Review

Re-irradiation for Recurrent Primary Brain Tumors

CARSTEN NIEDER^{1,2}, NICOLAUS H. ANDRATSCHKE³ and ANCA L. GROSU⁴

¹Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway;

²Department of Clinical Medicine, Faculty of Health Sciences,
UiT - The Arctic University of Norway, Tromsø, Norway;

³Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland;

⁴Department of Radiation Oncology, University Hospital Freiburg, Freiburg, Germany

Abstract. *Background:* Historically, radiation oncologists have been cautious about re-irradiating brain tumors because of concerns about the risks of late central nervous system (CNS) toxicity, especially radionecrosis, that may occur several months to years following treatment. Today there are still limited prospective data addressing this approach. *Materials and Methods:* Systematic review of published trials reporting clinical results after re-irradiation of patients with different types of brain tumors was performed. *Results:* Data mainly related to glioblastoma, anaplastic glioma, medulloblastoma, ependymoma and meningioma have been published. Randomized studies are scarce. As in first-line scenarios, efficacy of radiotherapy is influenced by histology. Based on the reported outcomes, preliminary recommendations for dose/fractionation regimens can be given. *Conclusion:* Re-irradiation of brain tumors is increasingly considered as our understanding of brain tolerance to radiation evolves and developments in radiation technology and imaging make highly accurate targeting of recurrent tumors possible. With developments in systemic therapy, further exploration of the role of re-irradiation on its own or in combination with novel agents is needed.

The current postoperative standard treatment for glioblastoma (GBM) is radiotherapy with concurrent and adjuvant temozolomide. With this approach, 5-year overall survival is 9.8% compared to 1.9% with radiotherapy alone

(1). Recent data suggest that maintenance therapy with tumor-treating fields in addition to temozolomide improves survival (2). Efforts have been made to standardize the target volume definition (3). Nevertheless, despite an increase in survival rates, the majority of patients progress within 10-15 months. Also for anaplastic astrocytomas and low-grade gliomas, radiotherapy remains a common first-line treatment. In these tumors, the time to progression is longer but the majority ultimately also recurs. Salvage therapy is indicated in the majority of recurrent gliomas and most patients receive systemic therapy and/or surgery at relapse.

Historically, many radiation oncologists have been cautious about re-irradiating brain tumors because of concerns about the risks of toxicity, *e.g.*, radionecrosis. Re-irradiation for brain tumors is now more frequently used because developments in radiation technology and imaging allow for highly accurate targeting of biologically relevant tumor volumes and, furthermore, several studies have demonstrated the feasibility of this treatment paradigm. This review summarizes radiobiological principles behind re-irradiation of different types of brain tumors and discusses the current evidence from clinical studies.

Overview of Treatment Options for Recurrent Gliomas

External-beam radiotherapy is an integral part of treatment of low- and high-grade gliomas. At relapse, treatment options have included further surgical resection, systemic therapy, including prospective trials of new agents, and re-irradiation. Currently, however, there is no agreed standard of care.

The extent of surgical resection at relapse is frequently limited by the infiltrative nature of these tumors and the need to avoid severe neurological deficits from further surgical intervention. For those patients able to undergo re-resection, the use of impregnated carmustine wafers in the surgical

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Correspondence to: Carsten Nieder, MD, Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway. Tel: +47 75578449, Fax: +47 75534975, e-mail: carsten.nieder@nlsh.no

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cavity improved median survival by 8 weeks in a placebo-controlled study (4). It has also been shown that the extent of repeat resection was associated with survival (5-7). Patients with complete resection of gadolinium-enhancing tumor at first recurrence did benefit from reoperation, in contrast to those with incomplete resection (7).

There are few randomized controlled clinical trials in the treatment of recurrent glioma. Wong *et al.* (8) published a review on outcomes and prognostic factors for recurrent gliomas treated within phase II trials. From the eight studies reviewed the progression-free survival at 6 months was 21%, median progression-free survival was 10 weeks and median overall survival was 30 weeks. GBM patients had significantly poorer outcomes than those with anaplastic astrocytoma. Results were also worse for those with more than two prior operations or two prior chemotherapy regimens. With investigator-declared non-efficacious regimens pooled from 16 studies, progression-free survival at 6 months was 9% and overall survival at 1 year 14% (9).

Huncharek and Muscat (10) published a systematic review of outcomes from treatment of high-grade gliomas at relapse. They analyzed 40 trials (36 non-randomized controlled trials and 4 randomized controlled trials). Thirty-two of the trials addressed the outcome after chemotherapy and only seven were radiotherapy trials. Chemotherapy with nitrosoureas was associated with significantly prolonged time to tumor progression compared to all other drugs (26.9 weeks). The nitrosoureas and platinum were the most active drugs with regard to overall survival (32 weeks). Average median survival for patients treated with radiation was 44.7 weeks but selection bias prevented comparison with chemotherapy studies.

The use of temozolomide at recurrence has been investigated in several phase II studies with different dose regimens and seems to be associated with improved progression-free and overall survival (11-13). New information on biomarker selection for patients who are likely to be sensitive to temozolomide (MGMT promoter methylation) may alter the proportion of patients who are deemed suitable for this treatment (14).

Angiogenesis inhibition with bevacizumab (a humanized monoclonal antibody against vascular endothelial growth factor (VEGF)) has been introduced in the clinic in several countries but there is still controversy about the role of this agent and whether it should be combined with chemotherapy (15, 16). In the BELOB phase 2 trial, 51 patients were assigned to receive bevacizumab alone, 47 to receive lomustine alone and 47 to receive bevacizumab plus lomustine (16). Nine-month overall survival was 43% (95% confidence interval (CI)=29-57) in the lomustine group, 38% (CI=25-51) in the bevacizumab group, 59% (CI=43-72) in the bevacizumab and lomustine 90 mg/m² group, 87% (CI=39-98) in the bevacizumab and lomustine 110 mg/m² group and 63% (CI=49-75) for the combined bevacizumab and lomustine

groups. After the reduction in lomustine dose in the combination group, the combined treatment was well-tolerated. The combination of bevacizumab and lomustine met pre-specified criteria for assessment of this treatment in a phase III trial, which has been published as abstract and did not show a survival advantage for combined therapy (17).

Retrospective data suggest that multimodal treatment with repeat surgery or re-irradiation and chemotherapy is better than chemotherapy alone (18). Other data suggest that no significant difference between re-irradiation and surgery exists (19). In this study, both local approaches were followed by dendritic cell vaccination.

The Biology of Late Central Nervous System (CNS) Toxicity

The biology of late CNS toxicity is thought to be a complex dynamic process involving many cell types and interactions with no known effective means of prevention or treatment (20-22). Available animal data come mainly from studies investigating spinal cord tolerance to irradiation (23, 24). The pathogenesis of radiation toxicity and recovery potential in the brain is assumed to be similar to the spinal cord and the structures of the CNS are assumed to have a low α/β ratio (25). Therefore, fractionation of the total radiation dose is a means to limit the risk of toxicity. Pre-clinical data suggest that there is significant recovery following irradiation. For example, pigs receiving spinal radiosurgery one year after an initial series of fractionated radiotherapy (30 Gy in 10 fractions of 3 Gy) tolerated re-irradiation without significantly increased risk of motor deficits compared to controls who received only one radiosurgery treatment (26). Overall, the toxicity resulting from re-treatment depends on dose, volume and time between exposures. A conservative estimate is that up to 50% recovery may occur within 1-2 years post initial treatment if doses below full tolerance have been given at first exposure. In animal models of spinal cord re-irradiation, no microscopic lesions were seen with a cumulative dose less than 110 Gy (27). Other animal experiments with histological and imaging assessment after thalamic radiosurgery showed that delayed effects also involved the white matter beyond the target (28). The exact contributions of soluble mediators and other microenvironmental signals on the chronic process of radiation-induced changes, both within and outside the high-dose region, are still under investigation (29, 30). With the advent of tumor-treating fields, additional experiments investigating their influence on the dynamics of radiation-induced changes appear warranted.

Prognostic Factors for Survival

Carson *et al.* published an evaluation on prognostic factors for patients with recurrent high-grade gliomas based on 10 prospective phase I and II trials by using a recursive

partitioning analysis to define seven prognostic groups (31). Relevant prognostic factors included performance status, initial histology, age and corticosteroid use. They concluded that patients with recurrent gliomas entering clinical trials have widely variable outcomes, many of which depend on initial clinical characteristics and baseline demographic variables. These may be applicable in selecting patients for re-irradiation.

Combs *et al.* used their database of fractionated stereotactic radiotherapy with 233 patients (32). Primary histology included GBM (n=89; 38%), WHO grade III gliomas (n=52; 22%) and low-grade glioma (n=92; 40%). Re-irradiation was applied with a median dose of 36 Gy in 2-Gy single fractions. Median survival was 8 months for GBM, 20 months for anaplastic gliomas and 24 months for recurrent low-grade tumors. The strongest prognostic factors significantly impacting survival after re-irradiation were histology ($p<0.0001$) and age (<50 vs. ≥ 50 , $p<0.0001$) at diagnosis and the time between initial radiotherapy and re-irradiation ≤ 12 vs. >12 months ($p<0.0001$). They generated a four-class prognostic score to distinguish patients with excellent (0 points), good (1 point), moderate (2 points) and poor (3-4 points) survival after re-irradiation. However, first attempts towards external validation of this score were not successful (33, 34). Reasons might include the frequent use of bevacizumab in one of the validation studies or their limited size and other methodological problems. A larger validation study was successful (35).

Müller *et al.* defined three prognostic classes based on histology, age and performance status (19). Regardless of local treatment approach (re-irradiation or surgery, each followed by dendritic cell vaccination), the 1-year survival rate was approximately 70% in the best prognostic group.

Evidence for Re-irradiation

There are over 50 clinical studies in the literature on re-irradiation of gliomas. The majority of these studies is retrospective and uses a variety of techniques, including brachytherapy, fractionated stereotactic radiotherapy, radiosurgery and conformal or intensity-modulated radiotherapy with or without new systemic agents (Table I). Besides differing techniques, the published data include a wide range of doses, emphasizing on the fact that no standard approach exists (63). Inter-study comparison is difficult because the literature is confounded by a lack of standardized recording of all radiotherapy and outcome variables. In addition, some patients were treated at first and others at second or third progression.

Although the biology of re-irradiation remains to be fully understood, there is now a large body of clinical and animal data that can guide recommendations. Mayer and Sminia identified and analyzed 21 re-irradiation studies and reviewed the available clinical data on re-irradiation of

gliomas with respect to tolerance of the normal brain (64). They discussed that the incidence of toxicity, including radionecrosis, may be under-reported since only symptomatic necrosis is likely to be recorded. According to their analysis, the major factor contributing to necrosis was the total dose received. There was no correlation between time to re-irradiation and the development of necrosis, although the minimum time interval between treatments in this analysis was 3 months. They concluded that the incidence of necrosis did not increase significantly until the total cumulative dose was 100 Gy.

Target Definition

Magnetic resonance imaging (MRI) plus gadolinium remains the gold standard imaging modality for target definition for gliomas (3). The problems are that, following surgery or radiotherapy, the signal change based on gadolinium enhancement can be non-specific, making accurate target definition a challenge. Additionally, in patients treated with bevacizumab, the true extent of recurrent or progressing tumor may be obscured and underestimated. Most gliomas recur close to the margin of the original lesion and this is often where non-specific signal changes due to prior treatment are also apparent (65).

To optimise the outcome of radiotherapy, accurate target definition is of paramount importance. In this context, biological imaging may improve the definition of the relevant target (66-69). Miwa *et al.* reported a small study of ¹¹C-methionine positron emission tomography (MET-PET)/CT/MRI fusion (70). Twenty-one patients with recurrent GBM received hypofractionated stereotactic IMRT planned by MET-PET/CT/MRI. The region of increased amino acid tracer uptake on MET-PET was defined as the gross tumor volume. The planning target volume encompassed the GTV by a 3-mm margin. Median survival was 11 months. In 42 patients with brain tumors (29 gliomas and 13 metastases from extracranial primary tumors) pre-treated with surgery and/or radiation therapy, FET-PET and MET-PET were performed on the same day. Standardized uptake value (SUV) for normal and tumor tissue, GTV and sensitivity (100%) and specificity (91%) were similar for both tracers (71). Especially after irradiation, FET-PET and MET-PET were able to distinguish treatment-related changes from tumor recurrence. Currently, there is no standard recommendation on what imaging modality has to be incorporated and what specific margins should be applied. The minimal consensus may be summarized as to confine GTV definition to gadolinium-enhancing regions. The GLIAA (NOA 10) study (NCT01252459), an ongoing multicentre, prospective randomized, phase II clinical trial, evaluates the impact of FET-PET *versus* T1Gd-MRI target volume delineation on the outcome of patients with recurrent

Table I. Summary of relatively large re-irradiation studies for patients with recurrent gliomas.

Authors	Case number	Technique/dose	Median survival
Brachytherapy			
Scharfen <i>et al.</i> 1992 (36)	66 GBM	Brachytherapy I-125 64.4 Gy	11.3 months
Sneed <i>et al.</i> 1997 (37)	66 GBM	Brachytherapy I-125 64.4 Gy	11.7 months
	45 WHO III		12.3 months
Simon <i>et al.</i> 2002 (38)	42 GBM	Brachytherapy Ir-192 40-60 Gy	50 weeks
Gabayan <i>et al.</i> 2006 (39)	81 GBM	Gliasis brachytherapy 60 Gy at 10 mm	35.9 weeks
	14 WHO III		43.6 weeks
Tselis <i>et al.</i> 2007 (40)	84 GBM	Brachytherapy Ir-192 40 Gy	37 weeks
Fabrini <i>et al.</i> 2009 (41)	18 GBM	HDR brachytherapy 18 Gy	8.0 months
	3 WHO III		
Kickingereder <i>et al.</i> 2014 (42)	98 GBM	Brachytherapy I-125 60 Gy	10.4 months
Schwartz <i>et al.</i> 2015 (43)	40 GBM	Brachytherapy I-125 50 Gy	13.4 months
	28 WHO III		
Stereotactic radiosurgery			
Shrieve <i>et al.</i> 1995 (44)	86 GBM	Stereotactic radiosurgery 13 Gy	10.5 months
Cho <i>et al.</i> 1999 (45)	46 GBM	Stereotactic radiosurgery 17 Gy	11.0 months
Combs <i>et al.</i> 2005 (46)	32 GBM	Stereotactic radiosurgery Median 15 Gy (10-20 Gy)	10.0 months
Combs <i>et al.</i> 2005 (47)	54 GBM	Stereotactic radiotherapy	8.0 months
	39 WHO III	36 Gy (15-62 Gy)	16.0 months
		5x2 Gy conventional fractionation	
Kong <i>et al.</i> 2008 (48)	65 GBM	Stereotactic radiosurgery 16 Gy	13.0 months
	49 WHO III		26.0 months
Patel <i>et al.</i> 2009 (49)	36 GBM	Stereotactic radiosurgery 18 Gy	8.5 months
		Fractionated stereotactic radiotherapy	7.4 months
		36 Gy in 6 fractions	
Martinez-Carrillo <i>et al.</i> 2014 (50)	46 GBM	Stereotactic radiosurgery	7.5 months
	41 WHO III	Median 18 Gy (14-20 Gy)	17.0 months
Bir <i>et al.</i> 2015 (51)	29 GBM	Stereotactic radiosurgery 10-20 Gy	7.9 months
Pinzi <i>et al.</i> 2015 (52)	128 High-grade	Stereotactic radiosurgery or hypofractionated	11.5 months
		Hypofractionated stereotactic radiotherapy	
Shepherd <i>et al.</i> 1997 (53)	33 GBM	Hypofractionated conformal radiotherapy	11.0 months
		Escalation 20-50Gy	
Lederman <i>et al.</i> 2000 (54)	88 GBM	Stereotactic hypofractionated radiotherapy	7.0 months
		Median 24 Gy in 4 fractions	
Grosu <i>et al.</i> 2005 (55)	44 GBM	Stereotactic hypofractionated radiotherapy	
		36 PET/SPECT 30 Gy	9.0 months
		8 CT/MRI (6x5 Gy)	5.0 months
Fokas <i>et al.</i> 2009 (56)	53 GBM	Stereotactic hypofractionated radiotherapy	9.0 months
		30 Gy in 10 fractions	
Fogh <i>et al.</i> 2010 (57)	105 GBM	Stereotactic hypofractionated radiotherapy	11.0 months
	42 WHO III	Median 35 Gy in 10 fractions	10.0 months
Dincoglan <i>et al.</i> 2015 (58)	28 GBM	Stereotactic hypofractionated radiotherapy	10.3 months
		25 Gy in 5 fractions	
Conventionally fractionated (stereotactic) radiotherapy			
Arcicasa <i>et al.</i> 1999 (59)	31 GBM	Fractionated conventional 2D-radiotherapy	13.7 months
		34.5 Gy in 23 fractions (1.5Gy/F)	
Cho <i>et al.</i> 1999 (45)	25 GBM	Conventional fractionated radiotherapy	12.0 months
		37.5 Gy in 15 fractions	
Koshi <i>et al.</i> 2007 (60)	11 GBM	Stereotactic radiotherapy	11.0 months
	14 WHO III	22 Gy in 8 fractions/8F (+ hyperbaric oxygen)	19.0 months
Combs <i>et al.</i> 2008 (61)	8 GBM	Stereotactic radiotherapy	9.0 months
	10 WHO III	36 Gy in 2 Gy per fraction	
	7 low-grade	(+ Temozolomide 50mg/m ²)	
Lee <i>et al.</i> 2016 (62)	21 GBM	Conventional fractionated radiotherapy	10.0 months
	8 WHO III	(median dose 45 Gy)	Not reported
	7 low-grade		Not reported

GBM, Glioblastoma; WHO, World Health Organization.

GBM treated with high-precision radiation therapy (39 Gy, 3 Gy per fraction).

Stereotactic Radiosurgery/Fractionated Stereotactic Radiotherapy

In brain radiotherapy, stereotactic methods offer optimal precision of target definition whilst sparing dose to the surrounding tissues. Shepherd *et al.* reported on 29 recurrent high-grade glioma patients treated with a variety of doses of stereotactic hypofractionated re-irradiation who had a median survival of 11 months (53). This compared favorably to a matched cohort of patients treated with nitrosourea chemotherapy with a median survival of 7 months. In this study, a stereotactic radiotherapy dose of >40 Gy was found to be a significant predictor of radiation damage. There was also a trend towards higher risk of complications for larger volumes (>35 cm³) irradiated.

Brachytherapy

A review by Combs *et al.* reported on the available but limited data on brachytherapy for recurrent gliomas (72) (Table I). It should be noted that patients that are selected for brachytherapy are normally those with resectable tumors, good performance status and small volume of disease. High re-operation rates and radionecrosis incidence have repeatedly been reported using these techniques, but not in all studies.

Combination Treatment

Few studies have addressed the combination of chemotherapy with re-irradiation. Temozolomide and re-irradiation has been found to be safe and effective. In a study combining fractionated stereotactic radiotherapy and concomitant temozolomide in 25 patients with recurrent gliomas, median survival from re-irradiation was 8 months. Treatment was completed in all patients without interruptions of more than 3 days and without severe side-effects (55). Minniti *et al.* reported a median survival of 12.4 months in a cohort of 54 patients (73). Greenspoon *et al.* published a prospective cohort study that included 31 patients who survived for a median of 9 months (25-35 Gy in 5 fractions) (74).

Darakchiev *et al.* reported on 34 patients with recurrent GBM treated with re-resection and implantation with I-125 seeds and Gliadel wafers to the resection bed (75). They documented, in line with many other studies, that patients with a Karnofsky performance status less than 70 were more likely to have a worse outcome. One-year survival was 66% in this small, non randomized study and brain necrosis was observed in 24% of cases.

An international randomized phase II GBM study demonstrated that the experimental agent APG-101 (a CD95 ligand-binding fusion protein) given weekly until progression in addition to re-irradiation (36 Gy in 2-Gy fractions) significantly improved the primary end point, progression-free survival (76). According to the manufacturer's website, future development is ongoing (www.apogenix.com).

Gutin *et al.* combined hypofractionated stereotactic radiotherapy (30 Gy in 5 fractions) with bevacizumab (77). They documented a 50% response rate in the GBM population and a median overall survival of 12.5 months. Minniti *et al.* used a lower dose (25 Gy in 5 fractions) with bevacizumab or fotemustine (78). Overall and progression-free survival were significantly better in the bevacizumab cohort. Combined with conventionally fractionated re-irradiation (median dose 36 Gy), median survival was 8.6 months (79). Compared with patients who did not receive bevacizumab (n=44), the patients who received bevacizumab after radiosurgery (n=11) in a case-control study had significantly prolonged progression-free survival (15 months vs. 7 months, $p=0.035$) and overall survival (18 months vs. 12 months, $p=0.005$) and were less likely to develop an adverse radiation effect (9 vs. 46%, $p=0.037$). Nine patients received irinotecan and one temozolomide with bevacizumab (80). A small randomized double-blind placebo-controlled trial with 14 patients suggested that bevacizumab might be a treatment option for patients with radiation necrosis (81). It is, therefore, difficult to assess radiological adverse effects and time to progression in patients who receive this or comparable, experimental anti-angiogenic drugs.

Magnuson *et al.* performed a retrospective analysis of 23 patients with recurrent GBM (after standard radiotherapy/temozolomide) treated with bevacizumab every 2 weeks until progression (82). Within 7-14 days of progression on bevacizumab, patients initiated re-irradiation to a dose of 54 Gy in 27 fractions using pulsed-reduced dose rate (PRDR) radiotherapy. The median planning target volume was large (424 cm³). At the start of re-irradiation, bevacizumab was given every 4 weeks for two additional cycles. The median survival after bevacizumab failure was 6.9 months. Re-irradiation was well-tolerated with no symptomatic grade 3-4 toxicities.

Data such as these may broaden the applicability of re-irradiation further since co-treatment with new agents may improve response rates and/or improve the therapeutic ratio by reducing the risk of major side-effects.

Relapsed Ependymoma and Medulloblastoma

The same limitations discussed above also apply to the literature on relapsed ependymoma and medulloblastoma. One example is a recent study of 108 children with relapsed

ependymoma where 66% received radiotherapy at relapse and 50% of older children were re-irradiated and where re-irradiation was associated with better outcome (83). In a Canadian study of 47 patients who relapsed, 3-year overall survival was $7\% \pm 6\%$ and $81\% \pm 12\%$ for non-re-irradiated and re-irradiated patients, respectively ($p < 0.0001$) (84). However, a decline in intellectual function from pre- to post re-irradiation assessment was observed. Merchant *et al.* reported on a smaller series of 38 patients (85). Re-irradiation included radiosurgery ($n=6$), focal fractionated re-irradiation ($n=13$) or craniospinal irradiation ((CSI); $n=19$). Their experience also suggests that re-irradiation might be a component of salvage therapy, even if it is not always without serious toxicity. Based on 18 lesions, Murai *et al.* reported that lesions receiving >25 Gy in 5 fractions or 21 Gy in 3 fractions did not recur within 1 year (86). Toxicity was limited to grade 2 or less. In a different study, 3-year local control was 89% (12 patients, fractionated stereotactic re-irradiation) and median event-free survival 3.4 years (87). In 6 patients, radionecrosis was diagnosed and three of these were symptomatic. Lobon *et al.* reported that 15 of 32 patients achieved greater progression-free survival after second radiotherapy than after initial irradiation (88). Five patients developed radionecrosis. For re-irradiated metastatic relapses ($n=17$), median progression-free survival was 6.8 years if CSI was administered, as compared to only 0.7 years in non-CSI cases, $p=0.07$.

In a small study, which included 25 patients with previously irradiated recurrent medulloblastoma, a trend towards better event-free survival was seen in patients who received additional radiotherapy as part of their retrieval therapy (89). Patients without gross disease at re-irradiation had favorable disease-free survival (90). High local control rates but significant rates of out-of-field metastases after re-irradiation for medulloblastoma were also reported by Milker-Zabel *et al.* (91). According to Wetmore *et al.*, the use of radiotherapy as a component of salvage treatment may prolong survival (92). The benefit was greatest for relapsed standard risk patients. However, imaging-detected necrosis was also more frequent after re-irradiation.

Relapsed Meningioma

Wojcieszynski *et al.* (93) reviewed an institutional database of patients with meningioma treated with stereotactic radiosurgery or fractionated stereotactic radiotherapy who underwent a second course for recurrent disease (median dose at relapse 15 Gy and 50.4 Gy, respectively). Three percent of their patients were re-irradiated. The median time interval was 40 months. After a median follow-up of 32 months, 11 of 19 patients (58%) experienced disease progression. Median time to second progression was 10 months. Freedom from progression at one year was lower in

patients with grade II or III tumors compared to those with grade I or unknown histology (17% compared to 92%, $p=0.005$). Cox regression showed that a grade II-III tumor affects progression-free survival, with a hazard ratio of 5.37 ($p=0.011$). Median time to progression for patients with grade II-III tumors was eight months. This end point was not reached for patients with grade I/unknown tumors. The Kaplan-Meier estimate for median survival time was 90 months. There were no reported serious (grade ≥ 3) toxic events attributed to re-irradiation.

Conclusion

There is a patient group with recurrent gliomas and other cranial tumors for whom re-irradiation may be appropriate. This recommendation is also reflected in two recent clinical practice guidelines (94, 95). The available literature suggests that re-irradiation is safe in well selected patients; however, more prospective data are needed to support this conclusion. With advances in functional imaging technology, new approaches to target definition are under investigation. Due to a lack of randomized studies, the additional benefit of chemotherapy is unknown, but several combinations seem promising for further studies.

Prospective trials are needed comparing re-irradiation to newer systemic agents or re-irradiation in combination with newer agents. These include different strategies of immunotherapy and vaccination. Despite a large body of clinical work, no standard protocol for re-irradiation of brain tumors has been defined yet. The heterogeneous dose definitions (prescription to different surrounding isodoses or the ICRU reference point) and individualized sequence of second- and third-line therapies also make comparisons between studies difficult. Some studies have used concomitant chemotherapy or bevacizumab, which may have been a confounding factor. The generally small study size is dangerous as inclusion of patients with a more favorable tumor biology in some studies could result in better survival and erroneous conclusions about treatment efficacy when comparing different subgroups. The impact of certain biological features has only been realized in recent years (96-98). In addition, some studies included patients with histological grade change, *e.g.* initial radiotherapy for grade II or III tumor and re-irradiation for GBM. The latter group is now regarded a biologically heterogeneous disease (96).

Ideally, radiotherapy should be highly conformal to keep the treated volume as small as possible and reduce late side-effects to organs at risk and other brain tissue. Many series suggest that limiting the target volume to approximately 4-5 cm minimizes the risk of toxicity and recommend that if larger volumes are being targeted, then, consideration should be made to reducing the dose. As evident from the review of treated volumes with different modalities, such as single-

Table II. Examples of re-irradiation techniques and regimens for patients with recurrent supratentorial gliomas.

Low-volume recurrence*	Consider SRS, brachytherapy or FSRT, <i>e.g.</i> 35 Gy in 5 fractions	Proximity to critical structures might require reduced EQD2, <i>e.g.</i> by reducing fraction size (35 Gy in 10 fractions)
Intermediate volume recurrence**	Consider FSRT, <i>e.g.</i> 30 Gy in 5 fractions	Proximity to critical structures might require reduced EQD2, <i>e.g.</i> by reducing fraction size (30 Gy in 10 fractions)
Large-volume recurrence	Consider FSRT, <i>e.g.</i> 25 Gy in 5 fractions	Proximity to critical structures might require reduced EQD2, <i>e.g.</i> by reducing fraction size (36 Gy in 18 fractions)

SRS, Stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy; EQD2, biologically equivalent dose in 2-Gy fractions. *Martinez-Carrillo *et al.* (50) have summarized volume data from 20 radiosurgery studies. The median volume in these studies ranged from 4.7 to 28 cm³, for a median of 10 cm³. **In stereotactic hypofractionated radiotherapy studies (Table I), the median volume ranged from 18 to 35 cm³ (median=27.5). Ongoing clinical trials: NCT02709226 (FSRT dose escalation from 10 fractions of 3.5 Gy to 12 and 14 fractions), NCT01925573 (FSRT 10 fractions of 3.5Gy or 5 fractions of 6Gy (physicians choice) with tumor-treating fields and bevacizumab), NCT01252459 (FSRT 13 fractions of 3 Gy, different imaging protocols (±PET) for target volume delineation), NCT01464177 (FSRT 5 fractions of 5 Gy or 7 Gy), NCT01666600 (18 fractions of 2 Gy), NCT02149459 (10 fractions of 3-3.5 Gy).

dose and fractionated stereotactic irradiation (Table II), some institutions preferred hypofractionation for recurrences that others treated with single doses. This finding reflects the lack of universally agreed dose-constraints for re-irradiation. Pooled analyses from several institutions are necessary to develop a more homogeneous clinical practice.

Most recurrent glioma patients will have received the equivalent of 54-60 Gy in 1.8-2 Gy per fraction when they were initially treated and, therefore, no more than 40 Gy equivalent in a hypofractionated regime should be delivered when re-irradiating aiming to keep the total dose less than 100 Gy (64). Fraction sizes of 3-5 Gy appear to be well-tolerated in limited-volume recurrences (<75 ml) as long as the total dose is limited to 30-35 Gy. Table II shows examples of possible fractionation regimens. A maximum dose of 20 Gy with concurrent chemotherapy has been prescribed in patients with diffuse intrinsic pontine glioma (99). This modest dose improved symptoms and delayed progression with minimal side-effects. Available data do not suggest that there is an obvious limitation on the time between treatment courses, although many clinicians would not treat within a year as these patients are likely to have primary treatment resistance.

Performance status of the patient and the potential impact on their quality of life should be taken into account. Consideration should be given to the impact of prolonged treatment courses in the context of poor prognosis disease. There are very few data on the quality of life following re-irradiation, which is an important consideration in a poor prognostic group.

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