm is 75 Gy(RBE) in 30 fractions to the regions at greatest risk using intensity modulated delivery and 50 Gy(RBE) to a lower risk margin.

Carbon ions remains the least well developed particle therapy as it requires a yet more complex and costly particle accelerator with extremely limited experience with regards to treating glioblastoma. The relative biological effectiveness (RBE) is significantly higher than that of photons or protons (protons comparable but corrected for 10% greater RBE) with in vitro studies suggesting a RBE of 2–5 compared to photons. The best published clinical experience of carbon ions in glioblastoma patients comes from Chiba, Japan that included 32 glioblastoma patients treated with 50 Gy by photons at standard fractionation, followed by a carbon ion boost of 5 dose levels delivered over 8 fractions, ranging between 16.8 and 24.8 Gy(RBE) [45]. Median survival was 17 months with improved PFS associated with higher doses. Concurrent chemotherapy with nimustine hydrochloride was given. The current most notable prospective investigation is the CLEOPATRA trial (ClinicalTrials.gov NCT01165671) conducted in Heidelberg, Germany, a phase 2 study of newly diagnosed glioblastoma patients treated with concurrent temozolomide with photons to 50 Gy and then randomized to either a proton boost of 10 Gy(RBE) in 5 fractions or carbon ion boost of 18 Gy(RBE) in 6 fractions.

Understanding the limitations of and recognizing the opportunities for radiation therapy in the treatment of gliomas

Radiation therapy provides a measurable but limited benefit in the treatment of GBM. To date, attempts at dose escalation with photon- and particle-based radiotherapy have shown minimal, if any, improvement in survival. It is reasonable to ask if there is any justification to expending

further effort on refining fields, defining targets and increasing dose. The answer is "no"... based on the current standard of care utilizing surgery, conventional radiotherapy and temozolomide.

However, consider the notional benefit of a local therapy, such as radiotherapy, on survival as a function of the efficacy of systemic treatment [46], as shown in Fig. 3a. Without an effective systemic therapy, radiotherapy may offer a modest, albeit limited benefit, since most patients will die from progression throughout the brain. As the ability to control systemic disease improves, the net benefit of radiotherapy increases, as the control of disease locally would improve progression and overall survival. However, with improved efficacy of the systemic treatment, control of local and global disease improves to the extent that the benefit imparted by radiotherapy declines. At the desired extreme, if systemic therapy is able to affect a cure, radiotherapy would offer no benefit and the side effects of treatment would result in an adverse outcome versus systemic therapy alone. A therapy that permits dose escalation while decreasing normal tissue complications could significantly shift this curve upward (Fig. 3b).

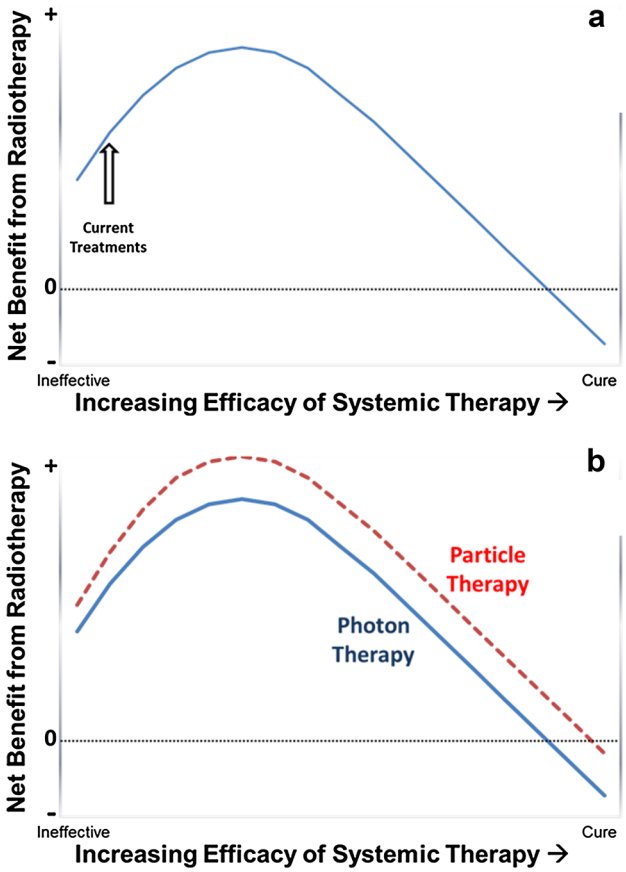

Fig. 3 **a** Notional impact of a conventional, highly conformal photon radiotherapy, an intervention that is moderately efficacious at controlling tumor local with moderate toxicity (*solid blue line*), on overall benefit of treatment of GBM (both local and systemic) as a function of the efficacy of systemic therapy. As the current efficacy of systemic treatments for GBM is quite limited, photon radiotherapy affords a limited (though significant) improvement in outcome; increasing the efficacy of systemic treatment would substantially improve the benefit from radiotherapy. **b** Introduction of particle therapy (*broken red line*) should improve the therapeutic ratio for the radiotherapeutic treatment of GBM, though the benefit would still be limited by the lack of efficacy of current systemic therapies. New, more effective systemic therapies in conjunction with particle therapy should further improve outcome

Future efforts to improve the therapeutic ratio with biology-guided target volumes, targeted radiotherapy, particle therapy, and radiosensitization should continue to help move the curve upward and the field forward until, hopefully, a systemic cure is found. While a detailed discussion of combined modality approaches is beyond the scope of this review, a variety of radiosensitization strategies have been and are being evaluated to enhance the efficacy of radiotherapy [47]. Furthermore, when used in combination with a more effective global brain treatment, a stereotactic radiosurgery boost could offer better local control that translates into improved outcome not observed in conventional treatment [10]. Developing more efficacious systemic treatments, including immunotherapy [48], alternating electric fields [49], disruption of tumor cell networks [50] and other approaches, as discussed elsewhere in this issue, will be key to deriving the maximum benefit from improved local therapies.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to report.

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