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REVIEW

# Re-irradiation for high-grade gliomas: Has anything changed?

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## Abstract

Optimal management after recurrence or progression of high-grade gliomas is still undefined and remains a challenge for neuro-oncology multidisciplinary teams. Improved radiation therapy techniques, new imaging methods, published experience, and a better radiobiological knowledge of brain tissue have positioned re-irradiation (re-RT) as an option for many of these patients. Decisions must be individualized, taking into account the pattern of relapse, previous treatment, and functional status, as well as the patient's preferences and expected quality of life. Many questions remain unanswered with respect to re-RT: Who is the most appropriate candidate, which dose and fractionation are most effective, how to define the target volume, which imaging technique is best for planning, and what is the optimal timing? This review will focus on describing the most relevant studies that include re-RT as salvage therapy, with the aim of simplifying decision-making and designing the best available therapeutic strategy.

**Key Words:** Re-irradiation; Recurrent glioma; High-grade gliomas; Glioblastoma; Radiosurgery; Stereotactic radiotherapy

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**Core Tip:** The optimal management after recurrence or progression of high-grade gliomas is still undefined. Improved radiation therapy techniques, new imaging methods, published experience, as well as better radiobiological knowledge of the brain tissue have positioned re-irradiation as a valid alternative for many of these patients. Many questions remain unanswered. This review will focus on describing the most

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relevant studies that include re-irradiation as salvage treatment, with the aim of simplifying decision-making and designing the best available therapeutic strategy.

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## INTRODUCTION

High-grade gliomas (HGG) are the most common primary malignant brain neoplasm in adults[1]. The most frequent type, glioblastoma multiforme (GBM), has an incidence of 3 cases/100000 inhabitants[2]. Its treatment is a macroscopically complete tumor resection, whenever possible, followed by external beam radiotherapy (60 Gy in 2 Gy/fr) with concurrent temozolomide (TMZ) and adjuvant TMZ until the completion of six cycles[3]. Nevertheless, approximately 40% of World Health Organization (WHO) grade III gliomas (anaplastic astrocytoma) and 90% of grade IV gliomas (GBM) progress within 2 years. The main site of relapse is in or near the tumor bed[3-5].

With standard treatment, median overall survival (mOS) for GBM is approximately 14.6 mo, and median progression-free survival (mPFS) is 6.9 mo[6]. This tumor has a poor prognosis and is very aggressive and fast-growing. The high rate of local failure suggests secondary therapeutic options for local salvage should be considered.

The first issue during the diagnostic-therapeutic approach is to confirm that we are dealing with true tumor progression. The phenomena of "pseudoprogression", described in 20%-30% of patients who have received radiochemotherapy and possible radionecrosis (RN), associated or not with tumor, may hinder or delay diagnosis[7]. The Response Assessment in Neuro-Oncology working group criteria[8] for HGG categorization has certain limitations.

Optimal management after recurrence or local progression remains to be defined. It has mostly been established by retrospective studies lacking a quality of life (QoL) evaluation. Established salvage treatment options include a second surgery (re-S), re-irradiation (re-RT), systemic treatment, or some combination thereof[9]. The addition of the "tumor treating field therapy" approach (alternating electrical fields that exert biophysical force on charged and polarizable molecules known as dipoles) has been found to extend survival for patients with newly diagnosed and recurrent GBM (rGBM)[10].

These suboptimal results have motivated multiple lines of research investigating new therapeutic approaches such as the addition of molecular targeted agents, immune checkpoint blockade, vaccines, viral therapy, or other irradiation modalities[11-14].

Current therapeutic approaches, including the radiation therapy techniques and parameters, are very diverse. Thus, a survey of expert radiation oncologists showed high variability, reflecting the scarcity of high-quality prospective data for decision-making[15]. Multiple questions remain unanswered with respect to re-RT: Who is the most appropriate candidate, which dose and fractionation are most effective, how to define the target volume, and which imaging technique is best for planning, as well as the optimal timing? This review will focus on describing the most relevant studies that include re-RT as salvage therapy, with the aim of simplifying de-cision making and designing the best available therapeutic strategy.

## RE-RT IN THE THERAPEUTIC STRATEGY

At present, any ablative treatment option offered to a selected patient with local failure is still palliative and has associated side effects that must be considered. The choice is complex, and the criteria are poorly defined. Decisions must be individualized, taking into account the pattern of relapse, previous treatment, and functional status, as well as the patient's preferences and expected QoL.

For patients with low functional status, unable to walk and totally dependent for daily activities, the best supportive care should be considered.

Historically, the fear of exceeding the dose tolerance of healthy brain tissue, and therefore the risk of severe side effects, kept radiation oncologists from considering re-RT with ablative doses. Thus, the most offered treatment has been systemic [chemotherapy/bevacizumab (BEV)], with a mOS of 6-9 mo, without a clear advantage of any drug or therapeutic scheme among those used[16,17]. Clearly this is the best strategy for patients with widespread or multifocal disease. However, in the case of a focal relapse, if the patient has favorable clinical criteria, the current trend is to consider a second local treatment such as re-S, re-RT, or both with or without systemic treatment.

The level of evidence supporting this approach is low, probably because the high failure rates (recurrence or progression) of these second treatments make it difficult to compare the different strategies.

Objective parameters are needed to simplify therapeutic decision-making. Scoccianti *et al*[18], based on a review of the literature, recommend the first algorithm to aid decision-making in daily practice between surgical salvage or re-RT. They consider local treatment for focal relapses in patients with life expectancy > 3 mo. The choice of re-S or re-RT depends on prognostic factors and the expected toxicity of each therapeutic option. The results of combined treatment are encouraging, and the tendency is to recommend it. The therapeutic decision should be interdisciplinary and requires expert neurosurgeons and radiation oncologists. Ultimately, the final decision should be agreed upon with the patient after discussion of the risks and benefits of the available therapeutic options.

## RESULTS

### *Re-resection*

A minority of patients (20%-30%) are considered eligible for re-S[19], with a higher morbidity-mortality than before initial resection. After re-S, overall survival from re-RT ranges from 4.9[20] to 13.5 mo[21] and PFS from re-RT from 1.9[22] to 8.3 mo[23]. These results are from retrospective, not comparative series. There is no evidence to suggest that these results are better than can be expected with radiation and/or chemotherapy alone[24,25]. The meta-analysis of Lu *et al*[26] suggests that re-S of rGBM in select patients confers a significant, prognostic OS advantage independent of other prognostic factors, and a cohort from The Director Trial[27] found that surgery at first recurrence of GBM improved outcome if complete resection of contrast-enhancing tumor was achieved. Preoperative and postoperative Karnofsky performance status (KPS), extent of surgery of first re-S, and chemotherapy after first re-S have been identified as the factors that have the greatest impact on survival[25].

Due to the absence of comparative studies, the role of re-S in rGBM is not yet established. The Randomized Controlled Comparative Phase II Trial on Surgery for Glioblastoma Recurrence trial comparing re-S of recurrence plus second-line treatment, *vs* second-line treatment without re-S, will quantify the contribution of re-S for rGBM.

### *Re-RT*

Based mostly on retrospective series, selected patients with small recurrent tumors and a good performance status may benefit from re-RT using modern high-precision techniques[28-31]. Prospective studies are very scarce, therefore the exact contribution of re-RT is uncertain.

The tumoricidal dose to be administered is limited by the possibility of generating severe side effects, given that most patients have already received doses in the maximum tolerance range at their first irradiation. Re-RT at the therapeutic doses used at diagnosis (60 Gy) is not recommended.

Potential benefits of re-RT include palliation by reducing corticosteroid use, improving neurologic symptoms, and, in selected patients, increasing PFS and possibly overall survival.

There are three most commonly used external radiation therapy techniques that, depending on the fractionation applied, the treatment volume, and the technology used we refer to as: Stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HFSRT), and conventionally fractionated external radiotherapy (CFRT). We also have results with intraoperative techniques[32]. The promising results of particle irradiation are described in the section on new irradiation strategies. The choice of technique, in addition to its geographical availability, depends on the size of the recurrence and consequently of the planning target volume (PTV) generated.

Unfortunately, the lack of comparative trials does not allow their results to be compared. However, even in the absence of randomized data, there is a tendency to use hypofractionated or SRS schemes for small volumes, assuming a slightly higher risk of RN.

Kazmi *et al*[33] published the first meta-analysis with the results of re-RT in rGBM. They included 50 studies with a total of 2095 patients. Overall survival from re-RT and PFS from re-RT at 6 mo were 73% and 43%, respectively, and at 12 mo were 36% and 17%. They found better PFS at 6 mo with SRS and with short fractionation schedules (≤ 5 fractions), probably due to the lower tumor volume.

### SRS as salvage treatment

Table 1 describes a selection of series published since 2005. They are characterized by: Including mostly GBM, a single dose of 12-18 Gy, a median volume of around 10 mL, and a time from the first radiation treatment of between 8.8 mo and 13.8 mo. The Kong series[34] is the largest and the only prospective series. The mOS for GBM is between 7.5 mo and 13 mo, while the range for mPFS, in those series that report it, is between 3.6 mo and 7 mo. Severe toxicity is not reported, except for RN, which in a couple of series is 24%-31% by radiological imaging. These data suggest that patients with small volumes can be safely treated with SRS.

### Fractionated stereotactic radiotherapy as salvage treatment

Hypofractionated schemes have been used mainly in larger recurrent HGG (rHGG). A selection of studies published in 2000 or later, including several prospective series, are presented in Table 2. Some contain anaplastic and low-grade gliomas. The median dose and fractionation used are highly variable, between 25 and 35 Gy (3-7 Gy/fr), with an equivalent dose at 2 Gy (EQD2) range of 37.5-78.7 Gy. The largest series is Fogh *et al*[29] with 147 patients, of which 42 had anaplastic astrocytomas, with an average dose of 35 Gy (3.5 Gy/fr) and a mOS of 11 mo for rGBM. Severe toxicity is also highly variable, with some series reporting none and others as much as 10.5% and a percentage of radiological RN between 6%-11%.

A recent study, in a large and heterogeneous series of 198 patients with rHGG, reports a mOS of 7 mo (6 mo for GBM and 14 mo for grade III gliomas) with good tolerance. The most common fractionation schedules were 41.8 Gy-49.4 Gy/3.8 Gy/fr [35].

The main study with CFRT is by Combs *et al*[36]. They analyzed 59 patients with rGBM treated with 36 Gy/2Gy/fr, achieving an mOS of 8 mo, with only 1.7% of histologically confirmed RN despite a large median tumor volume (49.3 mL). This indicates that it may be an adequate schedule in larger lesions.

Several retrospective papers have compared the different techniques (SRS, HFSRS, CFRT), reporting similar results between them, with mOS of 9.7-11 mo[37,38].

There are very few prospective studies on the efficacy of re-RT *vs* systemic treatment alone. RTOG 0525[39] has reported mOS of 8.2 mo with re-RT, 10.5 mo with chemotherapy, and 11.3 mo with radiochemotherapy. Patients who only received best supportive care had an mOS of 4.8 mo, probably selected for worse overall status. Available data in rGBM generally suggest that re-RT modestly improves PFS compared with systemic treatment alone, but OS is similar[40].

### Re-RT of larger volumes

The main hurdle for re-RT of voluminous relapses has been the risk of RN. Most re-RT studies describe a PTV < 40 mL[41,42]. The available evidence for large volume lesions is sparse and few studies include a median PTV greater than 75 mL. Two authors report the largest series to date. The study by Scholtyssek *et al*[43], with a median PTV of 110.4 mL and doses of 36 Gy (30 Gy-40.05 Gy) at 2-5 Gy/fr, did not describe severe toxicity or RN. Chan *et al*[44], with a median PTV of 145.3 mL and dose of 35 Gy/15 fr, in 67 patients, reported 4 cases of radiological RN. The mOS reported in these series were 7.7 and 7.8 mo, in the same range as reported in studies with small treatment volumes. We can conclude that re-RT of large volume disease is feasible, provided that the doses administered are appropriate.

### Re-RT with concurrent systemic treatment

Two drugs (TMZ, BEV) are mainly used. Although they have been shown to be safe combinations, their benefit has yet to be demonstrated.

**Table 1 Summary of selected publications reporting radiosurgery as salvage treatment in recurrent high-grade gliomas**

| Ref. | Study type | No. patients | Histology | Re-irradiation | | Median interval | Median tumor volume | Median PFS2 | Median OS2 | Severe toxicity | Radionecrosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total dose, median | Dose/fr, median | | | | | | |
| Combs *et al* [28], 2005 | R | 32 | All GBM | 15 Gy | 63.8 Gy | 10 mo | 10 mL | 7 mo | 10 mo | 0% | 0% |
| Hsieh *et al* [104], 2005 | R | 26 | All GBM | 12 Gy | 42 Gy | NR | 21.6 mL | NR | 10 mo | NR | 31.3% by image |
| Kong *et al* [34], 2008 | P | 114 | 65 GBM, 49 G3G | 16 Gy | 72 Gy | NR | 10.6 mL | 4.6 mo (GBM), 8.6 mo (G3G) | 13 mo (GBM), 26 mo (G3G) | 0% | 24.4% by image |
| Patel *et al* [68], 2009 | R | 26 | All GBM | 18 Gy | 90 Gy | 12.5 mo | 10.4 mL | NR | 8.4 mo | Limited toxicity | NR |
| Skeie *et al* [30], 2012 | R | 51 | All GBM | 12.2 Gy | 43.3 Gy | 11 mo | 12.4 mL | 6 mo | 12 mo | 0% | 0% |
| Martínez-Carrillo *et al*[31], 2014 | R | 87 | 46 GBM, 41 G3G | 18 Gy | 90 Gy | 13.8 mo | 8.7 mL | NR | 7.5 mo (GBM); 17 mo (G3G) | 0% | 0% |
| Kim *et al* [105], 2015 | R | 29 | All GBM | 15 Gy | 63.8 Gy | 8.8 mo | 11 mL | 3.6 mo | 9.2 mo | NR | NR |

α/β = 2; EQD2: Equivalent dose at 2 Gy fractions; G3G: Grade III glioma; GBM: Glioblastoma; NR: Not reported; OS2: Overall survival from re-irradiation; P: Prospective; PFS2: Progression free survival from re-irradiation; R: Retrospective.

**Re-RT with TMZ:** Table 3 summarizes the main results. The techniques used have been HFSRS or CFRT. Hematologic ≥ grade 3 toxicity of up to > 40% has been described. RN has been reported, either radiological (7%-8%)[45,46] or histopathological in 4.3%[47]. The mOS for GBM ranges from 9.7-14 mo[45,48] and mPFS between 4-7 mo[46,47], results reported without the combination of TMZ. However, in the Grosu *et al*[49] and Conti *et al*[47] series, patients receiving TMZ had higher mOS.

Overall, concurrent approaches with TMZ do not appear to improve re-RT outcomes and may carry increased risk of toxicity. However, these findings need to be confirmed in prospective series.

**Re-RT with BEV:** The association of BEV to treatment with first line radiochemotherapy did not demonstrate a benefit in OS in two phase III trials[50,51]. In recurrences, the role of concurrent BEV with re-RT is still not well defined, but several studies have confirmed the safety of this combination with reasonable survival results [52-57]. Table 4 summarizes the main results. The mOS ranges between 9.3-12.2 mo for rGBM, with mPFS between 5.2 and 6.8 mo. This combination has been shown to decrease the risk of RN, especially for re-RT of larger volumes[44,58]. The percentage of symptomatic RN/symptomatic edema, defined as the need for corticosteroids > 6 wk after re-RT, was lower with the BEV combination (21.8% *vs* 37.8%, $P$ = 0.025), with these differences increasing at 1 year (23.9% *vs* 54.1%, $P$ = 0.013).

The highly anticipated results from the NRG Oncology/RTOG 1205 phase II clinical trial (NCT01730950) are expected in 2023. It randomizes patients with recurrence to BEV alone or BEV with concurrent re-RT (35 Gy in 10 fractions for tumors smaller than 5 cm). Preliminary results of this study have confirmed the safety of the BEV-Re-HFSRT combination and that it provides a benefit in PFS at 6 mo, even without a benefit in mOS, as observed in first line.

### *Re-RT after progression to BEV*

Recently, a new scenario of re-RT has been explored, after progression to BEV. Several groups have published data on this approach, showing an mOS of 5.4 mo[59] and 4.8 mo[39]. The combination of minocycline, BEV, and fractionated re-RT after progression to BEV has been investigated in a phase I trial[60]. PFS3 was 64.6%, and mOS was 6.4 mo. This study adds a prospective trial to the literature showing that re-RT of HGG after BEV failure can be performed with acceptable tolerability. Another recently published phase I trial included 32 patients with rHGG and the combination of

**Table 2 Summary of selected publications reporting hypofractionated stereotactic radiosurgery as salvage treatment in recurrent gliomas**

| Ref. | Study type | No. patients | Histology | Re-irradiation | | | Median interval | Median tumor volume | Median PFS2/actuarial PFS2 | Median OS2 | Severe toxicity | Radionecrosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total dose, median | Dose/fr, median | EQD2 | | | | | | |
| Selch *et al*[106], 2000 | R | 21 | 15 GBM, 3 G3G, 2 G2G, 1 no biopsy | 25 Gy | 5 Gy | 43.8 Gy | 11 mo | 12 mL | 5 mo | 6.7 mo | 0% | 0% |
| Vordermark *et al* [107], 2005 | R | 19 | 9 GBM, 10 G2G | 30 Gy | 5 Gy | 52.5 Gy | 19 mo | 15 mL | 4.9 mo, 4.6 mo (GBM) | 9.3 mo, 7.9 mo (GBM) | 10.5% other than necrosis | 0% |
| Ernst-stecken *et al* [108], 2007 | P | 15 | 10 GBM, 3 G3G. 2 G2G | 35 Gy | 7 Gy | 78.7 Gy | 10 mo | 22.4 mL | 15 mo | 12 mo | 20% need to increase steroids dose without evidence of progressive disease | NR |
| Fokas *et al*[78], 2009 | P | 53 | All GBM | 30 Gy | 3 Gy | 37.5 Gy | NR | 35 mL | 22% at 12 mo | 9 mo | 0% | 0% |
| Fogh *et al*[29], 2010 | R | 147 | 105 GBM, 42 G3G | 35 Gy | 3.5 Gy | 48.1 Gy | 8 mo | 22 mL | NR | 11 mo (GBM) | 0.7% toxicity (severe headaches) | 0% |
| Mckenzie *et al*[69], 2013 | P | 33 | 29 GBM, 4 G3G | 30 Gy | 5 Gy | 52.5 Gy | NR | 8.54 mL | 62% at 6 mo | 8.6 mo | 9% toxicity other than necrosis | 9% by image |
| Ogura *et al*[80], 2013 | R | 30 | 15 GBM, 9 G3G. 6 G2G | 35 Gy | 7 Gy | 78.7 Gy | NR | 9 mL | 3 mo | 10.2 mo | 13.3% need to increase steroids dose without evidence of progressive disease | 6.1% by image |
| Miwa *et al*[109], 2014 | P | 21 | All GBM | 30 Gy | 5 Gy | 52.5 Gy | 12 mo | 27.4 mL | NR | 11 mo | 4.8% | 9.5% |
| Dincoglan *et al* [110], 2015 | R | 28 | All GBM | 25 Gy | 5 Gy | 43.8 Gy | 11.2 mo | 36.5 mL | 5.8 mo | 10.3 mo | 0% | 11% G2 by image |

$\alpha/\beta = 2$; EQD2: Equivalent dose at 2 Gy fractions; G: Grade; G2G: Grade II glioma; G3G: Grade III glioma; GBM: Glioblastoma; NR: Not reported; OS2: Overall survival from re-irradiation; P: Prospective; R: Retrospective; PFS2: Progression free survival from re-irradiation.

pembrolizumab, an anti-programmed cell death protein 1 (PD-1) monoclonal antibody, HFSRT, and BEV, with an mOS and mPFS of 13.4 mo and 7.9 mo, respectively. The authors concluded that this combination is safe and well tolerated, meriting further investigation[61].

### *Re-resection and re-radiation therapy*

Straube *et al*[62] was the first author to suggest that this strategy could be beneficial, after concluding that the pattern of relapse in 26 patients with complete re-S was solely local in 70%. Based on this, and taking into account the maximal safe resection, several groups have demonstrated the value of additional re-RT with different techniques[38,

**Table 3 Summary of selected publications reporting re-irradiation plus temozolomide as salvage treatment in recurrent high-grade gliomas**

| Ref. | Study type | No. patients | Histology | Re-irradiation | | | Median interval | Median tumor volume | Median PFS2/actuarial PFS2 | Median OS2/actuarial OS2 | Severe toxicity | Radionecrosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total dose, median | Dose/fr, median | EQD2 | | | | | | |
| Grosu *et al*[49], 2005 | P | 44 (TMZ 29) | 34 GBM, 2 Gliosarcomas, 8 G3G | 30 Gy | 5 Gy | 52.5 Gy | 16 mo | 15 mL | NR | 8 mo (11 mo RT + TMZ *vs* 6 mo without TMZ) | 0% | 0% |
| Combs *et al*[81], 2008 | R | 25 | 8 GBM, 10 G3G, 7 G2G | 36 Gy | 2 Gy | 36 Gy | 36 mo | 50 mL | 5 mo; 16% at 12 mo | 8 mo; 25% at 12 mo | 0% | NR |
| Minniti *et al*[45], 2011 | R | 36 | All GBM | 37.5 Gy | 2.5 Gy | 42.2 Gy | 14 mo | 13.1 mL | 5 mo; 8% at 12 mo | 9.7 mo; 33% at 12 mo | Thrombocytopenia G3: 2.8% | 8% by image |
| Conti *et al*[47], 2012 | R | 23 (TMZ 12) | All GBM | 20 Gy | 10 Gy | 60 Gy | 7 mo | < 30 mL | 7 mo (TMZ) *vs* 4 mo (no TMZ) | 12 mo (TMZ) *vs* 7 mo (without TMZ) | ≥ G3 hematological toxicity > 40% | 4.3% |
| Minniti *et al*[46], 2013 | R | 54 | 38 GBM, 16 G3G | 30 Gy | 6 Gy | 60 Gy | 15.5 mo | 9.8 mL | 6 mo (4 mo GBM) | 12.4 mo (11.4 mo GBM) | Thrombocytopenia G3: 3.7%, leukopenia G3: 3.7% | 7% by image |
| Greenspoon *et al* [111], 2014 | P | 31 | All GBM | 30 Gy | 5 Gy | 52.5 Gy | At least 6 mo | 12 mL | 7 mo | 9 mo | NR | G3: 9.6%, G4: 3.2% |
| Aktan *et al*[48], 2015 | R | 21 (17 TMZ) | 18 GBM, 3 G3G | 54 Gy | 2 Gy | 54 Gy | 39.4 mo | Recurrent tumor size was median 5.5 cm | NR | 18 mo (G3G) and 14.1 mo (GBM) | 0% | 0% |

α/β = 2; EQD2: Equivalent dose at 2 Gy fractions; G2G: Grade II glioma; G3G: Grade III glioma; G: Grade; GBM: Glioblastoma; NR: Not reported; OS2: Overall survival from re-irradiation; P: Prospective; R: Retrospective; PFS2: Progression free survival from re-irradiation; TMZ: Temozolomide.

63-65].

Combs *et al*[63] published the first study after rHGG re-S followed by early re-RT. It included 108 patients, most of whom received 36 Gy at 2-3 Gy *per* fraction. The mOS was 12 mo, with no serious toxicity. In multivariate analysis, the extent of surgery, methylguanine-DNA methyltransferase (MGMT) methylation, interval time between first and second irradiation, and KPS were independent prognostic factors for OS. A subsequent study[64], with 25 interventional rGBM cases treated with HFSRS and simultaneous integrated boost (37.5 Gy and 45 Gy in 15 fractions), reported an mPFS of 13 mo and mOS of 16 mo, with better outcomes in smaller recurrences, without eloquent area involvement and in patients with a good general condition.

On multivariate analysis, the macroscopic tumor volume (GTV) ≥ 100 mL *vs* < 100 mL was confirmed as an independent prognostic factor affecting OS. Radiologically suspected RN was observed in 16 patients (64%) at a median of 9 mo after re-RT, and 8 patients developed grade 3 RN requiring hospitalization.

**Table 4 Summary of selected publications reporting re-irradiation plus bevacizumab as salvage treatment in recurrent high-grade gliomas**

| Ref. | Study type | No. patients | Histology | Re-irradiation | | | Median interval | Median tumor volume | Median PFS2 | Median OS2 | Severe toxicity | Radionecrosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total dose, median | Dose/fr, median | EQD2 | | | | | | |
| Gutin *et al* [56], 2009 | P | 25 | 20 GBM, 5 G3G | 30 Gy | 6 Gy | 60 Gy | 14.5 mo | 34 mL | 7.3 mo | 12.5 mo | G3: 1 hemorrhage; G4: 3 (1 bowel perforation, 1 wound dehiscence and 1 GI bleed) | 0% |
| Cuneo *et al* [54], 2012 | R | 63 (41 BEV) | 49 GBM, 8 G3G, 6 prior G2G | 15 Gy | 15 Gy | 63.8 Gy | 21 mo | 4.8 mL | GBM: 5.2 mo (BEV) *vs* 2.1 mo (without BEV). 6 mo whole series | GBM: 11.2 mo (BEV) *vs* 3.9 mo (without BEV). 10 mo whole series | 11% | 10% |
| Niyazi *et al* [52], 2012 | R | 30 (20 BEV) | 22 GBM, 8 G3G | 36 Gy | 2 Gy | 36 Gy | NR | NR | 8 mo | Mean 12 mo | G3:1; G4: 1 wound dehiscence | 0% |
| Shapiro *et al* [112], 2013 | R | 24 | 20 GBM, 1 G3G, 3 G2G | 30 Gy | 6 Gy | 60 Gy | 12.6 mo | 35.3 mL | 7.5 mo (6.8 mo GBM) | 12.2 mo (whole series and GBM) | Toxicity BEV: G4: 12.5% | 0% |
| Cabrera *et al* [113], 2013 | P | 15 | 8 GBM, 7 G3G | 18 Gy. 25 Gy | 18 Gy. 5 Gy | 90 Gy. 43.8 Gy | 20 mo | NR (< 5 cm) | 3.9 mo | 14.4 mo | G3:1 | 0% |
| Flieger *et al* [57], 2014 | P | 71 (57 BEV) | 52 GBM, 19 G3G and G2G | 36 Gy | 2 Gy | 36 Gy | NR | NR | 5.6 mo (BEV) *vs* 2.5 mo (without BEV) | GBM: 9.3 mo (BEV) *vs* 6.1 mo (without BEV) | Toxicity BEV: G4: 5.3% | 4.2% (BEV) by image or histologically |

α/β = 2; BEV: Bevacizumab; EQD2: Equivalent dose at 2 Gy fractions; G: Grade; GBM: Glioblastoma; G2G: Grade II glioma; G3G: Grade III glioma; NR: Not reported; OS2: Overall survival from re-irradiation; P: Prospective; PFS2: Progression free survival from re-irradiation; R: Retrospective.

In the series by Chun *et al*[65] with 84 patients, the addition of radiation therapy (median dose of 45 Gy at 1.8 Gy/fr) to re-S was associated with a significant benefit in PFS, with mPFS for re-S being 3.5 mo and 9 mo for re-S plus re-RT. The benefit in OS was marginal, with an mOS of 12.7 mo with re-S *vs* 28.1 mo with re-S plus re-RT ($P$ = 0.066). Three risk factors (age ≥ 50, WHO grade IV, and unmethylated promoter of MGMT) were significantly associated with poor OS in multivariate analysis. The authors established three categories of risk groups based on these factors. The benefit of re-RT in both OS and PFS was established in patients with two or more risk factors (intermediate and high risk groups). There was no radiological or pathological evidence of RN during or after re-RT.

Results of the GlioCAVE/NOA 17 trial (NCT02715297) should better determine the contribution of early adjuvant radiotherapy after re-S in rGBM. It is a prospective phase II study with a schedule of 46 Gy at 2 Gy/fr or 36 Gy at 3 Gy/fr, with PFS as the primary endpoint.

### *Prognostic scales for re-RT*

The first scale to predict OS after re-RT published by Combs[66] derived from 233 patients with recurrent low- and HGG and included: WHO grade, age at the time of re-RT, and the time interval to re-RT. The same group published a modified version, the New Combs Score, which added other factors such as KPS, tumor volume, and re-S prior to re-RT[67]. This new revalidated scale[38,63] with a simple approach, is practical, useful, and widely used for decision making (Table 5).

Other reported prognostic features include the re-RT dose[31,57], use of salvage chemotherapy[43,57], extent of resection[28,43], MGMT promoter methylation status [46], and radiographic response[68-70]. However, how they should be quantified remains to be described.

Interestingly, Chapman *et al*[38], without finding an association of irradiation technique (SRS *vs* non SRS) or fractionation with survival, identified a threshold dose as a function of PTV size that should not be exceeded to minimize toxicity: 40 Gy Biological Equivalent Dose 10 for SRS (16 Gy in 1 fraction) and 45 Gy Biological Equivalent Dose 10 for non-SRS treatments (approximately 30 Gy in 5 fractions, 35 Gy in 10 fractions or 40 Gy in 20 fractions), from the same range as those identified in other series[29,57,71]. And, globally, it identifies a group of patients who can achieve an advantage in OS and PFS with re-RT, in particular young patients with good KPS, longer time interval from initial radiation to first progression, small recurrence volume, and an adequate re-RT dose.

## RADIOTHERAPY SPECIFICATIONS

### *Treatment volumes*

**Definition of target volumes:** The definition of re-RT target volumes should be conservative, minimizing the irradiation of healthy tissues to avoid severe toxicities (RN). It requires not only extreme precision and conformality during treatment but also precise images that identify the exact location of tumor tissues. Inaccuracies in tumor delineation may diminish any gain in local control achieved by dose escalation. One aspect to consider would be whether the relapse is located in the area of previous maximum dose or is marginal or remote from the first irradiation. In this case, and depending on the volume of the relapse, the dose prescription can be less conservative.

Several studies have shown that standard anatomic imaging modalities [computed tomography, magnetic resonance imaging (MRI)], while very accurate in visualizing normal anatomic structures, are limited in defining the exact extent of the tumor. Classically, volume delineation for irradiation is based on T1-weighted MRI with gadolinium. Contrast uptake is a consequence of blood-brain barrier disruption and does not necessarily reflect the actual tumor extent in gliomas. Macroscopic tumor masses far from the margins of contrast enhancement have been detected in surrounding edema and even in adjacent normal-appearing brain tissue[72-74]. Anti-angiogenic drugs may also condition contrast uptake, as they may initially have a stabilizing effect on the blood-brain barrier[75].

Multiple studies correlating imaging findings with histopathologic evaluation in surgically treated patients with HGG have indicated that molecular imaging with amino acid positron emission tomography (PET) is more specific and equally sensitive for tumor detection than MRI (T1 with gadolinium). Grosu *et al*[49] have postulated that target volumes for re-RT should be based on amino acid PET imaging in addition to MRI, to include the actual tumor dimension. Other imaging modalities have been used to delineate GTV, including spectroscopy MRI, perfusion-weighted imaging and diffusion-weighted imaging[76], 11C-methionine PET[49], and 18 F-dihydroxyphenylalanine PET[46]. However, there are no randomized trials that have evaluated the impact of molecular or functional imaging-based radiotherapy on the outcomes achieved.

The ongoing phase II GLIAA (NOA 10/ARO 2013-1) trial[77] is the first randomized study evaluating the impact of differences in planning volumes designed with molecular *vs* MRI imaging on PFS after re-RT in patients with rGBM. The limited availability of molecular and/or functional imaging equipment together with the lack of evidence of its superiority in the design of planning volumes conditions the continued use of MRI images for re-RT volume definition.

**Volumes-exclusive radiotherapy:** The definition of the target volume generally includes the GTV, defined as any contrast-enhancing lesion on T1-weighted MRI. In most studies, the clinical target volume (CTV) equals GTV[28,29,78]. Some papers add

**Table 5 Scoring scheme and new prognostic groups of the "New Combs Score"**

| Prognostic factors | Prognostic value |
|---|---|
| Primary histology | |
| Glioblastoma, WHO IV | 2 |
| Anaplastic glioma, WHO III | 1 |
| Low-grade glioma, WHO I/II | 0 |
| Age | |
| ≥ 50 yr | 1 |
| < 50 yr | 0 |
| Time between primary RT and re-RT | |
| ≤ 12 meses | 1 |
| > 12 meses | 0 |
| Re-resection performed | |
| No | 1 |
| Yes | 0 |
| KPS | |
| < 80% | 1 |
| ≥ 80% | 0 |
| Tumor volume (PTV) | |
| > 47 mL | 1 |
| ≤ 47 mL | 0 |
| Scoring group | Scoring value/mOS |
| a | 0–1/19.5 mo |
| b | 2–3/11.3 mo |
| c | 4–5/8.1 mo |
| d | 6–7/5.5 mo |

KPS: Karnofsky performance status; mOS: Median overall survival; PTV: Planning target volume; RT: Irradiation; WHO: World Health Organization.

a CTV to include the peritumoral edema visualized in the fluid-attenuated inversion recovery sequence of the MRI, since it is known that tumor cells can be found in this location[79,80]. Subsequently, a margin usually ≤ 5 mm is added for PTV expansion [45,49,78], although some authors include up to 1 cm[57,81].

**Volumes-adjuvant radiotherapy:** For re-S patients, Straube *et al*[62] proposed a GTV including the resection cavity and contrast enhancement areas, with a margin of 5-10 mm to generate the CTV and 1-3 mm to create the PTV. The GLIOCAVE-NOA 17 study[82] meets these criteria. The CTV encompasses the margins of the resection cavity, including all areas of contrast enhancement plus 5 mm.

## DOSAGE AND FRACTIONATION

The optimal dose and fractionation schedule in these patients is unknown. Re-RT is a well-known factor contributing to the risk of RN, which is directly associated with dose and irradiated volume.

Sminia and Mayer[83] examined > 25 glioma re-RT studies to assess tolerance dose and treatment volume of normal brain tissue. RN occurred with a cumulative EQD2 dose ($\alpha/\beta$ = 3) > 100 Gy for CFRT, > 105 Gy for fractionated stereotactic radiotherapy (FSRT), and 135 Gy for SRS.

Given that these patients have already received 60 Gy after initial diagnosis, there is a margin of at least 40 Gy for re-RT. Hence, the prescribed doses for re-RT in most published studies ranged from 30-45 Gy, thus maintaining a cumulative EQD2 of approximately 100 Gy[64]. However, given that brain tissue recovers over time, it seems safe to administer higher doses to smaller volumes, using FSRT or SRS, without increasing the likelihood of RN[83].

Scoccianti *et al*[42], after an extensive review of published series and always proposing schemes with reported severe toxicity ≤ 3.5%, described a treatment strategy depending on the volume to be irradiated. Thus, for small volumes (≤ 12.5 mL) SRS schemes are safe (*e.g.*, 12-15 Gy) provided that the EQD2 value does not exceed 65 Gy; HFSRT (*e.g.*, 5 × 5 Gy) for medium-sized lesions (> 12.5-35 mL), provided that the EQD2 value does not exceed 50 Gy and CFRT (*e.g.*, 36 Gy in 20 fr) for larger lesions (> 35-50 mL). These authors pointed out that this recommended strategy should be confirmed in prospective studies.

Whenever possible, hypofractionated schemes are preferred, avoiding unnecessary transfers in these patients with limited life expectancy.

### Organ-at-risk tolerance dose

In primary treatment, the maximum doses to the brainstem, chiasm, and optic nerves to avoid the risk of myelopathy are well defined[84,85]. In the context of re-RT in HGG, current evidence is limited[15,44]. Preclinical data suggest a 61% recovery in the spinal cord after 1 year since the first irradiation, and it is believed that this is likely to be applicable to other central nervous system tissues[86]. These models indicate that, in the context of re-RT, maximum summed doses of up to 86 Gy could be tolerated for the optic chiasm and brainstem.

Two series with low recorded toxicity analyzed cumulative dose in organ-at-risk with different doses and fractionations. Shen *et al*[71] reported a median maximum dose in the brainstem of 76.9 Gy and 56 Gy in the optic pathway, with a CFRT schedule and a mean dose of 41.4 Gy. In the series of Chan *et al*[44], with a dose mostly of 35-40 Gy/15 fr, the median maximum dose was 64 Gy for the brainstem and 54.9 Gy for the optic chiasm, although it is noted that concomitant BEV was administered, which may reduce the risk of RN.

It is essential to record and communicate doses to organ-at-risk before re-RTs in order to be able to design a toxicity risk model.

## TOXICITY AND QOL

### Toxicity

Data on re-RT toxicity are scarce in the literature (Tables 1-4), and its analysis and quantification are difficult. Late toxicity assessment is limited by poor prognosis, difficult differentiation between tumor recurrence, and RN, which is associated with the variety of techniques and fractionations used.

The only existing meta-analysis[33] reported a grade ≥ 3 toxicity rate of 7%, and the morbidity and mortality rate for re-RT ranged from 0%-31% and 0%-1%, respectively.

### QoL

Disease progression is associated with deterioration of neurocognitive function. The evidence supporting treatment in this population is evolving, but little is known about its impact on QoL. The survival benefit is desirable but must be carefully weighed against expected morbidities.

Analysis of pooled data from over 300 GBM patients from 13 published articles showed that overall, re-RT resulted in clinical improvement in 24%-45% of patients and a reduction in corticosteroid dependence in 20%-60% of patients. However, the subgroup with KPS < 70 appeared to have a higher risk of early progression and apparently had less benefit from re-RT[87].

Very few studies prospectively evaluate the impact on QoL and activities of daily living in the setting of salvage re-RT. Wick *et al*[88] analyzed QoL in 84 patients with rGBM from a phase II trial with Asunercept/APG 101 and re-RT *vs* re-RT alone, with a dose of 36 Gy at 2 Gy/fr. The EORTC QLQ-C15-PAL, EORTC QLQ-BN20, and Medical Research Council scale questionnaires were used, concluding that Asunercept plus re-RT significantly prolonged time to deterioration of QoL *vs* re-RT alone. More recently, Maitre *et al*[89] reported prospective data on QoL and activities of daily living in patients with recurrent/progressive glioma treated with re-RT (median dose EQD2 51.4 Gy). They used the QLQ-C30 and QLQ-BN20 questionnaires and the modified

Barthel index. They performed 225 evaluations in 60 patients, concluding that high-dose re-RT in selected patients is associated with stabilization of QoL and greater functional independence.

## NEW STRATEGIES FOR RE-RT

New re-RT strategies for the treatment of HGG recurrences include particle radiotherapy, as well as intraoperative radiation therapy (IORT) and brachytherapy. Although they are not novel techniques, they are re-emerging in recent years with technological advances.

### *Particle irradiation*

Proton therapy is emerging for the treatment of these patients. Due to its physical and radiobiological properties, this radiation modality offers dosimetric advantages over photons, achieving a better dose distribution and decreasing the irradiation of healthy tissue. The Proton Collaborative Group has published the largest series to date[90]. They analyzed 45 patients with a median of 20.2 mo between initial diagnosis and recurrence. The median dose was 46.2 Gy (range, 25-60 Gy), with a mean of 2.2 Gy/fr, achieving mPFS and mOS of 13.9 and 14.2 mo, respectively. The treatment was well tolerated, and the appreciated toxicity was related to a dose higher than 41 Gy (EQD2). Only prior surgery was positively associated with PFS and OS.

The first study of re-RT with carbon ion beams in rHGG analyzed 30 patients with a median interval between initial radiotherapy and re-RT of 10 mo[91]. The dose administered was 45 Gy in 15 fractions, with a mOS of 13 mo. Eight patients had grade 3 toxicity. Only initial histology with a Ki67 < 20% was a prognostic factor. Resection or chemotherapy did not significantly improve OS. A phase I/II trial to compare re-RT of recurrent gliomas with carbon ions *vs* re-RT with photons is ongoing (NCT 01166308).

### *IORT*

IORT data come from older series, mainly from HGG at diagnosis, and only a few papers included rGBM[32]. The results were promising, but the complexity of the procedure led to abandoning its use. The development of portable systems capable of being moved to the operating room has sparked interest in this technique. This approach is conceptually attractive because it allows the delivery of a large dose of radiation to the tumor bed and tumor debris close to the surgical cavity immediately after resection, while respecting the surrounding brain tissue, decreasing the likelihood of RN. In addition, local and systemic immune responses may be promoted, which could benefit oncological outcomes[92,93].

Recently, although in newly diagnosed GBM, Giordano *et al*[94] reported the results of a phase I/II dose-escalation trial, evaluating the safety and efficacy of the Zeiss INTRABEAM system, a miniaturized 50 keV LINAC with spherical applicators. Fifteen patients, mainly with subtotal resection, were included, receiving a dose of 30 and 40 Gy, with no evidence of limiting toxicity, achieving a PFS of 17.7 mo.

### *Brachytherapy*

Like IORT, it has the advantage of allowing immediate irradiation of the surgical cavity[95], without having to wait the usual 4 wk until the surgical wound is completely healed to start external radiotherapy. This delay is not desirable in HGGs, where in as little as 3 wk there is already a high rate of tumor repopulation. The most commonly used technique is permanent seed implantation. Initially the isotope used was I-125, but high complication rates were reported[96]. Suture-stranded Cs-131 seeds, with a shorter half-life, are now the most commonly used isotope. A study combining re-S with insertion of suture-stranded Cs-131 seeds and BEV (before or after the procedure) has recently been published[95]. Twenty patients were analyzed, with a dose of 80 Gy administered at 0.5 cm from the surface of the resection cavity. Seven patients had been previously salvaged with external radiotherapy. Local control was 85% and mOS was 9 mo. There were two wound infections and three seizures, with no case of RN.

These radiation techniques are safe and effective, but further prospective and comparative research is needed to draw solid conclusions.

## SPECIAL PATIENT GROUPS

### *Elderly patients*

As in younger patients, radiotherapy is the cornerstone of first-line treatment of older patients with GBM. However, they receive poor care after recurrence[97]. The evidence for re-RT in older patients is very scarce, as the median age in published papers is around 53 years[33]. However, the aging population is growing and treatment decisions in patients with rGBM and good general condition are increasing. To our knowledge, only one study on re-RT in older patients has been published. Straube *et al* [98] reported the results of 25 patients with a median age of 69.6 years (range 65-79) who received re-RT, most after reintervention. The mOS was 6.9 mo and mPFS at 4.3 mo, with no case of severe toxicity attributable to re-RT. This survival is within the range of series reported in younger patients[28]. Therefore, although prospective trials are needed, these results suggest that second-line salvage therapy should not be dismissed on the basis of age alone.

### *Pediatric patients*

As with adults, children with rHGG have limited treatment options. Re-RT has an emerging role as a palliative treatment for children with recurrent brainstem glioma (diffuse intrinsic pontine glioma or DIPG)[99-101], being associated with symptomatic improvement and longer survival compared to non-re-irradiated patients[99]. Indeed, re-RT in DIPGs is the subject of several ongoing or completed prospective studies (NCT01777633 and NCT03126266). Given that the irradiation dose tolerance of the supratentorial brain is higher than that of the brainstem, it stands to reason that re-RT in supratentorial rHGG should be equally safe and effective[102]. However, the role of re-RT has been little studied in non-pontine gliomas.

Recently, Tsang *et al*[103] have published the results of the largest known cohort of children with recurrent supratentorial HGG treated with re-RT compared to a group of non-re-irradiated children. They retrospectively analyzed 40 patients ≤ 18 years. Fourteen patients, with an interval of at least 6 mo after the first radiotherapy, were re-irradiated. Doses administered ranged from 30-54 Gy at 1.8 Gy/fr. Median survival was 9.4 mo for re-RT patients compared to 3.8 mo for the 26 who did not receive re-RT. The time elapsed between the first and second irradiation determined significant differences, being higher in children with an interval ≥ 12 mo. One patient presented grade 3 RN 4 mo after re-RT. There were no significant differences between patients with initial *vs* distant field re-RT, between those who received concurrent chemotherapy *vs* exclusive re-RT, or between those who were previously operated *vs* those who received radiotherapy alone. Thus, offering re-RT to these patients is associated with reasonable short-term control and survival without significant toxicity.

## CONCLUSION

The rHGG scenario remains devastating. Nevertheless, the available evidence, albeit low level, suggests that re-RT, at recommended doses and in selected patients, is safe and provides encouraging local control and survival rates.

The combination of re-S with early re-RT appears to be the most promising option.

Randomized clinical trials are needed to establish the optimal treatment strategy for these patients.

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