



Re-irradiation as salvage treatment in recurrent glioblastoma: A comprehensive literature review to provide practical answers to frequently asked questions

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ABSTRACT

The primary aim of this review is to provide practical recommendations in terms of fractionation, dose, constraints and selection criteria to be used in the daily clinical routine.

Based on the analysis of the literature reviewed, in order to keep the risk of severe side effects $\leq 3.5\%$, patients should be stratified according to the target volume. Thus, patients should be treated with different fractionation and total EQD2 (< 12.5 ml: EQD2 < 65 Gy with radiosurgery; > 12.5 ml and < 35 ml: EQD2 < 50 Gy with hypofractionated stereotactic radiotherapy; > 35 ml and < 50 ml: EQD2 < 36 Gy with conventionally fractionated radiotherapy).

Concurrent approaches with temozolomide or bevacizumab do not seem to improve the outcomes of re-irradiation and may lead to a higher risk of toxicity but these findings need to be confirmed in prospective series.

1. Introduction

The median overall survival of patients with GBM remains inferior to 15 months and nearly all patients recur eventually: in the long term follow-up of patients included in the European Organization for Research and Treatment of Cancer (EORTC)/ National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) trial (Stupp et al., 2005), only 6% were progression-free at 3 years (Stupp et al., 2009).

Median survival after progression for patients initially treated with temozolomide and radiotherapy is very poor (6.2 months in the EORTC/NCIC-CTG trial (Stupp et al., 2009)).

Feasible approaches for recurrent glioblastoma in patients with a good performance status are second surgery, reirradiation, systemic treatment or multimodal treatment, whereas best supportive care is the preferable option for patients with poor performance status.

In this paper, existing data on the efficacy and toxicity of various radiation treatment options including RS, HFSRT, and CFRT have been reviewed.

The interpretation of the literature is very difficult due to the retrospective nature of the majority of the studies on different treatment modalities, fractionation schedules and selection criteria.

The main pitfall of the existing studies is the extreme heterogeneity in baseline characteristics of the patients: some series included recurrent grade III or II gliomas as well, not only pure astrocytomas; some authors included temozolomide-naïve patients too; while some studies did not exclude cases of early progression, likely to be pseudoprogression.

Moreover, the different measures of the outcome of the different studies further complicated the analysis of the literature findings. Of note, although survival may not be an adequate measure to evaluate the outcome in this scenario (Ballman et al., 2007), other measures of outcome, as PFS, are rarely reported in the literature.

On the other hand, definitive data on radiation-induced severe toxicity are also troublesome to reach not only because the differentiation between tumor recurrence and radionecrosis after reirradiation may be very difficult, but also because some authors did not report the grade of toxicity either for radionecrosis or for other types of side effects.

The literature was thoroughly reviewed and the correlation between dose and response and between dose and toxicity was herein explored in order to define the optimal fractionation and prescription dose in terms of efficacy and tolerability. Moreover, some practical

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Table 1
Radiosurgery as salvage treatment in recurrent glioblastoma.

Author	Number of patients	Histotype	Median tumor volume	Median marginal dose	mOS and actuarial OS from the time of reirradiation	mPFS and actuarial PFS from the time of reirradiation		Severe toxicity	EQD 2 for second course RT (alpha/beta ratio = 2 Gy)
						Whole series	GBM only		
Hall et al. (1995)	35	26 GBM, 9 WHO III gliomas	28 ml	20 Gy	8 m	n.a.	n.a.	5.7% histologically confirmed radionecrosis	110 Gy
Shrieve et al. (1995)	86	All GBM	10 ml	13 Gy	–	–	10.2 m; 45% at 12 m	3.5% severe toxicity other than necrosis	48.75 Gy
Kondziolka et al. (1997)	19	All GBM	6,5 ml	15 Gy	–	–	16 m	0%	63.75 Gy
Cho et al. (1999)	46	27 GBM, 19 WHO III gliomas	10 ml	17 Gy	11 m; 42% at 12 m	n.a.	n.a.	4.3% histologically confirmed radionecrosis	80.75 Gy
Combs et al. (2005a)	32	All GBM	10 ml	15 Gy	–	–	10 m; 38% at 12 m	0%	63.75 Gy
Hsieh et al. (2005)	26	All GBM	21,6 ml	12 Gy	–	–	10 m	31.3% radiological radionecrosis	42 Gy
Kong et al. (2008)	114	65 GBM, 49 WHO III gliomas	10,6 ml	16 Gy	n.a.	n.a.	13 m; 58.4% at 12 m	24.4% radiological radionecrosis	72 Gy
Patel et al. (2009)	26	All GBM	10,4 ml	18 Gy	–	–	8,5 m	7.6% histologically confirmed radionecrosis	90 Gy
Skeie et al. (2012)	51	All GBM	12,4 ml	12,2 Gy	–	–	9 m	0%	43.3 Gy
Martinez-carrillo et al. (2014)	87	46 GBM, 41 WHO III gliomas	4 ml	18 Gy	10 m; 37.9% at 12 m	n.a.	7.5 m; 0.4% at 12 m	0%	90 Gy

HGG: high grade gliomas; GBM: glioblastoma; OS: overall survival; PFS: progression free survival; m: months.

considerations for radiation treatment planning are provided in terms of constraints to use, in order to minimize the expected toxicity.

2. Materials and methods

Literature data from 1995 to 2015 were identified by searching the PUBMED database with the following as keywords: "recurrent glioblastoma", "radiotherapy", "radiosurgery", "stereotactic radiotherapy", "second radiotherapy", "repeat radiation therapy", only including papers written in English. Only series with more than 5 patients with recurrent GBM were examined.

In order to understand the therapeutic value of repeat radiotherapy, we collected data on treatment characteristics (dose, fractionation, radiation technique, associated systemic therapies) and treatment outcome (OS, PFS, toxicity).

Literature findings were divided into two main parts: exclusive radiotherapy or concurrent approaches as salvage treatment of recurrent gliomas. Literature regarding the use of radiotherapy alone was divided into three different categories according to the fractionation: RS, HFSRT, and CFRT. Review on the concurrent approaches focused on reirradiation associated with the two most frequently used agents: temozolomide and bevacizumab.

When analyzing cases applying different fractionation, in order to compare different schedules, data were analyzed by converting the prescribed doses to EQD2 values, with EQD2 being defined as the total dose delivered in 2-Gy fractions at alpha/beta ratio of 2 Gy for normal brain tissue. Although this approach is not completely reliable for very high doses due to the fact that the underlying mechanisms implied by the LQ model do not consider the vascular and stromal damage produced when very high doses per fraction are given (Kirkpatrick et al., 2008), we decided to use it for all the hypofractionated schedules including radiosurgery, as already done by other authors (Mayer and Sminia, 2008).

Results referring exclusively to GBM patients have been reported when possible. On the other hand, it was clearly specified when only results for the whole series including other histologies were available.

When available, characteristics of the first radiotherapy course were recorded (dose, association with temozolomide, interval time to reirradiation).

To evaluate the efficacy in terms of outcome, all the data regarding OS and PFS were collected.

Efforts were made to provide results in terms of toxicity, differentiating radionecrosis from other adverse effects, reporting, when available, the grade of the toxic events.

With regard to radionecrosis, efforts were made to differentiate between histologically proven pure necrosis and radiologically diagnosed necrosis. In our analysis, cases of mixed tumor recurrence and necrosis were considered as tumor persistence and not as necrosis, considering the fact that the area of necrosis is a typical feature of the disease.

Given the dismal prognosis of a recurrent GBM, a risk < 3.5% of severe side effects was here arbitrarily defined as an acceptable toxicity.

3. Results

Twenty-nine reirradiation studies were identified and stratified according to the fractionation for studies of exclusive radiotherapy or to the concomitant drug for studies of radiochemotherapy. Number of patients, histologic subtypes, tumor volume, prescription dose, dose for fraction, number of fractions were listed. EQD2 values were specified for all the fractionated radiation schedules to allow comparisons of the different series.

Dose and schedule of systemic therapy were specified for concurrent approaches. Results in terms of OS and PFS were reported for GBM when available, and for the whole series for studies that included a mixture of different histotypes. Rates of severe toxicity were listed.

3.1. Radiosurgery as salvage treatment in recurrent GBM (Table 1)

Several retrospective series (Cho et al., 1999; Combs et al., 2005b; Hall et al., 1995; Hsieh et al., 2005; Kondziolka et al., 1997; Martínez-Carrillo et al., 2014; Patel et al., 2009; Shrieve et al., 1995; Skeie et al., 2012) have been published since the 90's on the use of radiosurgery as salvage treatment in recurrent gliomas; to our knowledge, only a prospective trial was conducted focusing on the use of radiosurgery for relapsing gliomas (Kong et al., 2008).

Median treatment dose ranged from 12.2 Gy (Skeie et al., 2012) to 20 Gy (Hall et al., 1995), with a very wide range in the median target volume, which ranged from 6.5 (Martínez-Carrillo et al., 2014) to 28 ml (Hall et al., 1995).

Considering only the series reporting results for patients with recurrent GBM, the OS ranged from 7.5 (Martínez-Carrillo et al., 2014) to 16 months (Kondziolka et al., 1997). Few series, all regarding GBM only, reported data about PFS: median PFS was 4.6 (Kong et al., 2008)-7 (Combs et al., 2005b) months.

The most frequently reported severe toxicity was radionecrosis: in some series the cases of suspected radionecrosis were histologically proven with a rate ranging from 1.6 (Kondziolka et al., 1997) to 7.6% (Patel et al., 2009), whereas some authors reported data on the radiological evidence of radionecrosis as detected with imaging techniques and they found a higher radionecrosis rate (up to 31.3% (Hsieh et al., 2005)). Rarely were reported other severe neurologic toxicities (acute herniation, hydrocephalus, and cranial nerve deficit) (Shrieve et al., 1995).

The rate of severe toxicity < 3.5% was reported in all the series where the median target volume was < 12.5 ml and the median prescription dose was ≤ 15 Gy.

These data seem to suggest that patients with a small target volume (< 125 ml) may be eligible for RS, and that median prescription dose should remain between 12 and 15 Gy (i.e. EQD2 < 65 Gy), considering that series using higher median doses had an unacceptable toxicity rate (Cho et al., 1999; Hall et al., 1995; Kong et al., 2008; Patel et al., 2009).

3.2. Hypofractionated stereotactic radiotherapy (HFSRT) as salvage treatment in recurrent GBM (Table 2)

Several authors published their experiences on HFSRT (Ernst-Stecken et al., 2007; Fogh et al., 2010; Fokas et al., 2009; Kim et al., 2011; Kong et al., 2008; McKenzie et al., 2013; Ogura et al., 2013; Selch et al., 2000; Vordermark et al., 2005). Unfortunately, most studies included relapsing WHO grade III gliomas (Ernst-Stecken et al., 2007; Fogh et al., 2010; Kim et al., 2011; Kong et al., 2008; McKenzie et al., 2013; Ogura et al., 2013; Selch et al., 2000; Vordermark et al., 2005) and several series even included some cases of recurrent WHO grade II (Ernst-Stecken et al., 2007; Ogura et al., 2013; Selch et al., 2000; Vordermark et al., 2005). Extremely different radiotherapy regimens were used, with fraction sizes ranging from 3 to 7 Gy and a number of fractions ranging from 5 to 10. EQD2 ranged between 37.5 and 78.5 Gy.

Considering only the series where results for glioblastoma patients were specified, the median overall survival ranged between 7.9 (Vordermark et al., 2005) and 11 months (Fogh et al., 2010), while median PFS was reported only rarely.

The rate of toxicity was highly variable. Some authors did not report any cases of severe toxicity (Ernst-Stecken et al., 2007; Fokas et al., 2009; Selch et al., 2000; Vordermark et al., 2005), whereas in some series the rate of pathologically proven radionecrosis rose up to 12.5% (Kim et al., 2011). Some authors reported toxicities other than radionecrosis with a rate ranging from 0.7 to 10.5%: hydrocephalus with a need of implant of Ommaya reservoir (Vordermark et al., 2005), dizziness (McKenzie et al., 2013), headache (Fogh et al., 2010; McKenzie et al., 2013) or the worsening of the existing neurological symptoms (McKenzie et al., 2013). A prolonged need for increased steroids dose was also reported (Ernst-Stecken et al., 2007; Ogura et al., 2013), and it

Table 2
Hypofractionated Stereotactic Radiotherapy as salvage treatment in recurrent glioblastoma.

Author	Number of patients	Histotype	Median tumor volume	Median marginal dose	Median dose per fraction	number of fractions	mOS and actuarial OS from the time of reirradiation		mPFS and actuarial PFS from the time of reirradiation	Severe toxicity	EQD 2 for second course RT (alpha/beta ratio = 2 Gy)
							Whole series	GBM only			
Cho et al. (1999)	25	15 GBM, 10 WHO III gliomas	40 ml	37.5 Gy	2.5 Gy	15	12 m; 50% at 12 m	n.a.	n.a.	n.a.	42.2 Gy
Selch et al. (2000)	21	15 GBM, 3 WHO III gliomas, 2 WHO II gliomas, 1 unbiopsied	12 ml	25 Gy	5 Gy	5	6.7 m; 15% at 12 m	n.a.	5 m	n.a.	43.7 Gy
Vordemark et al. (2005)	19	9 GBM, 10 WHO II or III gliomas	15 ml	30 Gy	5 Gy	6	9.3 m; 26% at 12 m	7.9 m	4.9 m	4.6 m	52.5 Gy
Ernst-stecken et al. (2007)	15	10 GBM, 3 WHO III gliomas, 2 WHO II gliomas	22.4 ml	35 Gy	7 Gy	5	12 m; 85% at 6 m; 43% at 12 m	n.a.	15 m; 75% at 6 m; 53% at 12 m	n.a.	78.7 Gy
Fokas et al. (2009)	53	All GBM	35 ml	30 Gy	3 Gy	10	–	9 m	–	22% at 12 m	37.5 Gy
Kim et al. (2011)	8	5 GBM, 3 WHO III gliomas	69.5 ml	25 Gy	5 Gy	5	7.6 m	n.a.	4.6 m	n.a.	43.7 Gy
Fogh et al. (2010)	147	105 GBM, 42 WHO III gliomas	22 ml	35 Gy	3.5 Gy	10	n.a.	11 m	n.a.	n.a.	48.1 Gy
McKenzie et al. (2013)	33	29 GBM, 4 WHO III gliomas	8.5 ml	30 Gy	5 Gy	6	8.6 m; 66% at 6 m; 34% at 12 m	n.a.	62% at 6 m	n.a.	52.5 Gy
Ogura et al. (2013)	30	15 GBM, 9 WHO III gliomas, 6 WHO II gliomas	9.0 ml	35 Gy	7 Gy	5	10.2 m; 83% at 6 m; 34% at 12 m	n.a.	3 m; 19% at 6 m; 10% at 12 m	n.a.	78.7 Gy

OS: overall survival; PFS: progression free survival; BED: biologically effective dose; HGG: high grade gliomas; GBM: glioblastoma; n.a: not available; m: months.

Table 3

Conventionally fractionated stereotactic radiotherapy as salvage treatment in recurrent glioblastoma.

Author	Number of patients	Histotype	Median tumor volume	Median marginal dose	Median dose per fraction	number of fractions	mOS and actuarial OS from the time of reirradiation		mPFS and actuarial PFS from the time of reirradiation		Severe toxicity
							GBM and other histologies	GBM only	GBM and other histologies	GBM only	
Combs et al. (2005b)	59	All GBM	49.3 ml	36 Gy	2 Gy	18	–	8 m: 23% at 12 m	–	6% at 12 m	1.7% histologically proven radionecrosis

OS: overall survival; PFS: progression free survival; BED: biologically effective dose; GBM: Glioblastoma; n.a: not available.

is seemed to be related to very high EQD2 (> 75 Gy).

As expected, the target volume had a significant impact on the tolerability of treatment. Cho et al (Cho et al., 1999) treated patients with a median volume of 40 ml and had 8% of severe toxicity rate, despite of the choice of a schedule with low EQD2 (42.2 Gy). Kim et al (Kim et al., 2011) used HFSRT in a series of patients with very large lesions (median tumor size = 69.5 ml) and they reported a very high rate of histologically confirmed radionecrosis, despite of the low EQD2 (43.75 Gy).

The analysis of the literature may suggest that hypofractionated regimens with an EQD2 < 50 Gy have an optimal toxicity profile (severe toxicity rate < 3.5%), provided that they are used in lesions < 35 ml.

3.3. CFRT as salvage treatment in recurrent GBM (Table 3)

Combs et al (Combs et al., 2005b) published their results for 59 GBM patients who were treated with a conventionally fractionated stereotactic technique for a total dose of 36 Gy. Of note, their rate of severe toxicity was very low (1.7%), despite of the large median tumor size (49.3 ml).

Despite the clear disadvantage of a longer treatment time, CFRT may be indicated for lesions with large volume, considering the lower incidence of severe late toxicity. A dose of 36 Gy in 2 Gy fractions seem to be safe for volumes up to 50 ml.

3.4. Concurrent approaches with temozolomide or bevacizumab

Our review focused on the existing clinical experiences regarding the two agents that have mainly been tested together with second radiotherapy as a concurrent approach for relapsing glioblastoma: Temozolomide and Bevacizumab.

3.4.1. Reirradiation and temozolomide (Table 4)

Temozolomide (TMZ) was tested together with a reirradiation only in a prospective trial (Grosu et al., 2005), all the other series being retrospective (Combs et al., 2008; Conti et al., 2012; Minniti et al., 2013, 2011).

TMZ was administered concurrently for the whole duration of reirradiation (50 mg/m² (Combs et al., 2008) or 75 mg/m² (Conti et al., 2012; Minniti et al., 2013, 2011), daily), or was given in a sequential administration according to different schedules (200 mg/m² for 5 days, q28 (Grosu et al., 2005) or 50 mg/m² continuously (Minniti et al., 2013)). The number of sequential cycles scheduled was very variable, ranging from 0 (no sequential chemotherapy [Minniti et al., 2011] to a maximum of 12 cycles [Minniti et al., 2013]

Chemotherapy with TMZ was associated either with CFRT (Combs et al., 2008) or HFSRT (Grosu et al., 2005; Minniti et al., 2013, 2011). Total dose for CFRT was 36 Gy (Combs et al., 2008). HFSRT was frequently used with high dose for fraction (5 Gy (Grosu et al., 2005), 6 Gy (Minniti et al., 2013) or 10 Gy (Conti et al., 2012)) but also a series with 2,5 Gy per fraction was published (Minniti et al., 2011). Again, all the

schedules were compared using the Linear Quadratic Model. EQD2 ranged between 36 and 60 Gy. Median OS reported for patients with relapsing glioblastoma and treated with reirradiation and temozolomide ranges from 9.7 (Minniti et al., 2011) to 12 months (Minniti et al., 2013), whereas median PFS ranged between 4 (Minniti et al., 2013) and 7 months (Combs et al., 2008) with an actuarial PFS at 12 months ranging between 8 (Minniti et al., 2011) and 10% (Minniti et al., 2013).

Myelotoxicity attributable to temozolomide were evidenced mostly during the sequential phase of the chemotherapy [Conti et al., 2012 and Minniti et al., 2013].

Severe (≥G3) hematological toxicity was reported in up to 33% of the cases (Conti et al., 2012), whereas radiological radionecrosis was reported in 7–8% of patients (Minniti et al., 2013, 2011), and histopathologically proven radionecrosis in 4.2% (Conti et al., 2012).

In conclusion, though prospective data are scarce, outcomes in terms of OS and PFS for recurrent GBM with reirradiation plus TMZ apparently did not differ significantly from results achieved with reirradiation alone; on the other hand, the addition of TMZ seems to lead to a high risk of severe myelotoxicity.

3.4.2. Reirradiation and bevacizumab (Table 5)

To our knowledge, all the existing studies where Bevacizumab (BEV) was associated with reirradiation are retrospective.

Concurrent approach with BEV was given together with RS (Cuneo et al., 2012), HFSRT (Hundsberger et al., 2013; Shapiro et al., 2013) and CFRT (total dose 36 Gy in 18 fractions (Flieger et al., 2014)).

BEV at 10 mg/kg q14 was administered during reirradiation only (Flieger et al., 2014), or in a sequential schedule (Hundsberger et al., 2013; Shapiro et al., 2013).

EQD2 for hypofractionated treatment ranged between 36 and 63.75 Gy. Considering the series that reported results in terms of outcome limited to GBM only, the mOS ranged between 9.3 (Flieger et al., 2014) and 12.2 (Shapiro et al., 2013) months, whereas mPFS ranged between 5.1 (Flieger et al., 2014) and 6.8 months (Shapiro et al., 2013).

Radionecrosis rate was less than 5% (Cuneo et al., 2012; Flieger et al., 2014), but no study reported a histologically proven necrosis rate. Severe toxicity attributable to the addition of bevacizumab was frequent (up to 40% (Hundsberger et al., 2013)). Severe adverse effects attributable to bevacizumab were CNS (Shapiro et al., 2013; Hundsberger et al., 2013) and extra-CNS hemorrhage (epistaxis (Hundsberger et al., 2013) and gastrointestinal bleeding (Shapiro et al., 2013), bowel perforation (Shapiro et al., 2013; Flieger et al., 2014), wound-healing complication (Shapiro et al., 2013; Flieger et al., 2014), deep vein thrombosis (Flieger et al., 2014), thrombocytopenia (Flieger et al., 2014), hypertonia (Hundsberger et al., 2013) and proteinuria (Hundsberger et al., 2013).

In conclusion, basing on the available retrospective studies, adding BEVA to reirradiation does not seem to change the outcome in terms of OS and PFS for recurrent GBM; at the same time, the addition of BEVA seems to lead to a higher risk of severe toxicity. However, prospective trials are warranted: results of the RTOG 1205 trial should be available soon and might add important information.

Table 4
Reirradiation plus temozolomide as salvage treatment in recurrent glioblastoma.

Author	Number of patients	Histotype	TMZ schedule	TMZ	Median tumor volume	Median marginal dose	Median dose per fraction of fractions	mOS and actuarial OS from the time of reirradiation				mPFS and actuarial PFS from the time of reirradiation				Severe toxicity				
								RT or RT + TMZ		RT + TMZ		RT only		RT or RT + TMZ			RT + TMZ		RT only	
								Whole series		GBM only		Whole series		GBM only			Whole series		GBM only	
								Whole series	GBM only	Whole series	GBM only	Whole series	GBM only	Whole series	GBM only					
Grossi et al. (20-05)	44	34 GBM, 10 WHO III gliomas	-Before RT: TMZ 200 mg/mq/d for 5 days (1-2 cycles) -After RT: TMZ 200 mg/mq for 5 days (4-5 cycles)	29/44	20 ml (for RT + TMZ)	30 Gy	5 Gy 6	8 m	n.a	11 m	n.a	n.a	n.a	n.a	n.a	0%				
Combs et al. (20-08)	25	8 GBM, 10 WHO III gliomas, 7 WHO II gliomas	- During RT: TMZ 50 mg/mq/d - 17/25 pts: sequential TMZ: dose n.a.	All	50 ml	36 Gy	2 Gy 18	-	-	8 m; 25% at 12 m	n.a	-	-	5 m; 16% at 12 m	n.a	0%				
Minniti et al. (20-11)	36	All GBM	- During RT: TMZ 75 mg/mq/d - No sequential TMZ: dose n.a.	All	13.1 ml	37.5 Gy	2.5 Gy 15	-	-	-	9.7 m; 33% at 12 m	-	-	-	5 m; 8% at 12 m	-	Radiological radionecrosis 8%; G3 thrombocytopenia 2,8%			
Conti et al. (20-12)	23	All GBM	- Starting from the first day of RT: TMZ 75 mg/mq/d for 21 days, q28	12/23	< 30 ml	20 Gy	10 Gy 2	-	n.a.	-	12 m; 58% at 12 m	-	7 m; 9% at 12 m	-	7 m; 66.7% at 6 m	4 m; 18% at 6 m	Pts treated with TMZ: Histologically confirmed radionecrosis 8.3%; ≥ G3 haematological toxicity 33%			
Minniti et al. (20-13)	54	38 GBM, 16 grade III gliomas	- During RT: TMZ 75 mg/mq/d - After RT: TMZ 50 mg/mq/d for a maximum of 12 months	All	9.7 ml	30 Gy	6 Gy 5	-	-	12.4 m; 53% at 12 m	11.4 m; 45% at 12 m	-	-	6 m; 24% at 12 m	4 m; 10% at 12 m	Radiological radionecrosis 7%; G3/G4 lymphopenia 185%; G3 thrombocytopenia 3,7%; G3 leukopenia 3,7%				

TMZ: temozolomide; RT: radiotherapy; OS: overall survival; PFS: progression free survival; GBM: Glioblastoma; AOD: anaplastic oligodendroglioma; AOA: anaplastic astrocytoma; AA: anaplastic astrocytoma; OA: oligoastrocytoma; A: astrocytoma; PTV: planned target volume; HFSRT: hypofractionated stereotactic radiotherapy; n.a: not available; m: months.

Table 5
Reirradiation plus bevacizumab as salvage treatment in recurrent glioblastoma.

Author	Number of patients	Histo type	BEVA schedule	Pts treated with BEVA	Median tumor volume	Median marginal total dose	Median dose per fraction	mOS and actuarial OS from the time of reirradiation				mPFS and acturial PFS from the time of reirradiation				Severe toxicity				
								RT and RT + BEVA		RT + BEVA		RT only		RT and RT + BEVA			RT + BEVA		RT only	
								Whole series	GBM only	Whole series	GBM only	Whole series	GBM only	Whole series	GBM only		Whole series	GBM only		
Cuneo et al. (2012)	63	49 GBM, 8 WHO 3 gliomas, 6 prior LGG	n.a.	41/63	4.8 ml	15 Gy	15 Gy	n.a.	n.a.	11.2 m; 50% at 12 m	n.a.	n.a.	n.a.	5.2 m at 18% 12 m	2.1 m	Pts treated with Beva: Radiological or histologically proven radionecrosis 4.9%				
Shapiro et al (2013)	24	20 GBM, 1 WHO III gliomas, 3 WHO II gliomas	10 mg/kg every 14 days until treatment failure	24/24	35.3 ml	30 Gy	6 Gy	-	-	12.2 m	12.2 m	-	-	7.5 m	6.8 m	-	Pts treated with Beva: G4 toxicity attributable to Beva 12.5%			
Hundsberger et al. (2013)	14	8 GBM, 6 WHO III and WHO II gliomas	10 mg/kg every 14 days for 2 cycles before RT and, then, until treatment failure	10/14	190 ml	41.6 Gy	2.77 Gy	9.0 m	-	8.4 m	-	14.3 m	-	5.1 m	-	3.7 m	Any grade toxicity attributable to Beva 40%			
Flieger et al. (2014)	71	52 GBM, 19 WHO III and WHO II glioma	10 mg/kg every 14 days during RT	57/71	34.9	36 Gy	2 Gy	7.9 m	9.1 m	8.6 m	9.3 m	n.a.	6.1 m	4.9 m	5.1 m	2.5 m	Pts treated with Beva: Radiological or histologically proven radionecrosis 4.2%; \geq G4 toxicity attributable to Beva 5.3%			

BEVA: Bevacizumab; GBM: Glioblastoma; OS: overall survival; PFS: progression free survival; RS: radiosurgery.

Since we think that serious toxicity should be avoided in such frail patients, in our opinion, currently there are no sufficient data to recommend the routinely use of reirradiation with systemic therapy.

4. Definition of the target volume

In most cases, the gross tumor volume (GTV) was defined as the contrast-enhancing lesion on MR imaging.

In few experiences, other imaging modalities were used to delineate the GTV: MR-spectroscopy, perfusion-weighted imaging and diffusion-weighted imaging (Conti et al., 2012), 11 C-Methionine positron emission tomography (MET-PET) (Grosu et al., 2005), 18 F-dihydroxyphenylalanine (DOPA) PET (Minniti et al., 2013) or 123I-alpha-methyl-tyrosine (IMT) single-photon computed emission tomography (SPECT) (Grosu et al., 2005).

In the majority of the studies (Hall et al., 1995; Shrieve et al., 1995; Kondziolka et al., 1997; Cho et al., 1999; Combs et al., 2005a; Hsieh et al., 2005; Patel et al., 2009; Skeie et al., 2012; Martínez-Carrillo et al., 2014; Selch et al., 2000; Vordermark et al., 2005; Ernst-Stecken et al., 2007; Fokas et al., 2009; Fogh et al., 2010; McKenzie et al., 2013; Combs et al., 2005b, 2008; Minniti et al., 2011; Shapiro et al., 2013), the clinical target volume (CTV) was equal to GTV, whereas only three studies (Kim et al., 2011; Ogura et al., 2013; Hundsberger et al., 2013) included in their CTV also the peritumoral edema, as defined on fluid attenuated inversion recovery (FLAIR) sequences.

A further millimetric margin was usually added to CTV in order to create a planning target volume (PTV). This safety margin was ≤ 5 mm in most of the cases (Hall et al., 1995; Shrieve et al., 1995; Combs et al., 2005a, b; Martínez-Carrillo et al., 2014; Selch et al., 2000; Vordermark et al., 2005; Ernst-Stecken et al., 2007; Fokas et al., 2009; McKenzie et al., 2013; Ogura et al., 2013; Grosu et al., 2005; Minniti et al., 2011, 2013; Shapiro et al., 2013) but in some series was up to 10 mm (Combs et al., 2005b, 2008; Flieger et al., 2014). In all the series where patients were treated with Gamma Knife radiosurgery (Kondziolka et al., 1997; Hsieh et al., 2005; Skeie et al., 2012), obviously no margin for PTV was used, since the use of the invasive frame does not require to correct the set-up errors.

In summary, we would recommend to delineate the contrast-enhancing lesion on T1-weighted images, adding a variable margin for PTV. We also would recommend to use Image Guided Radiation Therapy (IGRT) in order to minimize the margin to add to create PTV.

5. Selection of patients

An appropriate selection of the patients for a second course of radiation therapy should be based on the prognostic factors that have proven to be important in reirradiation series: both patient-related factors (good performance status (Cho et al., 1999; Cuneo et al., 2012; Fokas et al., 2009; Hall et al., 1995; Hsieh et al., 2005; Martínez-Carrillo et al., 2014), age (Cho et al., 1999; Cuneo et al., 2012; Fogh et al., 2010; Hall et al., 1995; Shrieve et al., 1995) and RPA class (Martínez-Carrillo et al., 2014)) and recurrent disease-related factors (monofocality (Ogura et al., 2013; Skeie et al., 2012), target volume (Cho et al., 1999; Kondziolka et al., 1997; Kong et al., 2008; Shrieve et al., 1995) and long time to progression (Combs et al., 2008; Skeie et al., 2012)) may help in the selection.

Recently, Combs et al (Combs et al., 2013) developed a prognostic score index in order to define patients with a clearer benefit deriving from reirradiation of relapsing gliomas: this score is based on histology (WHO grade II vs WHO grade III vs WHO grade IV), age (< 50 vs. > 50 years) and time between the initial RT and the second course of radiation treatment (≤ 12 months vs > 12 months).

On the other hand, individual treatment decisions should not include only factors influencing the outcome, but also factors that may impact the potential morbidity of the treatment. The incidence and severity of radionecrosis can be increased by chemotherapy, age,

diabetes (Lawrence et al., 2010). Disease-related factors may influence the risk of toxicity: lesion size (Lawrence et al., 2010), proximity to eloquent area or to organs at risk, overlapping with the target of the initial treatment are factors to take into account whenever a second irradiation is weighted against other therapeutical alternatives.

6. Toxicity of reirradiation of the brain

An essential component of the decision-making process of treating a relapsing GBM with reirradiation is the expected toxicity of a second radiation treatment.

Obviously, the risk of severe side effects depends on the overlapping of the target volume with the volume previously treated, leading to toxicity to the brain parenchyma. In most cases, overlapping of the target with the previously irradiated tissue is of considerable extent because the relapse of GBM typically occurs in-field or marginal to the field of the first-course treatment.

Moreover, the risk of reirradiation also depends on the proximity to the intracranial organs at risk (which might have already received doses near to the standard dose constraints).

6.1. Brain parenchyma

Reirradiation of the brain may lead to different extents of damage to the parenchyma: the major complication is radionecrosis. Noteworthy, although radionecrosis is occasionally associated with serious neurologic sequelae, few authors reported its presence and the severity of symptoms, and rarely was the clinical severity of the radionecrosis reported according to Common Terminology Criteria for Adverse Events (CTCAE) (Ogura et al., 2013). Hence, the existing literature was herein analyzed in order to differentiate the radiologically diagnosed necrosis from the histologically proven necrosis.

Radiological diagnosis of radionecrosis is frequently reported: its rate ranged between 4% (Cho et al., 1999) and 31.3% (Hsieh et al., 2005). Some authors did not specify whether this situation was associated with symptoms or not (Cho et al., 1999; Flieger et al., 2014; Hsieh et al., 2005; Kong et al., 2008; McKenzie et al., 2013), whereas few described the presence of symptoms (Cuneo et al., 2012) or added information about the need for steroids (Minniti et al., 2013, 2011).

There are few articles that reported the histologically proven radionecrosis rate: the rate of histologically proven pure radionecrosis ranged between 1.7 (Combs et al., 2005a) and 12.5% (Kim et al., 2011). Characteristics of the population included in this series were analyzed: interval time between the first course RT and reirradiation in these series ranged between 5 (Kondziolka et al., 1997) and 12.5 months (Patel et al., 2009); all the patients included in these series had received 60 Gy as median prescription dose of the primary treatment; median time between reirradiation and the second surgery that showed the presence of pure radionecrosis ranged between 2 (Patel et al., 2009) and 11 (Kim et al., 2011; Patel et al., 2009) months.

More interestingly, up to 21.7% (Cho et al., 1999) of the patients included in those series received surgery for suspicious radionecrosis, but only some of them had pure radionecrosis: in many series pure radionecrosis was found in $< 33\%$ of the operated patients (Cho et al., 1999; Hall et al., 1995; Kondziolka et al., 1997; Patel et al., 2009). These data suggest that up to two-thirds of patients with a radiological diagnosis of radionecrosis may be found to have an active disease at the time of resection.

In 2008, Mayer et al (Mayer and Sminia, 2008) published a review on radiation tolerance of the human brain, considering the existing literature reporting about brain reirradiation performed with conventional radiotherapy, FSRT or radiosurgery technique. The authors concluded that normal brain tissue necrosis was found to occur for a cumulative equivalent dose in 2-Gy fractions > 100 Gy, > 105 and > 135 , for patients treated with conventional external beam radiotherapy, fractionated stereotactic radiotherapy and radiosurgery,

respectively. In other words, patients with GBM who had received a prior radiotherapy with a total dose of 60 Gy in 2 Gy fractions, could receive reirradiation for an additional EQD2 of 40 Gy, 45 Gy and 75 Gy with conventional external beam radiotherapy, fractionated stereotactic radiotherapy and radiosurgery, respectively. The authors commented that the applied reirradiation dose and EQD2 cumulative were found to increase with a change in the irradiation technique from a conventional to a conformal technique such as FSRT to radiosurgery retreatment, without increasing the risk of normal brain necrosis.

Our analysis significantly differed from that review not only because more recent papers were included and the analysis focused on recurrent GBM (and not on other recurrent gliomas), but also for the following reasons: firstly, we focused on the histologically proven brain tissue necrosis, whereas Mayer et al included clinically diagnosed radionecrosis as well; secondly, we also took into account severe toxicities other than radionecrosis, while Mayer et al considered only radionecrosis rate; thirdly, we arbitrarily chose a cut-off of 3.5% of severe toxicity as a treatment-related acceptable risk, whereas Mayer et al wanted to define the dose that does not involve any risk of radiological or pathological radiation necrosis. Moreover, our findings showed that the volume of the target influences the risk of toxicity and, consequently, the choice of fractionation: accepting a risk of severe toxicity < 3.5%, exclusive reirradiation may require different fractionations according to different target volumes: radiosurgery with EQD2 < 65 Gy may be a choice for small lesions (target volume < 12.5 ml), hypofractionated stereotactic radiotherapy with EQD2 < 50 Gy is feasible for medium lesions (target volume up to 35 ml), whereas conventionally fractionated treatment with EQD2 < 36 may be used for reirradiation of large lesions (target volume up to 50 ml).

6.2. Brainstem and optic pathways

Ideally, during the planning process of a second radiation course, the "classical" constraints for the organs at risk should be met. The QUANTEC review reported a tolerance dose of 54 Gy in 1.8/2 Gy fractions for the entire brainstem, while 1–10 ml could tolerate a total dose of 59 Gy in 1.8/2 Gy fractions (Mayo et al., 2010b); radiation-induced optic neuropathy is near 0 for doses less than 50 Gy, unusual for doses between 50 and 55 Gy, whereas its incidence is 3–7% for doses of 55–60 Gy, while for doses > 60 Gy in a single course is 7–20% (Mayo et al., 2010a). However, if the primary disease was in a critical site, these standard constraints are difficult to meet in the setting of reirradiation, considering that the relapsing disease in most of the case is in close proximity to the initially irradiated volume.

Obviously, as a general rule, the doses to critical OARs must be kept as low as feasibly possible. It should also be considered that the short interval between the first and second radiotherapy course for GBM may negatively influence the chances of recovery of CNS structures (Chen et al., 2011; Merchant et al., 2008).

To our knowledge, very few data are available in the literature regarding the tolerance of the brainstem or the optic pathways to the reirradiation.

Much of the data regarding the safety of reirradiation of brainstem derived from pediatric studies. Of course, data from these reports should be cautiously applied to adult patients, considering the different radiosensitivity between children's and adult's brain.

Merchant et al. (Merchant et al., 2008) presented a series of reirradiation of pediatric patients with recurrent ependymoma. Thirty-two patients were treated with reirradiation using standard fractionation at a median interval of 23 months after prior radiation. Twenty-four patients received a cumulative dose to the brainstem ranging from 86.4 to 120 Gy with no case of necrosis to the brainstem. One out of these 24 patients had necrosis in the cerebellum where he had received a cumulative dose of 99 Gy.

Of note, radiosurgery as a salvage resulted in significant brainstem

toxicity (6 patients out of 6 treated with radiosurgery developed radionecrosis) and one death of radiation necrosis at 40 months.

Ray et al (Ray et al., 2014) reported about 11 pediatric patients who underwent salvage radiotherapy and received a documented brainstem dose in excess of 60 Gy. Reirradiation occurred at a median interval of 29.5 months after prior radiation with a median dose of reirradiation was 56.7 Gy, given in daily fractionation of 1.8 Gy. Cumulative dose to the brainstem was < 70 Gy in 6 patients, between 70 and 80 Gy in 2 patients, between 80 and 110 Gy in 1 patient, > 110 Gy in two patients. With a median follow-up of 10.4 months, grade 3 + CNS toxicity including radiation necrosis was seen in 4 patients (36%); two of these patients had received doses to the brainstem inferior to 70 Gy, whereas two had received doses > 100 Gy.

Some data on dose constraints for brainstem and optic pathways to be used for reirradiation could be extrapolated from series of patients who underwent a second course of RT after radical treatment for nasopharynx cancer. Unfortunately, only one study reported about the cumulative dose received by the brainstem: Zwicker et al. (Zwicker et al., 2011) evaluated 38 patients with locally recurrent head and neck cancer, who received the second irradiation with IMRT. The authors reported a median cumulative maximum dose of 62.7 Gy to the brainstem (10 patients who receive a cumulative maximum dose between 60 and 70 Gy and 11 cases when a cumulative maximum dose between 71 and 86 Gy was given): 8% of the patients developed cranial neuropathy.

Another series of 17 patients affected by recurrent nasopharyngeal carcinoma treated with IMRT was published in 2011 (Roeder et al., 2011): unfortunately, details about the cumulative dose to the critical organs were not reported. The authors reported a risk of 5.9% of developing cranial neuropathy with a median retreatment maximum dose of 30 Gy to the brainstem (range 10–49 Gy). In the same experience, no case of optic toxicity was revealed with median doses of 25 Gy (range 1–43 Gy), 20 Gy (range 1–43 Gy), and 11 Gy (range 1–39 Gy), for right optic nerve, left optic nerve and chiasm, respectively.

In a retrospective experience about conventionally fractionated treatment (Chua et al., 2005), the authors did not report cases of optic toxicity using a very cautious dose-constraint for optic pathways (V8 < 5%).

Bearing in mind that most patients will succumb to their disease, we feel that reirradiation of targets in strict proximity of critical organs that had already received maximal dose is possible. Due to the scarcity of data in literature, our practical recommendations for treating such targets are: 1) use highly conformal techniques to minimize the volume of the organs at risk included in higher isodoses; 2) use conventional fractionation avoiding radiosurgery and hypofractionation; 3) minimize the total dose to as low as feasibly possible.

7. Practical recommendations

There are some practical recommendations for the centers that are interested in reirradiating patients with recurrent glioblastoma and, more generally, patients with recurrent brain tumors.

First of all, a preventive sparing of the organs at risk may be performed in the first line treatment of brain tumors, as already suggested for head and neck cancers (Farace et al., 2014).

Secondly, all the Dicom files of the initial irradiation must be provided for a proper reirradiation planning (simulation CT, RTplan, RTstructure and RTdose files).

Thirdly, accurate and consistent contouring of the organs at risk according to existing contouring atlases (Sun et al., 2014; Scoccianti et al., 2015) should be recommended both for first and second course of radiotherapy, in order to avoid mislead treatment planning, resulting in inadequate target volume coverage or OAR overdose.

Moreover, during the contouring process, different portions of the organs at risk may be differentiated in order to precisely calculate the dose to the organs at risk. Again, this concept has already been proposed for reirradiation of head and neck cancers (Parashar et al., 2009).

Table 6

Strategy proposed in the present analysis (to be confirmed in prospective further studies): patients should be stratified according to different disease volume and then, treated with differentiated total dose and fractionation. RS: radiosurgery; HFSRT: hypofractionated stereotactic radiotherapy; CFRT: conventionally fractionated radiotherapy.

Tumor Volume	Technique	EQD2	Example of total dose and number of fractions
≤ 12.5 ml	RS	< 65 Gy	12–15 Gy in a single fraction
> 12.5 ml and < 35 ml	HFSRT	< 50 Gy	25 Gy in 5 fractions
> 35 ml up to 50 ml	CFRT	36 Gy	36 Gy in 20 fractions

For example, brainstem may be differentiated in its different anatomic portions (mesencephalon, pons and medulla oblongata) to define the cumulative dose for each single portion. The same may apply to the optic chiasm that may be differentiated in right and left intracisternal portion of the optic nerves, crossing portion of the fibers and optic tracts (Scoccianti et al., 2015): this could help to understand the cumulative dose and, moreover, to understand the expected treatment-related visual toxicity.

Lastly, we think that the clinical use of software which utilizes deformable registration algorithm should be encouraged in order to achieve a more precise dose summation of the two treatment for each organ at risk.

8. Reirradiation vs second surgery

When patients are in good performance status, another feasible local approach for recurrent glioblastoma that are located in non-eloquent areas is second surgery. Comparison of these two salvage options is very difficult due to the scarcity of the existing studies that directly compared the outcomes of repeat surgery vs reirradiation, whose interpretation is very difficult due to their retrospective nature with high risk of selection bias.

In a large cohort study from a prospective registry (Nava et al., 2014) reoperation did not affect survival, whereas the analysis revealed a significant relative reduction in risk of death after recurrence for patients receiving radiosurgery at the recurrence (HR = 0.52; 95% CI, 0.37–0.75), compared with patients who did not receive reirradiation.

Another question for further research is whether survival can be increased by a combined approach, consisting in reoperation plus adjuvant therapy, such as systemic treatment or reirradiation. Van Linde et al (Van Linde et al., 2017) evaluated treatment outcomes of the different treatment strategies used in two university medical centers for patients with recurrent GBM. After adjustments for confounders, patients receiving surgery had a significant longer survival (110 months) than patients receiving best supportive care (3,1 months). Median survival for patients receiving RT was 9.2 months but this was not significantly better than patients receiving best supportive care.

Azoulay et al [Azoulay et al., 2017] found that repeat surgery followed by salvage chemotherapy and/or re-irradiation provides survival benefit if compared with outcome of patients treated with exclusive second-line chemotherapy and/or reirradiation. This survival advantage was not statistically significant when compared with patients treated with repeat surgery alone.

So, given the scarcity of comparative studies, the key issue may be an appropriate selection of the patients. Factors proposed for decision making regarding reoperation are tumor localization, probability of total resection, age and performance status. A scale including location of the relapse in non-eloquent areas, small tumor volume (< 50 cm³) and good performance status was proposed by Park et al [Park et al., 2010]. More recently, a simple scale to identify favorable surgical candidates among patients with recurrent glioblastoma, basing on KPS and ependymal involvement was developed [Park et al., 2013]. An

important advantage to consider surgery is the acquisition of tumor tissue at relapse. This may be valuable not only for confirmation of initial histology but also for differential diagnosis with radiation necrosis. Factors that may impact the potential morbidity of the surgical treatment (recurrence site and comorbidities that may increase the anaesthesiologic risk) should be considered as well.

In conclusion, until prospective studies become available, no strategy can be recommended for patients who are operable: currently, treatment can be only based on center-specific preferences and patients' preferences.

9. Conclusions

This overview of the scarce currently available clinical data on re-irradiation of glioblastoma patients suggests that the retreatment of a recurrent glioma must be tailored to each single patient in order to have a relatively good outcome with an acceptable risk of severe toxicity (< 3.5%). Firstly, we recommend stratifying patients according to the different volumes of the target (small: < 12.5 ml, medium: < 35 ml, and large: < 50 ml). Then, patients should be treated with the following re-irradiation strategy, using different fractionation and differentiated total EQD2: small volume: EQD2 < 65 Gy with RS (for instance 15 Gy in single session); medium volume: EQD2 < 50 Gy with HFSRT (for instance 25 Gy in 5 fractions); large volume: EQD2 = 36 Gy with CFRT (Table 6).

Focus on results regarding specifically GBM, report of the grade of toxicity, and recommendations for criteria to be used in the clinical practice are the main advantages of the present review.

Prospective trials are required to further consolidate the strategy proposed in the present analysis. Future prospective trials should not only include only GBM patients at the first recurrence after a homogeneous standard treatment at the diagnosis (60 Gy and temozolomide), but cases likely to be pseudoprogression should also be excluded. Furthermore, precise dosimetric data should be collected and related to the toxicity for the brain and for the critical structures, which should be collected according to a standardized scale of toxicity.

Conflicts of interest

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