Image guidance in malignant gliomas: a focused strategy

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Practice Points

- Standard therapy for newly diagnosed glioblastomas includes maximal safe resection followed by fractionated radiation therapy with concurrent and adjuvant temozolomide.
- Following initial treatment, surveillance imaging with MRI is recommended 2–6 weeks after radiation, then every 2–4 months for the first 2–3 years, and then every 6 months following this.
- Disease recurrence may be indistinguishable from pseudoprogression within the first 3 months after completion of radiation. Neuroimaging modalities such as magnetic resonance spectroscopy, magnetic resonance perfusion, or brain PET may be utilized to distinguish necrosis from recurrence.
- Upon confirmation of local disease recurrence, maximal safe resection followed by image-guided hypofractionated radiation with concurrent bevacizumab should be considered.

SUMMARY The standard of care for malignant gliomas is maximal surgical cytoreduction followed by concurrent chemoradiation and adjuvant chemotherapy with temozolomide. Chemotherapy adds a modest improvement in overall survival. Unfortunately, tumor recurrence is the rule and typically occurs at the initial site of disease. Salvage reirradiation may be a useful approach in selected patients with recurrent glioblastoma. Image-guided technology coupled with highly conformal treatment planning techniques have allowed the safe delivery of high-dose radiotherapy in the setting of tumor recurrence. Defining the optimal combination of hypofractionated stereotactic radiotherapy with chemotherapy is under investigation. In this perspective, we examine the role of image guidance in malignant gliomas.

“The Spartans do not enquire how many the enemy are, but where they are.”

– Attributed to Agis II, 427 BC

During the ancient battle of Thermopylae, a unit of 300 Spartans held the mountain pass vastly outnumbered against a Persian force that modern historians estimate at 300,000. The accomplishment of the defenders is often highlighted as a symbol of fortitude and perseverance. The

small unit was nearly impregnable due to advantages in training and equipment, and good use of terrain with strategic positioning. Likewise, great strides have been made in cancer therapy with strategic positioning due to the development and implementation of image guidance in radiation delivery. Image-guided radiation therapy (IGRT) allows more focused, accurate and higher doses of radiation to be delivered to the target areas that need radiation most. IGRT

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now has an established role in a multitude of malignancies, including brain, lung and liver. IGRT enables the safe delivery of highly conformal radiation near dose-sensitive organs, even in the setting of prior radiation therapy. Here, we examine the role of IGRT in malignant gliomas.

Gliomas account for approximately 80% of all primary CNS malignancies and constitute a histologically and biologically diverse group of tumors. Of all high-grade gliomas, glioblastomas (GBMs) comprise 90%, and the incidence is approximately 10,000 cases per year in the USA [1]. These neoplasms exhibit aggressive behavior, with a disproportionate share of cancer morbidity and mortality, with almost equivalent rates of incidence and mortality. Despite advances in medical management, including imaging, surgical and radiation techniques, as well as biologic agents, the 5-year survival rates are estimated at 5%.

The current standard of care for GBM includes maximal surgical resection followed by adjuvant radiation concomitantly with temozolomide, an oral alkylating agent. The utility of radiation therapy is based on randomized trials performed in the 1970s that showed a 5-month survival advantage with adjuvant radiation [2,3]. Following conventional doses of 55–65 Gy delivered via conventionally fractionated radiation, the most common site of tumor recurrence is at the original site of disease. Since the 1970s, localized dose escalation has been evaluated in prospective trials via various radiation techniques that include protons, boron neutron capture, carbon ion therapy, low-dose brachytherapy and high-dose stereotactic brachytherapy [4–7].

In the prospective Phase II trial by Fitzek *et al.*, dose escalation was assessed with accelerated hyperfractionation on 23 patients with a combination of photon and proton therapy to 93.5 cobalt gray equivalent to small residual disease; approximately 45% of these patients had no evidence of postoperative residual disease. The median survival was 18.6 months after initiation of radiation, with median survival time and maintenance of Karnofsky performance score (KPS) ≥ 70 limited to 12 months. While central tumor was controlled, tumor recurred peripherally and virtually all patients required reoperation for radiation necrosis [4]. A number of other prospective trials that have been performed with various dose escalation strategies have been similarly disappointing. Although, conventionally, fractionated radiotherapy (RT)

plays an important role in the treatment of GBM, localized dose-escalation prospective trials unfortunately have failed to show a survival benefit.

Stereotactic radiosurgery (SRS) is another technique in which escalated dose may be delivered in a single session with millimeter accuracy. At its inception, rigid frame-based skull fixation enabled stereotactic target localization and the use of steep dose gradients with minimal dose to the surrounding normal tissues. Technological advances in image guidance have revolutionized the field of radiosurgery. The global definition of IGRT includes the utility of modern functional imaging technologies at any point in the radiation planning process to enhance target delineation. A more relevant and robust definition of image guidance is the use of in-treatment room imaging allowing for positional adjustments for set-up uncertainties and target motion, ultimately advancing quality assurance and precise radiation delivery [8]. The use of IGRT has significantly impacted radiosurgery delivery, facilitating frameless radiosurgery. The aim of these techniques is to improve the therapeutic window by increasing local tumor control and minimizing toxicity. This prompted Radiation Therapy Oncology Group 93-05, a Phase III trial whereby patients were randomized to postoperative adjuvant conventional RT to a total dose of 60 Gy with concurrent carmustine with or without upfront SRS boost of 15–24 Gy. Despite dose escalation, patterns of failure did not change and local failure was evident in 92.5% of all patients. The median survival was approximately 13.6 months, and there was no significant difference in median survival or cognitive function between the two groups [9]. The data suggest that RT dose escalation does not significantly impact overall survival (OS). A multitude of clinical trials aimed at identifying effective chemotherapy agents for GBMs also proved disappointing until the debut of temozolomide.

For decades, nitrosourea-based chemotherapy, which is lipid soluble and crosses the blood–brain barrier, was the focus of adjuvant chemotherapy. A meta-analysis of 12 randomized trials of adjuvant chemotherapy for GBM revealed a modest benefit in 1-year survival of 6% from a baseline of 35% [10]. A profound leap to chemotherapy was cemented with the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group Phase III trial by Stupp *et al.* in which 573 patients

with GBM were randomized to postoperative conventional RT to 60 Gy alone, versus same RT with concomitant daily low-dose temozolomide [11]. The 2- and 5-year OS rates improved from 10.9 to 27.2%, and 1.9 to 9.8%, respectively [12]. Overall median survival was significantly improved with the addition of temozolomide, from 12.1 to 14.6 months – an improvement of 2.5 months. The OS rates reported, however, were confounded by salvage chemotherapy after disease progression. Methylation of the promoter of the methyl guanine methyl transferase (MGMT) repair gene was both prognostic as well as predictive for response to temozolomide. For patients without methylation, the 2-year survival was 2% with RT alone, versus 15% with the addition of temozolomide. In contrast, patients with methylation had a 2-year survival rate of 24 and 49% [13]. Prospective studies aimed at validating the diagnostic accuracy of MGMT testing and predictive value of MGMT promoter methylation are ongoing. The median survival after tumor progression was dismal in both groups at 6.2 months, and response to salvage therapy was not recorded. Notwithstanding the benefits of temozolomide, most patients will develop tumor recurrence at the original disease site. Moreover, the number of long-term survivors will continue to increase, and salvage treatment in the setting of disease recurrence will become an important clinical quandary.

Radiation will take center stage in the salvage setting of tumor recurrence. Due to the infiltrative nature of GBM, reoperation is feasible in approximately a quarter of patients and carries a significant risk of morbidity and mortality [14]. Additionally, the benefits of surgical intervention are only revealed if coupled with additional adjuvant therapies such as radiation and/or systemic therapy. Reirradiation for recurrences is feasible due the high precision of IGRT, which optimizes targeting and tighter, more conformal margins. An alternative to single-fraction SRS is hypofractionated stereotactic RT (HFSRT), whereby radiation is given in multiple sessions, typically five or less. Both single-fraction SRS and HFSRT have been used successfully in the setting of recurrence. In the largest prospective SRS trial, which included 114 patients treated with a single fraction of median 16 Gy to a median tumor volume of 10.6 ml, survival was significantly improved when compared with historical controls, 23 months versus 12 months ($p < 0.0001$), and median progression-free survival (PFS) after

SRS was 4.6 months. The benefits to survival, however, did come at a cost. Radiation-induced necrosis was observed in 24.4% of the patients [15]. The efficacy of stereotactic RT in the setting of large tumor recurrence has been retrospectively evaluated by Cho *et al.*, who compared multiple-fraction HFSRT (median dose: 37.5 Gy in 15 fractions) versus single-fraction SRS (median dose: 17 Gy). In their series, the two treatment arms were not balanced, and favored the single-fraction SRS group. Patients with more unfavorable prognostic factors, including larger median tumor size of 25 ml (range: 4–115) versus 10 ml (range: 1–54), median age of 53 years versus 48 years, and a KPS of 60 (range: 40–80) versus 70 (range: 50–90), were treated with HFSRT. In spite of the unbalanced arms, median OS was comparable at 12 months for HFSRT versus 11 months for SRS ($p = 0.3$), while late toxicity was decreased 8% (two patients) for HFSRT versus 30% (14 patients) for SRS ($p < 0.05$) [16]. In another trial with similar design and more balanced treatment arms by Patel *et al.*, there was no difference in response to SRS (median dose: 18 Gy) or HFSRT (36 Gy in six fractions) ($p = 0.29$). Tumor response, however, predicted for survival after reirradiation, with a median survival of 15.8 months in responders, versus 7.3 months in nonresponders ($p < 0.05$). Median survival after salvage reirradiation with SRS was 8.4 months, and for HFSRT 7.4 months ($p = 0.42$) [17]. In order to capitalize on the radiobiological advantage of large doses and minimize toxicity, HFSRT using image guidance is an excellent recourse that will surely herald reirradiation in the salvage setting.

HFSRT fractionation schemes that have been used in the setting of GBM recurrence vary widely amongst and within institutional reports (Table 1). In one of the largest series of 53 patients treated with a median total dose of 30 Gy (20–60 Gy), with a median fraction size of 3 Gy (2–5 Gy), the median survival was 9 months after retreatment. While the median tumor size was notably large at 35.01 ml (3–204), retreatment was well tolerated and there was no evidence of acute or late >grade 2 toxicity [18]. In another series that included even larger lesions, median size of 47.7 ml (7.5–636), 53 patients were treated to a total dose of 36 Gy with small daily fraction sizes of 2 Gy. The median survival after retreatment was 8 months [19]. Multiple series, mostly retrospective, have shown similar findings with limited toxicity. In the study by

Table 1. Re-irradiation studies for recurrent glioblastoma using hypofractionated stereotactic radiotherapy.							
Study (year)	Patient (n)	Tumor size; ml (range)	Median dose/ fractions (n)	Concurrent chemotherapy	Late toxicity	Median OS (months)	Ref.
Combs <i>et al.</i> (2005)	53	47.7 (7.5–636)	36 Gy/12	–	None reported	8	[19]
Fokas <i>et al.</i> (2009)	53	35.01 (3–204)	30 Gy/10	–	None reported	9	[18]
Henke <i>et al.</i> (2009)	29	55 (0.9–277)	20 Gy/4	–	Two cases of necrosis	10.2	[20]
Lederman <i>et al.</i> (2000)	88	32.7 (1.5–150)	36 Gy/4	Paclitaxel	11 patients required reoperation (nine of these patients had evidence of necrosis)	7	[21]
Gutin <i>et al.</i> (2009)	20	34 (2–62)	30 Gy/5	Bevacizumab	Three cases of grade 3 toxicity attributed to bevacizumab. No cases of necrosis	12.5	[22]

OS: Overall survival.

Henke *et al.*, recurrent lesions were treated to a total dose of 20 Gy (4–5 Gy per fraction). There were two cases (6.8%) of necrosis and median OS was 10.2 months [20].

The value added with a combined treatment modality in the salvage setting with HFSRT and chemotherapy or molecular targeted agents is an active area of clinical research development [21]. In the prospective pilot trial by Gutin *et al.*, patients with recurrent GBM were treated with bevacizumab for one cycle (10 mg/kg intravenous), followed by HFSRT 30 Gy in 6 Gy fractions to median tumor size 34 cm³ (2–62 cm³), with additional bevacizumab until progression for a median total of seven cycles (2–30 cycles) [22]. The median PFS was 7.3 months, with a 6-month PFS of 65%. The median OS after retreatment was excellent at 12.5 months, with 1-year survival of 54%. There was no clinical or radiographic evidence of radiation necrosis; however, three patients discontinued treatment secondary to toxicity associated with bevacizumab – specifically, wound dehiscence, intratumoral hemorrhage and bowel perforation.

The addition of bevacizumab to HFSRT resulted in superior clinical outcomes as compared with HFSRT alone. VEGF inhibition enhances radiosensitization of tumor endothelium and normalizes tumor vessel architecture, facilitating the delivery of chemotherapeutic agents [23]. Current studies are focusing on elucidating the synergism of HFSRT in combination with bevacizumab and various chemotherapy agents in the setting of recurrence, including a randomized study evaluating combination with lomustine [101]. Translational research is focusing on further dismantling the biology of GBM tumors through a multitude of radiosensitizers such as PARP inhibitors [24] and novel molecular

targeted therapies such as Notch inhibitors [25]. The combination of these agents with HFSRT appears promising.

The outcomes with HFSRT and systemic agents compares favorably with other treatment modalities for recurrent malignant gliomas [26]. High-dose rate brachytherapy has proven to be a feasible treatment, but with high rates of toxicity. In the largest series examining high-dose rate brachytherapy, the reoperation rate was 46% [27]. The multi-institutional pooled retrospective of the surgically inserted Gliasite balloon catheter containing radioactive ¹²⁵I reported a median survival of 36.6 weeks – a modest improvement of 13 weeks when compared with surgery alone [28]. Others have used boron neutron capture therapy for glioma recurrences, reporting a median survival of 9.1 months versus a median survival time of 4.4 months for the same original high-risk recursive partitioning analysis (RPA) class [29]. Systemic agents as monotherapy have also been used in the setting of recurrence with limited efficacy. In a pooled study by Wong *et al.*, which included various chemotherapy agents from eight consecutive Phase II trials of 225 patients with recurrent glioblastoma, 9% of patients had a complete or partial response, and median PFS and OS were 10 and 30 weeks, respectively [30]. More recent studies examine temozolomide or temozolomide-containing regimens. While latest studies include alternate dosing regimens including rechallenges of 1 week on/1 week off and metronomic continuous dosing, the most robust data published to date utilize standard-dose temozolomide. In a large multicenter Phase II study of 225 patients randomized to standard-dose temozolomide versus procarbazine, while 6-month PFS was improved at 21 versus 8% (p = 0.008), there was no significant improvement

in median survival with temozolomide ($p = 0.33$) [31]. Bevacizumab has also been studied as monotherapy or in combination with other systemic agents such as irinotecan or in combination with kinase inhibitors [32]. The combination of bevacizumab with irinotecan resulted in a median PFS and OS of 20 and 40 weeks, respectively. In summary, median OS with HFSRT and combination chemotherapy is over 10 months, versus 8 months with systemic treatment alone.

In spite of the multitude of published studies evaluating response of recurrent gliomas to various therapies, most trials are uncontrolled and assume a homogeneous patient population. In the setting of newly diagnosed malignant glioma, factors such as extent of resection, age, Mini-Mental State Examination and performance status have been shown to be prognostic for survival in the RPA by the Radiation Therapy Oncology Group [33]. RPA retained overall prognostic significance in patients receiving temozolomide, and patients in prospective trials are now stratified [34]. Similar analysis in the recurrent setting identified initial histology of GBM, KPS ≥ 80 , age < 50 years and extended corticosteroid use over 4.4 months as prognostic for survival [35]. The ideal candidates for retreatment have good performance status and minimal steroid use, with tumor volumes amenable to HFSRT. Since patient inclusion criteria are not uniform amongst published trials, including those for HFSRT, selection bias may influence reported differences in survival outcomes. Moreover, the radiation trials use different radiation fractionation schemes and tumor volumes,

which introduce other variables. Randomized controlled trials should be performed to further elucidate the true impact of every treatment method, including HFSRT.

Conclusion & future perspective

Currently, GBM remains an incurable disease with devastating consequences to those afflicted. In comparison with most treatment modalities, salvage HFSRT is an effective treatment and has shown great improvements in OS. Medicine is entering an era of personalized and tailored medicine. Chemotherapy agents such as temozolomide preferentially benefit patients who have MGMT methylation and carry a better prognosis. Prospective studies have shown superior outcomes with salvage HFSRT, doubling the survival of patients with recurrent tumors, without the toxicity associated with radiosurgery. HFSRT using image guidance should be an integral component of glioma treatment, and cancer research funding should include continued support for advances in radiation delivery and randomized controlled trials.

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