Published in final edited form as:

Expert Rev Anticancer Ther. 2016 ; 16(3): 347–358. doi:10.1586/14737140.2016.1143364.

External beam re-irradiation, combination chemoradiotherapy, and particle therapy for the treatment of recurrent glioblastoma

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SUMMARY

Glioblastoma is a common aggressive primary malignant brain tumor, and is nearly universal in progression and mortality after initial treatment. Re-irradiation presents a promising treatment option for progressive disease, both palliating symptoms and potentially extending survival. Highly conformal radiation techniques such as stereotactic radiosurgery and hypofractionated radiosurgery are effective short courses of treatment that allow delivery of high doses of therapeutic radiation with steep dose gradients to protect normal tissue. Patients with higher performance status, younger age, and longer interval between primary treatment and progression represent the best candidates for re-irradiation. Multiple studies are also underway involving combinations of radiation and systemic therapy to bend the survival curve and improve the therapeutic index. In the multimodal treatment of recurrent high-grade glioma, the use of surgery, radiation, and systemic therapy should be highly individualized. Here we comprehensively review radiation therapy and techniques, along with discussion of combination treatment and novel strategies.

Keywords

Radiation therapy; high grade glioma; glioblastoma; stereotactic radiosurgery

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Introduction

Glioblastoma (GBM) is the most lethal primary central nervous system (CNS) malignancy in adults with nearly 100% mortality. Median survival, despite best radiation therapy (RT), surgery, and chemotherapy, is only 15 months, and 5-year overall survival (OS) is less than 10% [1]. The addition of RT to surgery has improved OS from 4 months to nearly 12 months [2]. Most patients will have recurrence within approximately 8 months after primary treatment [3,4]. Patients with recurrent disease have very poor prognosis despite multimodality therapy. There is little consensus on how best to treat recurrent GBM based on practitioner and institutional practice patterns and the heterogeneous nature of recurrent disease [5].

Despite difficulties in managing patients with recurrent disease, continued treatment is necessary to manage symptoms and potentially extend survival. A variety of treatment strategies are in practice to manage these patients, sometimes utilizing maximal safe resection, re-irradiation strategies, chemotherapy, targeted agents, and combinations of all these approaches. As such, treatment is highly individualized and multiple clinical trials are under way to establish best practice. Key decision factors in retreatment include patient performance status, age, tumor size, location (eloquent vs. not non-eloquent), and steroid use. A subset of patients with poor performance status and diffuse recurrence may instead be offered best supportive care [6].

Salvage re-irradiation has been utilized in the treatment of recurrent disease for years. Re-RT as a sole modality in recurrent disease allows for a 6-month progression-free survival (PFS) between 28 and 39% with palliative intent, or even 10-month median OS using a single-fraction approach [7,8]. Modern high conformal techniques, including stereotactic and hypofractionated treatments, potentially improve the therapeutic ratio by delivering high biologically equivalent dose while reducing high-dose RT to normal brain tissue. External beam approaches avoid the morbidity of resection and intracavitary or interstitial brachytherapy.

We present a comprehensive review of RT approaches in re-irradiation for recurrent GBM focusing on conventionally fractionated RT, hypofractionated stereotactic radiosurgery (FSRT), stereotactic radiosurgery (SRS) alone, combination treatment with RT and systemic therapy, and palliative RT. We also offer insight to where the treatment of recurrent disease will focus with other advanced RT techniques and concurrent treatment with systemic agents.

Fractionated radiation therapy

Fractionated radiation therapy (FRT) represents the earliest used method in re-irradiation of GBM. A very favorable aspect of FRT is that by using a smaller fraction size compared to stereotactic doses, it may be possible to use larger treatment volumes. However, without highly conformal approaches, the cumulative dose can get very high and lead to significant toxicity.

Veninga et al. reported on 42 patients who received re-irradiation therapy for recurrent primary brain tumors. Median dose of the first and second courses of RT was 50 and 46 Gy, respectively, with at least 1 year in between treatment courses. Treatment was delivered using opposing lateral beams or a wedged pair. There was clinical improvement in nearly one quarter of patients, median PFS was 8.6 months, and OS was 10.9 months. The majority of patients had preserved reasonable quality of life (QoL). WHO performance status, treatment interval between courses of RT, tumor histology, and response to initial treatment were independent prognostic variables for survival[9].

Kim et al. reported on 20 patients re-irradiated at the University of Michigan with three-dimensional conformal radiation therapy (3D-CRT). Patients received a median 59.4 Gy before a median of 38 months (range 9 months to 19 years) before re-irradiation. Patients were unsuitable for both brachytherapy and radiosurgery. Mean re-irradiation dose was 36 Gy. 1-year actuarial OS was 26% with median survival of 9 months. 68% of patients had stabilization of disease or regression[10].

Pulsed reduced-dose-rate RT (PRDR) is another fractionation technique used for re-irradiation. 103 patients with recurrent glioma requiring re-irradiation (86 with WHO Grade IV disease) were treated with PRDR at a dose rate of 0.0667 Gy/min to a fraction size of 1.8–2.0 Gy fractions to a total median dose of 50 Gy. 2-cm margins were used around the contrast-enhanced T1 MRI volume. Median time from first course to re-treatment was 14 months. Median survival for patients with Grade IV disease was 5.1 months after retreatment[11]. A second series utilizing PRDR used 54 Gy in 27 fractions re-RT with a median planning target volume (PTV) of 424 cm³ with concurrent bevacizumab. The median OS was 6.9 months and there were no symptomatic grade 3 and 4 toxicities[12].

Although FRT may be useful in large-volume re-irradiation with diffuse disease and patients can rapidly start treatment, radiation oncologists should strongly take into account normal tissue tolerances in retreatment and may even consider easily implemented techniques such as PRDR.

Fractionated stereotactic radiosurgery

Fractionated stereotactic radiosurgery (FSRT) offers the most robust body of literature in practice, mostly retrospective, but with several prospective trials and others under way. FSRT offers practitioners the ability to reduce treatment margins and volumes with more conformal treatment compared to even primary treatment, and allows for higher dose per fraction treatment. There is less concern for potential severe side effects than may be with SRS alone given reduced dose per fraction. FSRT requires the use of 3D-CRT or intensity-modulated radiation therapy (IMRT) to accurately estimate the normal tissue dose. Also required is the use of custom immobilization with a head mask to safely deliver treatment.

Combs et al. reported on a total of 172 patients with recurrent glioma, 54 of which had Grade IV disease. All were treated with FSRT to a median dose of 36 Gy (range 15 to 62 Gy) with a median fractionation of 5×2 Gy/week. A 0.5–1 cm margin was added to the T1-weighted contrast-enhancing region on MRI for treatment planning purposes, with a median

PTV of 49.3 cm³. No patients received concurrent systemic therapy. Median follow-up for patients with GBM was 7 months, with median OS (from diagnosis) of 21 months and 8 months OS after completing FSRT [13]. One patient in the entire series developed necrosis. It is noted that in this series, stereotactic techniques were used but treatment was not hypofractionated.

Several early series reported on hypofractionated (>2 Gy per fraction) radiotherapy. Laing et al. treated 22 recurrent glioma patients with 30–50 Gy in 6–10 fractions in a phase I/II study. Patients received median 55 Gy as part of initial glioma treatment. Median OS after completion of FSRT was 9.8 months without significant acute toxicity. However, five of the 22 patients developed late radiation toxicity with steroid-responsive neurologic compromise[14]. This was presumed to be due to radiation toxicity; however, it is difficult to determine recurrence from radiation necrosis.

Hudes et al. reported on 25 lesions in 20 patients with either persistent or recurrent GBM. Primary RT was median 60 Gy and the time between completing primary treatment and initiating salvage RT was median 3.1 months (range 0.7–45.5 months). In this phase I dose escalation study, treatment was 24 Gy/3 Gy fractions up to 35 Gy/3.5 Gy fractions. There was no grade 3 toxicity, median survival after re-RT was 10.5 months, 45% of patients improved neurologically, and 60% had decreased steroid requirements[15]. Another series reported on 88 patients treated with FSRT with four weekly treatments of median dose 6.0 Gy per fraction and concurrent paclitaxel chemotherapy. Median tumor volume was 32.7 cm³. Median OS was 7 months with acceptable toxicity, and 40% of patients had stable disease. Patients with smaller tumor volumes (<30 cm³) survived longer than those with large volumes[16].

Fogh et al. published a large series of patients with recurrent GBM treated with FSRT using moderate hypofractionation, median 35 Gy in 3.5 Gy fractions. Median survival after treatment was 11 months. An important finding was craniotomy and chemotherapy did not add have significant additional benefit. Younger patients, smaller gross tumor volume (GTV), and interestingly shorter interval to recurrence were associated with improved survival. In this study, the GTV was defined at the contrast-enhanced lesion on T1-weighted imaging without edema and equaled the PTV[17].

Multiple additional series also report on the efficacy of FSRT, but in combination with systemic therapy[18–21]. The concomitant use of systemic therapy and targeted agents to improve efficacy or reduce toxicity is a critical area of study. The most studied agent is bevacizumab, which will be discussed in detail later in this article.

FSRT represents a well-tolerated and excellent treatment option in re-irradiation. However, there remains no consensus on the optimal target volume. Most institutions will define the GTV as the T1-weighted contrast-enhancing lesion, generally less than 5 mm or smaller margins are used in most series to create the PTV.

SRS

SRS is capable of delivering a single high dose of radiation to a tumor with capacity to spare healthy surrounding normal tissue, due to the very steep dose gradient generated by conformal treatment. SRS can be considered in patients who have small volume and well-defined disease[22].

Kong et al, in a single-institution prospective cohort, evaluated 114 recurrent malignant gliomas patients who received salvage SRS. The median tumor volume was 10.6 cm³ and the median prescription dose was 16 Gy. Note that this generally represents small-volume disease and corresponds roughly to a 2.5 cm tumor. For patients with GBM, the median PFS after SRS was 4.6 months, which represents a short interval to progression. The authors compared their results against historical controls and they observed that SRS treatment was related to significantly long survival time in patients with relapsed GBM (12 months vs. 23 months; $p < 0.0001$). SRS was well tolerated, but radiation-induced necrosis was seen radiographically in 24.4% of patients. However, only four patients underwent surgical resection for suspicious radiation-induced necrosis[23].

Shrieve et al. assessed 86 patients with recurrent GBM treated with SRS. The median peripheral dose was 13 Gy and the median tumor volume was 10.1 cm³. Median actuarial OS was 10.2 months. Survival rates at 12 and 24 months were 45% and 19%, respectively. The subgroup analyses demonstrated that smaller tumor volume and younger age were associated with improved outcomes [24].

Combs et al. studied 32 patients with recurrent GBM who underwent salvage SRS. The median interval between first irradiation and SRS was 10 months and the median dose of SRS was 15 Gy. Median OS and median PFS after SRS were 10 months and 7 months, respectively. The OS at 6 and 12 months after re-irradiation were 72% and 28%, respectively. No grades 3 and 4 acute and late toxicities were detected [7]. The survival rates outperformed those in other series, and this may represent better patient selection.

Pinzi et al. performed a retrospective analysis of 128 patients treated with salvage SRS (single-fraction: $n = 42$; multi-fraction: $n = 86$). Median doses of single- and multi-fraction treatment were 15 Gy and 23 Gy, respectively. No acute high-grade toxicity was observed and only seven patients had radiation necrosis. Median survival after SRS was 11.5 months. OS after 1, 2, and 3 years following SRS were 48, 20, and 17%, respectively [25].

Multiple series have been published on the use of single-fraction SRS as treatment for recurrent GBM. The toxicity profile is acceptable and the treatment outcomes are in line with even longer courses of therapy. As previous series have shown, the best candidates for SRS for recurrent GBM are those with small-volume disease.

RT combined with systemic therapy

Bevacizumab is a humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF) shown to reduce cerebral edema and radionecrosis. It extends PFS in primary treatment, without an effect on OS. Since RT increases VEGF signaling, combining

the two modalities has been investigated for potential therapeutic synergy with promising results [26].

SRS combined with bevacizumab

Park et al. reported a case-control study of 11 patients treated with concurrent Gamma Knife (Elekta, Stockholm, Sweden) SRS with and without bevacizumab. The target volume was defined as the contrast-enhanced tumor volumes defined by high-definition MRI. The median tumor volume was 13.6 cm³ (range 1.2–45.1 cm³). The median prescription dose delivered to the tumor margin was 16 Gy (range 13–18 Gy), and the maximum dose varied from 26 to 36 Gy (median 32 Gy). Median OS was 18 months versus 12 months ($p = 0.005$), 6-month PFS of 73% versus 58% (p value not reported), and median PFS of 15 months versus 7 months ($p = 0.035$), for combined treatment versus Gamma Knife treatment alone, respectively [27].

Cuneo et al. published a retrospective series of 63 patients with recurrent WHO grade 3 or 4 malignant gliomas who failed initial salvage with chemotherapy and were subsequently treated with salvage SRS combined with multiple agents, including bevacizumab. The GTV was defined based on T1-weighted contrast-enhanced axial MRI images, occasionally with guidance by positron emission tomography. There was no further comment on PTV expansion. Patients with GBM who were treated with concurrent bevacizumab and SRS had a median OS of 11.2 months when compared with those receiving SRS without bevacizumab ($p = 0.005$). PFS was 5.2 months compared to 2.1 months, for patients treated with concurrent SRS with or without bevacizumab, respectively ($p = 0.014$). The 6-month PFS for patients treated with SRS with and without bevacizumab were 39.4% and 37.5%, respectively. SRS was well tolerated with only 12.7% of patients experiencing WHO grade 3 or higher toxicity. Notably, most patients were heavily pretreated prior to SRS and underwent further systemic therapy thereafter [28].

Both previous studies were retrospective reviews. Cabrera et al. published the results of a prospective trial with 15 patients with recurrent malignant gliomas treated with concurrent bevacizumab and either SRS (24 Gy or 18 Gy if lesion measured <2 cm or 2–2.9 cm, respectively) or hypofractionated stereotactic radiotherapy (25 Gy in five fractions if lesion measured 3–5 cm). GTV was defined as the contrast-enhancing lesion on T1-weighted MRI. GTV was uniformly expanded by 1 mm to create the PTV. The first dose of bevacizumab (10 mg/kg intravenously) was administered 24 hours before the start of SRS, and the second dose of bevacizumab was given 2 weeks after the first dose. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) suggested a decrease in tumor perfusion and permeability following SRS without negatively affecting neurocognition or Karnofsky performance status (KPS). Median survival was 14.4 months and the median PFS was 3.9 months [26].

Hypofractionated and conventionally fractionated RT and bevacizumab

We see that SRS combined with bevacizumab therapy can offer a reasonable toxicity profile and potentially improved PFS, or even OS. FSRT and conventionally fractionated treatment

allow physicians to potentially treat larger volumes. A prospective study from Memorial Sloan Kettering Cancer Center (MSKCC) evaluated the efficacy and safety of FSRT (30 Gy in five fractions) with concurrent bevacizumab in patients with recurrent high-grade gliomas. GTV was designed based on the contrast-enhancing lesion. The planning treatment volume PTV typically was defined as the GTV plus a 5-mm margin. Patients received bevacizumab 10 mg/kg every 14 days on days 1 and 15 of 28-day cycles until treatment failure. Of the 20 patients with GBM, the 6-month PFS was 65% and median OS was 12.5 months. Importantly no radionecrosis was reported in patients who had received prior radiation [29]. The median tumor volume was 34 cm³, which is relatively large compared to other series. In addition, the PFS and survival rates were excellent.

Flieger et al. reported the salvage treatments at a single institution of high-grade glioma patients with histologically or radiographically confirmed recurrent disease. Of the 57 patients who received concurrent bevacizumab and RT (36 Gy in 12 fractions), there was median OS of 8.6 months and a 6-month PFS of 42.1%. This was a significant improvement when compared with the cohort of patients treated with re-irradiation alone, who demonstrated a median OS of 5.7 months and 6-month PFS of 14.3% ($p = 0.003$). Patients were able to tolerate combined treatment well, with only four (7%) exhibiting grade 3 toxicity. Bevacizumab was administered at 10 mg/kg IV on day 1 and day 15 of RT [30].

Niyazi et al. retrospectively evaluated 30 patients with recurrent high-grade malignant glioma treated with 36 Gy in 18 fractions with or without bevacizumab. Six-month PFS was 72% for re-irradiation with bevacizumab and 24% with re-irradiation alone ($p = 0.045$).

Pretreatment MRI was fused with the treatment planning CT, and the GTV was delineated based on the T1-weighted contrast-enhancing lesion. The GTV typically did not exceed 5 cm in the longest axis. A 10-mm maximum margin was added to the GTV to create the PTV. Additional [18F]fluoroethyltyrosine positron emission tomography (FET-PET) information was used to modify the GTV if necessary. Bevacizumab was administered at 10 mg/kg IV on day 1 and day 15 of RT [31].

This combination of FSRT combined with bevacizumab is being further evaluated in RTOG 1205 with bevacizumab, with or without 35 Gy in 10 fractions of RT. The primary endpoint is OS. MSKCC, along with the University of California at San Francisco (UCSF), is conducting a phase I study of FSRT in combination with bevacizumab (MSKCC 11-057). The primary aim is to determine the maximum tolerated dose of FSRT. The RT treatment is three fractions of 9 Gy, escalating up to three fractions of 14 Gy each. Tumors must be less than 40 cm³. Accrual is continuing on both of these important studies.

SRS combined with temozolomide

Temozolomide (TMZ) is an oral alkylating agent used first-line in the treatment of GBM. TMZ exploits epigenetic silencing via methylation of the *MGMT* gene. Patients with *MGMT* promoter methylation benefit from TMZ. Level I evidence indicates that addition of TMZ to radiation in the primary treatment of GBM is beneficial, and has minimal additional toxicity [2,32,33].

Conti et al. reported on 23 patients undergoing Cyberknife SRS (Accuray, Sunnyvale, California, USA) to median dose 20 Gy in two fractions. Twelve patients received concurrent TMZ. The median OS, 6-month PFS, and median time to progression were 12 months versus 7 months ($p < 0.01$), 66.7% versus 18% ($p = 0.03$), and 7 months versus 4 months ($p = 0.01$), for combined modality treatment versus SRS alone, respectively. GTV was defined as the contrast-enhancing area. PTV was defined by FLAIR, magnetic resonance spectroscopy imaging, and perfusion weighted imaging and diffusion weighted imaging. There were three RT dose levels: 15–16 Gy/single fraction for PTV <10cc; 20 Gy in two fractions for PTV ranging between 10 and 20cc; 24 Gy in three fractions or 25–27.5 Gy in five fractions for PTV >20 cc. TMZ was administered 75 mg/m²/day for 21 days every 28 days [34].

TMZ is already the standard of care in primary treatment of GBM, and we summarize in Table 1 the elected studies combining RT and TMZ in retreatment showing that it has activity in patients requiring salvage treatment.

Palliation

Treatment of recurrence should be based on a multi-disciplinary team with individualized treatment based on patient age, performance status, histology, extent of initial resection, type of and response to initial therapy, time since diagnosis, interval free of disease, and whether the recurrence is local or diffuse[42,43]. However, physicians must discuss with patients that GBM is almost uniformly fatal, and retreatment is not always advised. Despite increasing publications, there is little high-quality evidence toward best practices in recurrent disease[44].

Palliative re-irradiation can be offered as an exclusive treatment modality and can provide median survival of 26–60 weeks and a freedom from recurrence time of 20–28 weeks. Retreatments, generally with palliative intent, may be considered for patients presenting with long interval since prior RT and/or recurrence outside the prior RT field and/or good response to prior RT, KPS ≥ 70, and younger age[8]. As palliative retreatment is a non-curative approach, outcomes analysis should focus on the patient's clinical course, QoL, side effects, and surrogate endpoints such as reduction in corticosteroid use. Little data is available on these endpoints.

Veninga et al. reported the use of external-beam RT in 17 patients with GBM (29 patients with glioma) after re-resection. Median re-irradiation dose was 46 Gy at 2 Gy per fraction. Clinical improvement was seen in 24% of patients and median time to progression was 4.3 months[9]. Nieder et al. reported their results on a group of 24 patients treated with EBRT to 45 Gy. None underwent re-resection and PFS6 was 39%. Improvement or stabilization in performance status was in 60%, with 59% of patients reducing corticosteroid dose[8]. Although survival remains poor, palliative treatment should be considered to improve clinical symptoms and reduce steroid use. In Table 2, we summarize contemporary studies on GBM re-irradiation with conformal EBRT using stereotactic techniques.

A recent meta-analysis showed that any radiation, including FRT, FSRS, or SRS, for GBM could maintain or improve neurological status, reduce steroid use, and possibly improve QoL. The group also reports that retreatment can improve tumor control. Previously published data from nearly 300 retreated GBM patients show 6-month PFS of 28–39% and a 1-year OS of 18–48%. When conventional or fractionated stereotactic RT were used, serious late toxicities were still rare as long as total dose was limited to 30–35 Gy and caution was taken in precisely creating target volumes[8].

Offering supportive care is critical in discussion when recommending management of patients with recurrent or progressive GBM. Patients presenting with low performance status, older age, or with significant toxicity from prior treatment may be optimally treated with best supportive care.

Toxicity

Toxicity of re-irradiation therapy can be significant if normal tissue tolerances are not respected and larger margins are used. The radiation course used should be highly individualized to each patient's location of recurrence, size of recurrence, and estimated survival. Acute toxicity in most re-RT regimens is generally mild and generally includes resolving fatigue, likely permanent alopecia at areas of field entry and exit, and resolving radiation dermatitis. More difficult to manage might instead be pre-, concurrent, or post-treatment steroid use and subsequent side effects such as weight gain, myopathy, psychomotor agitation, and gastritis.

Radionecrosis is the most important late adverse effect of retreatment. Diagnosis is based on abnormal MRI or PET scan findings, coupled with neurologic deterioration. The risk of radiation necrosis is a possible adverse outcome in upfront treatment that utilizes doses of 60 Gy or more. Re-irradiation adds to that risk, particularly if there is a short interval between primary treatment and salvage treatment. Clinically, though, radionecrosis is less of a concern or management issue than recurrent disease. The rate of severe late complications remains relatively low in FSRT, particularly compared to early data in re-irradiation with SRS [17]. Early SRS studies indicate severe late complication rates in up to 40% of patients[47,48]. Agents, such as bevacizumab, may mitigate this risk of radionecrosis. As discussed in detail earlier in the manuscript, a study from MSKCC prospectively evaluated bevacizumab with FSRT and of the 20 patients with GBM there were no cases of radionecrosis and only one case of CNS hemorrhage. In three patients who underwent reoperation and two who underwent autopsy, there was no significant pathologic evidence of radionecrosis. Further study is needed to clarify the mechanism for this effect, for example radiosensitization effect to allow for efficacy, or decrease in vascular permeability allowing adequate vascularity in the tumor bed[18].

Flickinger et al. used different versions of the integrated logistic formula to estimate the probability of necrosis at different SRS doses. Dose–volume curves to estimate a 3% risk of necrosis were generated[49]. Mayer et al. found that the normalized total doses of conventional re-irradiation were lower than those used in either SRS or FSRT[50]. There was no association of the time interval between treatment courses and risk of radionecrosis.

Radionecrosis occurred at normalized total doses >100 Gy[51]. Stereotactic and conformal techniques have generally allowed for safer re-treatment with a satisfactory risk of radionecrosis due to limiting normal tissue irradiation.

Ideally, we are able to bend the survival curve enough that we can evaluate late effects in long-term survivors, particularly neurocognitive effects and functional deficits. Patients may initially present with baseline deficiencies from direct tumor damage from the primary and recurrent tumor. Furthermore, patients are often treated with aggressive multimodality therapy including surgery, steroids, chemotherapy, and radiation, each of which may confound determination of any decline from re-irradiation[52]. This is compounded by inherent challenges in various neurocognitive assessments to accurately represent changes. Functional imaging, such as dynamic susceptibility-enhanced perfusion MRI, diffusion imaging, and PET scan may identify early normal tissue changes that may lead to later functional and neurocognitive deficit [53,54].

Particle therapy and novel combinations

Advances on drug therapy and characterization of molecular targets have raised the hope of improving outcomes in recurrent GBM. However, the role of additional chemotherapy or targeted agents is not very well defined, both as monotherapy and in combination therapy. Newer agents would need to be prospectively tested against re-irradiation alone, or in combination.

Bevacizumab is an intravenous humanized anti-VEGF monoclonal antibody that impairs angiogenesis via targeting the VEGF ligand and also may decrease the permeability of tortuous and leaky capillaries. Induction of VEGF by ionizing radiation enhances blood vessel protection and subsequently tumor resistance. Anti-VEGF therapies block this protection and enhance the effect of therapeutic radiation[55,56]. Activity has been seen in a number of cancers with combined modality therapy[57].

The most promising systemic options for recurrent GBM include bevacizumab, either in combination with chemotherapy and/or radiation. Nitrosoureas and a second course of TMZ are options for patients who are not candidates for therapy with bevacizumab or who have progressed on bevacizumab[58]. Combining the two modalities (radiation and bevacizumab) is under investigation for therapeutic synergy. The Radiation Therapy Oncology Group (RTOG) is evaluating bevacizumab with or without hypofractionated RT in patients with recurrent GBM in a phase II trial (ClinicalTrials.gov, number NCT01730950). This protocol examines patients who will receive bevacizumab alone every 2 weeks, with or without radiation 35 Gy in 10 fractions. Proton therapy (PT) is allowed. The primary endpoint is OS and the estimated completion date is July 2016. In Table 2, we present contemporary series on combination radiotherapy with TMZ and bevacizumab, which are the best-studied systemic therapies in conjunction with re-irradiation.

The University of Maryland is performing a pilot study on Optune (NOVOTTF-100A, Novocure, Jersey Isle) plus bevacizumab plus FSRT in bevacizumab-naïve recurrent GBM patients. The estimated completion date is December 2016 (ClinicalTrials.gov, number

NCT01925573). Optune functions by delivering a regional anti-mitotic therapy with tumor treating electrical fields. In a phase III randomized trial of the device versus chemotherapy in patients with recurrent GBM, PFS6 was improved from 21.4% in Optune patients versus 15.1% in active chemotherapy patients ($p = \text{NS}$). OS was equivocal[59]. MSKCC and collaborators are assessing dose escalation in hypofractionated stereotactic radiotherapy with bevacizumab in the treatment of recurrent malignant gliomas (ClinicalTrials.gov, number NCT01392209), with results potentially available in July 2016.

Advances in planning technology including volumetric arc therapy (VMAT) and IMRT, and RT techniques, such as SRS and FSRT, have allowed RT to become an appealing treatment in recurrent GBM. However, large cumulative doses of RT (e.g. first course up to 60 Gy and re-irradiation to an additional 30–35 Gy), primary treatment, and re-irradiation have been associated with neurotoxicity and radionecrosis, with incidence from 0% to 20%[13,17,21,60,61].

PT for recurrent GBM is an option for treatment; however, it has never been compared to photon RT. Compared with photon therapy, PT has dosimetric advantages including nearly zero RT dose distal to the characteristic Bragg peak at the target. Since there is virtually no exit dose beyond the target, there is further reduction in the volume of previously irradiated brain tissue.

The potential for protons application in the CNS relies on its physical characteristics and the possibility to reduce the normal tissue complication probability (NTCP), thereby increasing the therapeutic index. Few studies have reported the safety and feasibility of PT re-irradiation. There are a limited number of recurrent GBM patients treated with proton therapy, and meaningful clinical endpoints require longer follow-up.

A small series from Indiana reported the use of PT on recurrent glioma. Twenty-nine patients were included and PT was generally well tolerated with a median survival of 7.8 months and a 10% crude rate of radiation necrosis[62]. Another series reported PT to recurrent brain tumor was feasible and effective[63]. A phase I/II protocol is currently ongoing at the University of Heidelberg and compares carbon ion (similar to PT, and even better, in dosimetric characteristics) RT to FSRT in patients with recurrent gliomas (ClinicalTrials.gov, number NCT01166308).

Desai et al. reported their single-institution retrospective data on 19 consecutive adult patients with recurrent large-volume glioma treated with proton re-irradiation. Population median age was 42 and median KPS 90. The PTV included MRI T2/FLAIR and contrast-enhancing abnormality. Median PTV volume of 224cc and median dose was 50.4 cGyE. Median OS was 12.3 months for bevacizumab-naïve patients and 9.4 months for all patients. One patient experienced grade 3 radiation necrosis for a recurrent brainstem glioma and a second patient had grade 2 radiation. These efficacy and safety data are quite promising and certainly require both longer follow-up and confirmatory clinical study[64].

Novel combination therapy with new radiotherapy techniques may improve the outcomes on recurrent GBM. Agents targeting the EGFR, PI3K/Akt/mTOR, and the glutamate pathways, among others, are under active investigation particularly in primary treatment. There are a

number of alternative treatment strategies such as radionuclide therapy, convection-enhanced delivery, and immunotherapy also under investigation[65–67]. However, there is a paucity of studies (<1% of all phase III oncology trials) combining novel targeted agents with RT, not just in this re-irradiation of GBM setting, but across all cancer types[57]. Exploiting improved dosimetry of advanced particle therapies may further spare normal tissue and reduce potential serious adverse events from retreatment. Although dosimetric studies suggest a reduction in the normal tissue dose, more studies must be conducted in patients to show clinical advantage with endpoints such as reduced neurocognitive dysfunction, reduced rates of radionecrosis, and improved PFS. There is a significant need to extend these novel combination and particle therapies with activity in the primary treatment setting, to the retreatment setting after initial therapy.

Expert commentary

GBM is a very aggressive primary tumor with high mortality. The majority of patients will progress after primary treatment. Re-irradiation therapy remains an excellent treatment option for patients with recurrent GBM. Surgery has a less-clear role given the diffuse and infiltrative nature of the disease. Systemic therapy is most often employed, but alone still does not often provide sufficient local control. RT has improved to deliver higher tumor doses and reduce high-dose treatment to normal tissue.

Hypofractionated and single-fraction courses offer the most conformal and convenient treatment schedules, but require smaller treatment volumes. This is compared to conventionally fractionated retreatment or PRDR schedules, which may accommodate larger treatment volumes. Steep dose gradients in stereotactic techniques allow for improved normal tissue sparing. Smaller target volumes and highly conformal treatment allow for favorable treatment outcomes without significant long-term toxicity, most notably radionecrosis. Generally, patients with better performance status (> 70), younger age, smaller target volumes, and longer time to re-irradiation will have improved survival. However, salvage treatment is still not curative, as virtually all these patients will fail.

We recommend treatment with hypofractionated, stereotactic approaches when feasible with patients with small-volume, well-defined disease, and otherwise good prognosis. Practitioners should be aware of various techniques and target volume definitions. Surgery may be considered for patients with well-defined and accessible lesions, but will likely require subsequent RT. Patients should be offered concurrent systemic therapy particularly bevacizumab if can be tolerated, or clinical trials when available to study the activity of combination therapy. Single-agent systemic therapy shows activity, but is likely insufficient as monotherapy. Patients with limited prognosis or expected to tolerate curative intent treatment poorly should be offered palliative therapy with fractionated radiation or best supportive care.

Key issues

- GBM is the most aggressive malignant primary brain tumor. The disease is nearly uniformly fatal. Virtually all patients will progress after primary treatment.

- Re-irradiation can be a treatment option and may be considered for patients presenting with long interval since prior RT and/or recurrence outside the prior RT field and/or good response to prior RT, PS $\leq$ 70, younger age. Multimodality treatment should be highly individualized.
- Creation of conformal target volumes must rely on MRI (contrast-enhancing (CE) lesion T1). Improvements in target volume delineation from integration of functional and biological imaging would enhance patient selection and possibly outcomes.
- With highly conformal treatments, the rates of radionecrosis, a serious late adverse event, remain generally acceptable. Acute toxicity is low.
- The safety and efficacy of combination treatment of RT with targeted agents and/or chemotherapy are under way. There are multiple promising studies under way to improve the therapeutic ratio.
- Best supportive care should be discussed with patients with poor prognosis or poor performance status. Palliative radiation can be discussed with patients to improve neurologic status and reduce steroid dependence.
- Most data are retrospective and are from single-institution series. High-quality level I evidence is required to compare treatments and offer best practices.

There is a significant need for an updated study of RT as many studies were conducted with now-outdated techniques, and most data are retrospective single-institution studies subject to the bias of each treating institution's practice patterns. We believe the largest clinical benefit will come from the study of combinations of RT with systemic therapy, particularly targeted agents. There is insufficient evidence to routinely recommend particle therapy, but dosimetric data shows promise in reducing normal tissue toxicity.

Five-year view

The most important advances in radiation treatment will likely be in emerging combinations of RT with chemotherapy or targeted agents. These combinations, including bevacizumab with hypofractionated treatment to be studied in RTOG 1205, aim to improve the therapeutic ratio of this otherwise progressive and uniformly fatal disease. We expect that the next several years will produce multiple prospective trials to investigate novel combination therapies beyond anti-angiogenic therapies and dose escalation. The integration of rationally selected targeted agents after gaining an improved understanding of the genomic landscape of GBM will be critical to significantly improve outcomes[68].

Most data on re-irradiation are retrospective and single-institution series. High-quality level I evidence generated by multicenter-prospective trials is necessary. While trials mature, we expect consensus to form on best practices in treatment, including recommended PTV

margins, volume of disease best suited to hypo-fractionated and single-fraction treatment, and dose.

Finally, radionecrosis is a known possible complication of re-irradiation. Contrast-enhanced MRI scan with perfusion imaging and PET scan are both useful in detecting necrosis versus progression. However, in series with the surgical resection of presumed radiographic necrosis, viable tumor may be found instead indicating progression rather than necrosis. Improved PET imaging used novel ligands and tracers and improved MRI assessment will help differentiate necrosis from progression, and may also be used for theranostic purposes. Given the disease's poor prognosis, we expect that these emerging improvements will continue to bend the survival curve and improve QoL for these patients.

Acknowledgments

The authors would like to thank Dr. Naomi Koisa for her critical review of the manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Table 1

Contemporary series of radiosurgery alone in single (SRS) or fractionated stereotactic radiotherapy (FSRT) for recurrent high-grade gliomas.

Author	Year	N	Median target volume (ml)	Median fraction number, prescription dose	Median OS after re-RT (months)	Toxicity
Elliott et al. [35].	2011	26	1.22	1 fx, 15 Gy	13.5	RN 7.7 %; RTOG Grade4 3.8 %
Maranzano et al. [36].	2011	SRS 13 FSRT 9	SRS 5.3 FSRT 44	SRS 17 Gy FSRT 10 fx, 30 Gy	11	RN 23 %
Conti et al. [34]	2012	11	N/A	2 fx, 20 Gy or 3–5 fx, 24–25 Gy	7	Corticosteroid dependency 63 %
Skeie et al. [37]	2012	51	N/A	1 fx, 12.2 Gy	12	Complications 9.8 %
Koga et al. [38]	2012	9 (Group A); 9 (Group B)	15 (A); 13 (B)	1 fx, 20 Gy (A); 1fx, 20 Gy (margin dose) (B)	10.5 (A); 9 (B)	RN 6.5% (A); RN 29% (B)
McKenzie et al. [39]	2012	35	8.54	5 fx, 30 Gy	8.6	RTOG (G3–G4) 9 %
Martínez-Carrillo et al. [40]	2014	87	6	1 fx, 18 Gy	10	NONE
Anand et al. [41]	2014	16	NA	5–6 fx, 30 Gy	9.3	RTOG > G1 6.2 %
Pinzi et al. [25]	2015	SRS 42 FSRT 67	SRS 2 FSRT 11	SRS 15 Gy FSRT 3 fx, 23 Gy	11.5	RN 6%

mOS: median overall survival. ReRT: Re-irradiation, SRS: radiosurgery, FSRT: fractionated stereotactic radiotherapy (multisession radiosurgery), RTOG: radiation therapy oncology group, G: toxicity grade, N/A: not available, BN: brain necrosis, fx: fraction(s).

Table 2

Contemporary series of systemic therapy (temozolomide or bevacizumab) and radiotherapy in single (SRS) or multi-fraction (FSRT) for recurrent high-grade gliomas.

Author	Year	N	Therapeutic approach	Median fraction number, prescription dose	Median OS after reRT (months)	Toxicity
Gutín et al. [18]	2009	25	FSRS + BEV	5 fx, 30 Gy	12.5	RTOG G3 = 1 (hemorrhage); G4 3 (1 bowel perforation; 1 wound dehiscence; 1 GI bleed)
Torcuator et al. [45]	2010	23	SRS/FSRT + BEV	SRS 18–20 Gy FSRT 6fx, 36 Gy	7.2	Not reported
Minniti et al. [21]	2011	36	FSRT + TMZ	15 fx, 37.5 Gy	9.7	Neurologic deterioration 3
Cuneo et al. [28].	2012	63	SRS/FSRT ± BEV	SRS 18 Gy FSRT 5 fx, 25 Gy	11	RTOG G3 = 11%; RN 10%
Niyazi et al. [31]	2012	30	FSRT +/- BEV	18 fx, 36 Gy	Not reached	RTOG G3 = 1; G4 = 1 (wound dehiscence); 2 RN
Park et al. [27]	2012	11	SRS + BEV	1 fx, 16 Gy	18	RTOG G3 = 1
Cabrera et al. [26]	2013	15	SRS/FSRT + BEV	SRS 18 or 24 Gy FSRT 5 fx, 25 Gy	13	RTOG G3 = 1
Greenspoon et al. [46]	2014	31	SRS + TMZ	5 fx, 25–35 Gy	9	RN RTOG G3 = 3, G4 = 1

ReRT: Re-irradiation, SRS: radiosurgery, FSRT: fractionated stereotactic radiotherapy (multisession radiosurgery), RTOG: radiation therapy oncology group, G: toxicity grade, NA: not available, RN: Radionecrosis, fx: fraction(s).