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Local treatment for relapsing glioblastoma: A decision-making tree for choosing between reirradiation and second surgery

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ABSTRACT

In case of circumscribed recurrent glioblastoma (rec-GBM), a second surgery (Re-S) and reirradiation (Re-RT) are local strategies to consider. The aim is to provide an algorithm to use in the daily clinical practice. The first step is to consider the life expectancy in order to establish whether the patient should be a candidate for active treatment. In case of a relatively good life expectancy (>3 months) and a confirmed circumscribed disease(i.e. without multiple lesions that are in different lobes/hemispheres), the next step is the assessment of the prognostic factors for local treatments. Based on the existing prognostic score systems, patients who should be excluded from local treatments may be identified; based on the validated prognostic factors, one or the other local treatment may be preferred. The last point is the estimation of expected toxicity, considering patient-related, tumor-related and treatment-related factors impacting on side effects. Lastly, patients with very good prognostic factors may be considered for receiving a combined treatment.

1. Introduction

No standard of care for recurrent glioblastoma (rec-GBM) is universally accepted: all the treatment options have limited activity. Patients enrolled in the Stupp trial (Stupp et al., 2009) had a median overall survival from first progression of 6.2 months. This survival time of about 6 months applied to the whole series, including patients who received only supportive care (39 % of the total) and patients who were treated with exclusive or combined active treatment [salvage chemotherapy (54 %), second surgery (24 %) or repeat radiotherapy (5%)].

The most common strategy proposed in case of recurrence is systemic therapy; however, in case of a limited and well-defined recurrent disease, Re-S and Re-RT are both local treatments to consider.

Unfortunately, the level of evidence supporting the use of these local strategies is low because the majority of the studies are retrospective with strong selection bias. In addition, recurrent lower grade gliomas, secondary glioblastomas and suspected cases of pseudoprogression were not systematically excluded. Furthermore, data focusing on molecular features, grading of toxicity, quality of life or neurocognitive performance are seldom reported. The lack of comparative trials with a control group is another weak point. Nevertheless, all the major and recently published guidelines (Weller et al., 2014; Stupp et al., 2014; Cabrera et al., 2016; Sulman et al., 2017; National Comprehensive Cancer Network, 2018) list both Re-S and Re-RT as options to consider for treating rec-GBM.

Since there is no evidence of superiority in terms of the efficacy of one or the other strategy, the choice between these two treatments need to be based on other factors. A four step-decision tree to select which patients should be treated with one or the other local strategy is herein proposed. This algorithm has been derived by an interpretation of the existing literature: to our knowledge, this is the first attempt to provide a tool to use in the daily clinical practice in order to make a choice between Re-S or Re-RT in rec-GBM.

This algorithm cannot be thoroughly detailed: it may suggest the

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recommendable therapeutic approach, but obviously, each case of rec-GBM should be discussed within a multidisciplinary team in order to make an individualized therapeutic decision. For instance, the great impact of the different anatomical sites on the possibility of performing both the local treatments (surgery and radiotherapy) was not weight up. This stresses the importance of evaluation of each single case by skilled neurosurgeons and dedicated radiation oncologist with expertise in neurooncology

2. Search strategy

To ensure all appropriate publications were included, a systematic approach was used to search and select studies. A literature search was carried out of Pubmed database for re-RT using the following search term strategies: "reirradiation and glioblastoma", "second radiotherapy and glioblastoma", "repeat radiation therapy and glioblastoma", "radiotherapy and recurrent glioblastoma", "radiosurgery and recurrent glioblastoma". Literature data for re-S were identified by searching the Pubmed database with the following as keywords: "reoperation and glioblastoma", "second surgery and glioblastoma", "repeat surgery and glioblastoma" "surgery and recurrent glioblastoma". All initially identified articles were assessed (title, abstract ± full text) for relevance based on inclusion criteria (*articles written in English, clinical series published between January 2005 and May 2019; adult population ≥18 years diagnosed with rec-GBM undergone re-RT or re-S; series specifically focusing on the results of patients affected by relapsing primary GBM; studies including more than >20 rec-GBM patients*) and exclusion criteria (*review articles and editorials; studies in abstract form only; studies assessing the role of special modalities such as BCNU wafers, brachytherapy, seed implants, radioimmunotherapy; studies reporting results generically referred to high grade gliomas or to any grade gliomas*).

3. Outcome of Re-S and Re-RT

The results of Re-S and Re-RT in terms of overall survival from the time of relapse (OS_2) and progression free survival from the moment of recurrence (PFS_2) vary a lot in the existing literature (Table 1a and 1b). OS_2 for Re-S (Tihan et al., 2006; Mandl et al., 2008; Park et al., 2010; Rusthoven et al., 2011; Clarke et al., 2011; Skeie et al., 2012; Bloch et al., 2012; De Bonis et al., 2013; Woodworth et al., 2013; Park et al., 2013; Quick et al., 2014; Yong et al., 2014; McNamara et al., 2014; Sonoda et al., 2014; Oppenlander et al., 2014; Sughrue et al., 2015; Franceschi et al., 2015; Kim et al., 2015; Tully et al., 2016; Ringel et al., 2016; Chen et al., 2016; Pessina et al., 2017; Zanovello et al., 2016; Brandes et al., 2016; Zolal et al., 2016; Ellsworth et al., 2017; Perrini et al., 2017; Suchorska et al., 2016; Brandes et al., 2017;

Table 1a
Outcome of Re-Surgery for relapsing glioblastoma patients.

Authors	Year	Total number of patients	Number of GBM cases	Results specifically referred to GBM patients (if other histologies were included)		
				Median PFS_2 (months)	Median OS_2 (months)	Median OS from diagnosis (months)
Tihan et al (Tihan et al., 2006)	2006	27	all	4,0	9,3	18,3
Mandl et al (Mandl et al., 2008)	2008	20	all	.	13	.
Park JK et al (Park et al., 2010)	2010	34	all	.	7,4	.
Rusthoven et al (Rusthoven et al., 2011)	2011	51	34	.	4,9	14,2
Clarke et al (Clarke et al., 2011)	2011	181	all	1,9	7,2	.
Skeie et al (Skeie et al., 2012)	2012	26	all	2	6	16
Bloch et al (Bloch et al., 2012)	2012	107	all	.	Range 7,4-16,7	Range 15,9−20,4
De Bonis et al (De Bonis et al., 2013)	2013	17	all	.	6	.
Woodworth et al (Woodworth et al., 2013)	2013	59	all	.	8	20
Park CK et al (Park et al., 2013)	2013	55	all	.	13	.
Quick et al (Quick et al., 2014)	2014	40	all	.	13	21,7
Yong et al (Yong et al., 2014)	2014	97	all	.	12,4	.
Mc Namara et al (McNamara et al., 2014)	2014	107	all	.	7,1	20,9
Sonoda et al (Sonoda et al., 2014)	2014	61	all	.	11	25
Oppenlander et al (Oppenlander et al., 2014)	2014	170	all	5,2	.	19
Sughrue et al (Sughrue et al., 2015)	2015	59	all	7,8	.	.
Franceschi et al (Franceschi et al., 2015)	2015	102	all	,	9,6	25,8
Kim et al (Kim et al., 2015)	2015	38	all	4,3	13,2	.
Tully et al (Tully et al., 2016)	2016	49	all	8,3	.	20,1
Ringel et al (Ringel et al., 2016)	2016	503	all	.	11,9	25
Chen et al (Chen et al., 2016)	2016	20	all	6,3	13,5	25,4
Pessina et al (Pessina et al., 2017)	2016	64	all	6,8	10,3	.
Zanovello et al (Zanovello et al., 2016)	2016	39	all	.	9,1	20
Brandes et al (Brandes et al., 2016)	2016	270	all	.	11,4	27,6
Zolal et al (Zolal et al., 2016)	2016	31	all	4,5	7,8	19,1
Ellsworth et al (Ellsworth et al., 2017)	2017	38	all	.	7,7	16,2
Perrini et al (Perrini et al., 2017)	2017	48	all	.	7	21
Suchorska et al (Suchorska et al., 2016)	2017	71	all	.	11,4	.
Brandes et al (Brandes et al., 2017)	2017	108	all	.	10,3	24,4
Delgado-Fernandez et al (Delgado-Fernandez et al., 2017)	2017	31	all	7,9	.	24,2
Straube et al (Straube et al., 2017)	2017	26	all	6,0	12,8	30,2
Azoulay et al (Azoulay et al., 2017)	2017	69	all	.	6,8	.
Pala et al (Pala et al., 2018)	2018	51	all	7	.	31
Hager et al (Hager et al., 2018)	2018	27	all	.	.	20,8
Goldman et al (Goldman et al., 2018)	2018	89	all	.	9	18,8
Wann et al (Wann et al., 2018)	2018	60	all	.	9,6	22
Dalle ore et al (Dalle Ore et al., 2018)	2018	110	all	.	10,8	26,2
Sastry et al (Sastry et al., 2018)	2018	77	all	.	12,8	.
Salvati et al (Salvati et al., 2019)	2019	78	42	8,1	11,2	.
Bagley et al (Bagley et al., 2019)	2019	37	all	.	6,9	.

PFS_2: Progression Free Survival from local treatment (reoperation or reirradiation); OS_2 Overall Survival from local treatment (reoperation or reirradiation).

Table 1b
Outcome of exclusive Re-Irradiation for glioblastoma patients. Only results referring exclusively to GBM patients are here reported.

Authors	Year	Total number of patients	Number of WHO grade IV gliomas	Prescription Dose		Results specifically referred to GBM patients (if other histologies were included)		
				Median Dose per fraction (Gy)	Median Total dose (Gy)	Median PFS_2 (months)	Median OS_2 (months)	Median OS from diagnosis (months)
Combs et al. Combs et al. (2005a)	2005	32	all	15	15	7	10	22
Combs et al. (Combs et al. (2005b))	2005	59	all	2	36	.	8	21
Hsieh et al. Hsieh et al. (2005)	2005	26	all	12	12	.	10	14,3
Kong et al. (Kong et al. (2008))	2008	114	65	16	16	4,6	13	23
Patel et al. Patel et al. (2009)	2009	26	all	18	18	.	8,4	24,4
Fokas et al. (Fokas et al. (2009))	2009	53	all	3	30	.	9	27
Fogh et al. Fogh et al. (2010)	2010	147	105	3.5	35	.	11	23
Skeie et al. (Skeie et al. (2012))	2012	51	all	12.2	12.2	6	7,5	19
Martinez-Carrillo et al. (Martínez-Carrillo et al., 2014)	2014	87	46	18	18	.	7,5	18,5
Kim et al (Kim et al., 2015)	2015	29	all	15	15	3,6	9,2	.
Dincoglan et al (Dincoglan et al., 2015)	2015	28	all	5	25	5,8	10,3	22,4
Imber et al (Imber et al., 2017)	2016	174	all	16	16	.	10,6	19,1
Frischer et al (Frischer et al., 2016)	2016	42	all	10	10	4,4	9,6	25,6
Van Linde et al (van Linde et al., 2017)	2017	21	all	n.a.	n.a.	7,7	9,2	.
Zwirner et al (Zwirner et al., 2017)	2017	51	all	n.a.	n.a.	.	9.8	28.8
Shi et al (Shi et al., 2018a)	2018	24	all	n.a.	n.a.	.	8.2	.
Guseynova et al (Guseynova et al., 2018)	2018	126	all	12	12	8,5	7	20

PFS_2: Progression Free Survival from local treatment (reoperation or reirradiation); OS_2 Overall Survival from local treatment (reoperation or reirradiation).

Delgado-Fernandez et al., 2017; Straube et al., 2017; Azoulay et al., 2017; Pala et al., 2018; Hager et al., 2018; Goldman et al., 2018; Wann et al., 2018; Dalle Ore et al., 2018; Sastry et al., 2018; Salvati et al., 2019; Bagley et al., 2019) ranged between 4.9 (Rusthoven et al., 2011) and 13.5 months (Chen et al., 2016) and the PFS_2 ranged from 1.9 (Clarke et al., 2011) to 8.3 months (Tully et al., 2016). Similarly, patients treated with Re-RT (Skeie et al., 2012; Kim et al., 2015; Combs et al., 2005a, b; Hsieh et al., 2005; Kong et al., 2008; Patel et al., 2009; Fokas et al., 2009; Fogh et al., 2010; Martínez-Carrillo et al., 2014; Dincoglan et al., 2015; Imber et al., 2017; Frischer et al., 2016; van Linde et al., 2017; Zwirner et al., 2017; Shi et al., 2018a; Guseynova et al., 2018) had a value of OS_2 ranging from 7 (Guseynova et al., 2018) to 13 months (Kong et al., 2008) and PFS_2 ranging from 3.6 (Kim et al., 2015) to 7.7 months (van Linde et al., 2017). Median OS from time of initial diagnosis was heterogeneous as well: it ranged between 14.2 (Rusthoven et al., 2011) and 30.2 months (Straube et al., 2017) for reoperation series and between 14.3 (Hsieh et al., 2005) and 28.8 months (Zwirner et al., 2017) for second irradiation series.

Kamzi et al. (Kazmi et al., 2019) recently published a meta-analysis pooling the outcomes of re-RT, including 50 studies for a total number of 2095 patients undergoing a second course of radiotherapy. The authors reported pooled results of 6-month OS_2 and PFS_2 of 73 % (95 % CI 69–77 %) and 43 % (95 % CI 35–50 %) respectively; 12-month OS_2 and PFS_2 were equal to 36 % (95 % CI 32–40 %), and 17 % (95 % CI 13–20 %), respectively.

4. Definition of recurrent disease

Progression of disease (PD) should be defined referring to the RANO (Response Assessment in Neuro Oncology) Working Group criteria (Wen et al., 2010) as reported in Table 2.

Before considering a therapeutic approach for a recurrent disease, suspected cases for the so-called "pseudoprogression" phenomenon should be excluded. Pseudoprogression is defined as a transient increase in tumor enhancement that occurs in in 20%–30% of patients after the end of the radiotherapy (Wen et al., 2010). It is the result of different processes such as increased vascular permeability, epithelial cell damage, local tissue inflammation and the appearance of necrosis induced by radiation therapy and the concomitant use of temozolomide. Pseudoprogression can be associated with clinical deterioration and it seems to occur more frequently in patients with methylated MGMT gene promoter (Brandes et al., 2008). This phenomenon is of clinical relevance not only because of its relatively high incidence but also because the RANO criteria are not sufficient for characterizing it. So far, no existing imaging modality is able to differentiate recurrent disease from pseudoprogression with high specificity and sensitivity. However, the use of diffusion weighted MRI, perfusion or spectroscopy MR imaging may help in understanding whether a new enhancement is more probably due to sequelae or recurrent disease (Thust et al., 2018). Furthermore, nuclear medicine imaging can facilitate the distinction between pseudoprogression and real progression with variable sensitivity and specificity (100 % and 91 %, 75 % and 100 %, 75–100 % and 60–100 % for 18 F-FET-PET (Galldiks et al., 2014), Methionine-PET (Glaudemans et al., 2013) and SPECT (Abdulla et al., 2015), respectively). The importance of PET in the differentiation of glioma recurrence from treatment-induced changes, with a higher diagnostic accuracy than MRI (Albert et al., 2016), is also stressed in the recently published joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards

Table 2
Definition of progression of disease according to RANO Criteria (Perrini et al., 2017): progressive disease is defined according to one of the following criteria.

25 % increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids
Significant increase in T2/FLAIR non enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by concomitant events
Any new lesion
Clear clinical deterioration not attributable to other causes apart from the tumor or changes in corticosteroid dose
Failure to return for evaluation as a result of death or deteriorating condition
Clear progression of non-measurable disease

(Law et al., 2019).

Recently, Hansen et al. (Hansen et al., 2018) showed that the application of 3D technology with post-gadolinium imaging data with segmentation and analysis of contrast enhancing portions of the relapse, may help in differentiating tumor progression from pseudoprogression.

Lastly, the analysis of the radiation dose distribution in the prior treatment plan may help in suspecting a real progression: pseudoprogression seems to be excludable if the area of new enhancement is outside of the the 80 % isodose line (Wen et al., 2010).

5. First step of the algorithm: assessment of life expectancy

The first step in the decision tree (see graphical abstract) is to consider the life expectancy of each individual case, as patients with a poor life expectancy should be excluded from active treatment. Since the survival time of patients treated with the best supportive care ranges from 2 (Steffens et al., 2016) to 5.2 (Azoulay et al., 2017) months, active treatment should not be recommended for patients with a life expectancy <3 months.

Gorlia et al. (Gorlia et al., 2012) analyzed 300 patients who were enrolled in trials conducted by the EORTC Brain Tumor Group in order to develop a prognostic model. The authors found that the most important prognostic factors for OS_2 and PFS_2 in patients who were initially treated with radiotherapy plus temozolomide, were performance status, need of steroids, number and size of lesion. They also provided a prognostic calculator that is available on the internet (http://www.eortc.be/tools/recgbmcalculator/calculator.aspx). By setting the above mentioned parameters, the expected survival times in terms of OS_2 and PFS_2 can be estimated. For example, a patient with all the favorable parameters is expected to have a median survival of 18.2 months; whereas a case with all the unfavorable factors has an expected OS_2 of 2.6 months.

6. Second step of the algorithm: evaluation of the extent of the disease

Once a patient has been considered suitable for active treatment, the next point to take into account is whether the disease is limited. In case of a multicentric disease, defined as the presence of multiple lesions that are widely separated (e.g. in different lobes/hemispheres) (Hong Toh et al., 2019), the patient should be treated with systemic therapy. On the contrary, in case of a limited disease (i.e. absence of multiple lesions that are in different lobes/hemispheres), a local treatment should be considered.

7. Third step of the algorithm: comparison in terms of prognostic factors (Table 3)

In case of relatively good prognosis and a circumscribed disease, the assessment of prognostic factors specific to local treatment should be addressed. Patients with unfavorable factors for local treatment will receive only systemic treatment. At the same time, these prognostic indices may help in choosing between Re-RT or Re-S.

A prognostic scoring system to predict survival after Re-S was proposed by Park et al. (Park et al., 2020). Three factors associated with poor postoperative survival were identified: performance status, involvement of an eloquent region and tumor volume. Any unfavorable factor (KPS < 80, tumor in eloquent area, volume >50cc) gives the patient one point. Patients with a score of 3 should not be treated with Re-S.

The application of this scale in daily clinical practice is not very easy because the definition of the critical areas and the measurement of tumor volume are not intuitional processes. For this reason, it is important to know that a few years later, a simpler method of identifying prognostic groups for repeat surgery was published (Park et al., 2013). The authors suggested giving one point for KPS < 70 or for the presence of ependymal involvement and they did not recommend to operate patients within the worst prognostic group (i.e. patients with a score of 2 points)

Table 3
Negative prognostic factors for Re-surgery and Re-irradiation as shown by the existing literature.

	Against the use of Re-surgery	Against the use of Re-irradiation
Unfavorable factors included in validated prognostic indices	- KPS ≤80 and Critical/ Eloquent region involvement and Tumor volume >50cc (Wann et al., 2018) - KPS <70 and Ependymal involvement (Dalle Ore et al., 2018)	- Age ≥50 y and/or Time between RT-Reirradiation<12 m (Salvati et al., 2019) - Reirradiation Risk Score ≥0,5 (based on Age and KPS) (Bagley et al., 2019)
Unfavorable factors that were shown to be significant when tested in a multivariate analysis	- Advanced age (Park et al., 2013; Yong et al., 2014; Sonoda et al., 2014; Sastry et al., 2018) - Short interval between diagnosis and relapse (Park et al., 2013; Yong et al., 2014; Oppenlander et al., 2014) - Multiple lobes involvement (Park et al., 2013) - Neutrophil/ Lymphocyte ratio >4 (Rusthoven et al., 2011)	- Presence of neurodeficits (Patel et al., 2009) - Unfavourable RPA class (Sughrue et al., 2015) - Large target volume (Chen et al., 2016; Brandes et al., 2016; Ellsworth et al., 2017) - No complete response after first course of RT (Fokas et al., 2009)

In addition, the preoperative estimate of the possibility of performing a gross total resection (GTR) is another crucial point in the decision process, since several authors found that the extent of resection (EOR) had a strong impact on survival (Bloch et al., 2012; Quick et al., 2014; Yong et al., 2014; Oppenlander et al., 2014; Sughrue et al., 2015; Tully et al., 2016; Ringel et al., 2016; Chen et al., 2016; Pessina et al., 2017; Brandes et al., 2016; Ellsworth et al., 2017; Suchorska et al., 2016; Delgado-Fernandez et al., 2017; Pala et al., 2018). Some authors stressed the prognostic value of EOR at recurrence, regardless of the primary type of surgery (GTR or subtotal resection) performed at the diagnosis (Bloch et al., 2012; Perrini et al., 2017). Noteworthy, the definition of GTR was heterogeneous: Tully et al. (Tully et al., 2016) reported that EOR ≥ 50 % significantly influenced postoperative OS of the patients, whereas Oppenlander et al. (Oppenlander et al., 2014) found that the EOR during second surgery ≥80 % had a strong impact on OS. These data suggest that highly skilled neurosurgeons with experience in high grade glioma surgery are necessary when proposing Re-S.

On the other hand, there are two studies focusing on prognostic scores for Re-RT (Combs et al., 2013; Niyazi et al., 2018). Patients with lower grade gliomas were included in both of these studies and, as expected, histological grade was found to be a significant prognostic factor.

More than 230 patients, including 89 GBM, were analyzed by Combs et al. (Combs et al., 2013). Beyond histology, the strongest prognostic factors impacting survival after Re-RT were age and interval time <12 months between initial radiotherapy and Re-RT. For treatment decisions, Re-RT was not strongly recommended for patients with rec-GBM who were >50 years old or in case they had received the first course of radiotherapy in the previous 12 months. The value of this score proposed by Combs et al. (Combs et al., 2013) was validated by the same group (Kessel et al., 2017) and confirmed by other independent authors (Muller et al., 2015) but, noteworthy, two external validations failed (Scholtyssek et al., 2013; Niyazi et al., 2014).

Recently, a new score system for Re-RT has been published by Niyazi et al. (Niyazi et al., 2014). The score system was defined with a development cohort of more than 350 patients. Of note, this score was independently validated in an external patient cohort of almost 200 patients. The majority of the patients had a GBM (77.9 % and 90.6 % for development and validation cohort, respectively). The authors provided a formula to define the Re-RT risk score for each patient, based on age, KPS and grade. A calculator on the internet can be used in daily practice to calculate this score (http://www.ibe.med.uni-muenchen.de/mitarbeiter/ *professoren/boulesteix/rrrs.html*): patients with a score $\geq$0.5 should not receive Re-RT.

Thus, based on the above-mentioned prognostic score systems (Park et al., 2013, 2020; Combs et al., 2013; Niyazi et al., 2014), patients who should be excluded from local treatments may be identified. For the remaining patients, other prognostic factors may be extrapolated from the literature in order to define which patients are likely to benefit from one or the other local treatment.

Advanced age (Bloch et al., 2012; Yong et al., 2014; Oppenlander et al., 2014; Ringel et al., 2016; Brandes et al., 2016; van Linde et al., 2017), poor performance status (Yong et al., 2014; Kim et al., 2015; Sastry et al., 2018; Bagley et al., 2019), multiple lobes involvement (van Linde et al., 2017) and, eventually, short interval between diagnosis and relapse (Sughrue et al., 2015; Kim et al., 2015; Ringel et al., 2016; Bagley et al., 2019; van Linde et al., 2017), were shown to be significant factors impacting on prognosis after Re-S, when tested in a multivariate analysis. Biochemical, radiological and pathologic factors may also have a role. McNamara et al. (McNamara et al., 2014) demonstrated that patients who underwent Re-S had a longer median OS than those who underwent primary surgery alone, and among them, patients with a Neutrophil Lymphocytes Ratio (NLR) $\leq$ 4 showed a significantly better OS (9.7 vs 5.9 months p:0.02). Zolal et al. (Zolal et al., 2016) found that MRI diffusion parameters of the enhancing tumor at relapse may have a prognostic role. Bagley et al. (Bagley et al., 2019) observed that Ki67 value on pathological specimen of the second surgery had an impact on OS. The presence of necrosis was independently associated with survival after reoperation in the series published by Rusthoven et al. (Rusthoven et al., 2011). Conflicting data have been published about the prognostic value of MGMT. Some authors (Brandes et al., 2016; Pala et al., 2018) found that methylation of MGMT promoter in patients with rec-GBM surgically treated was associated with a better prognosis; on the contrary, Brandes et al. (Brandes et al., 2017) found that methylation status of MGMT promoter obtained at second surgery is not predictive of survival after second surgery.

Of note, biological factors derived from pathological specimen, such as Ki67 value, presence of necrosis or status of MGMT, cannot be used to select the patients since they are unknown factors during the treatment decision process.

On the other hand, the presence of neuro-deficits (Bir et al., 2015), unfavorable RPA class (Martínez-Carrillo et al., 2014), large target volume (Fogh et al., 2010) and incomplete response after the first course of radiotherapy (Veninga et al., 2001) were shown to strongly affect the survival outcomes after Re-RT when tested in a multivariate analysis.

8. Fourth step of the algorithm: comparison in terms of expected toxicity (Table 4)

In case of a relatively good prognosis and a circumscribed disease and in case the patient has favorable prognostic factors for local treatment, the last point to assess is the expected toxicity..

Data regarding the toxicity of second surgery and the second course of radiotherapy are scarce. Since, as already mentioned, most of the series are retrospective, inconsistencies in collecting and reporting toxicity were very common. In addition, a grading of toxicity according to validated scales was seldom reported.

Morbidity and mortality rate ranged between 0–49 % and 0–5 % for Re-S (Mandl et al., 2008; Skeie et al., 2012; De Bonis et al., 2013; Sonoda et al., 2014; Oppenlander et al., 2014; Sughrue et al., 2015; Ringel et al., 2016; Delgado-Fernandez et al., 2017; Pala et al., 2018; Chang et al., 2003) and between 0–31 % and 0–1 % for Re-RT (Skeie et al., 2012; Combs et al., 2005a, b; Hsieh et al., 2005; Kong et al., 2008; Patel et al., 2009; Martínez-Carrillo et al., 2014; Hall et al., 1995; Cho et al., 1999), respectively.

Table 4
Factors influencing toxicity for Re-surgery and Re-irradiation.

	Re-surgery	Re-irradiation
Patient-related factors Tumor-related factors	- Advanced age - Comorbidities - Lesion size - Time interval from first surgery - Proximity to eloquent areas	- Advanced age - Comorbidities - Lesion size - Time interval from first course radiotherapy - Proximity to eloquent areas or organs at risk - Overlapping with target of the initial treatment

The only existing meta-analysis on re-RT (Kazmi et al., 2019) reported a grade $\geq$3 toxicity rate equal to 7% (95 % CI 4–10 %).

Given these inconsistencies, all the factors impacting on toxicity rate should be taken into account during the decision process: they are patient-related factors, tumor-related factors and treatment-related factors. All efforts to reduce the treatment related morbidity should be made: all the advanced neurosurgical techniques and highly conformal radiotherapy techniques should be used with the aim to reduce the risk of severe toxicity of Re-S and Re-RT, respectively.

Prescription dose and fractional dose have a huge impact on radiation-induced toxicity. Mayer et al. (Mayer and Sminia, 2008), based on a comprehensive review of the studies published until 2006, concluded that radionecrosis is likely to occur when cumulative doses of more than 100 Gy in 2 Gy-fractions are given. Therefore, given that nearly all the patients with glioblastoma are nowadays treated with 60 Gy at the time of diagnosis, their data seem to suggest there is still room for 40 Gy in 2 Gy-fractions at the time of re-RT. This hypothesis was confirmed by the experience of Combs et al. (Combs et al., 2005b), who reported 59 patients with 36 Gy in 18 fractions with a very low incidence of radionecrosis. Of note, the median tumor volume of this series was quite large (49.3 mL).

Mayer et al. suggested that, the applied reirradiation dose and equivalent doses in 2-Gy fractions (EQD2) may increase when fractionated stereotactic radiotherapy or radiosurgery are used, without increasing the probability of brain necrosis. Thus, providing a definition of patients who may be treated with HFSRT or RS becomes extremely relevant, considering the fact that dose escalation may result in better efficacy and that a shorter treatment time should be preferred for these patients, given their poor life expectancy.

Our previous review (Scoccianti et al., 2018), based on the analysis of the studies on Re-RT published before 2016, seems to suggest that patients should be stratified according to their tumor volume: we concluded that HFSRT can be used for medium-size lesions (up to 35 cc), provided that EQD2 value does not exceed 50 Gy (Fokas et al., 2009; Fogh et al., 2010; Selch et al., 2000). Even RS may be safely used in case of a small volume of the target (<12,5 mL), provided that the prescription dose ranges between 12 and 15 Gy (Skeie et al., 2012; Combs et al., 2005a).

9. Elderly patients

An active therapeutic approach may be beneficial for elderly patients, compared with best supportive care (Socha et al., 2016) but particular attention should be given to elderly patients due to their frailty and to their worse prognosis. Elderly patients with good KPS may be considered for Re-S at recurrence (Socha et al., 2016; Zanello et al., 2017; Chen et al., 2018; D'Amico et al., 2015). Straube et al. (Straube

et al., 2019) reported on 25 patients with more than 64 years of age who received Re-RT: they had a median OS of 6.9 months and a median PFS equal to 4.3 months, without any case of severe toxicity attributable to second RT. Re-S, re-RT and use of temozolomide and bevacizumab at progression were all significant independent predictors of better survival in a group of 117 elderly patients (>70 years) included in a large multicentric retrospective study (Zanello et al., 2017).

Despite the fact that prospective trials are needed, these results suggest that a maximal second-line treatment should not be withheld based exclusively on age.

10. Combined treatment

Although the majority of data for rec-GBM focused on exclusive treatments, combined strategies are currently under investigation.

10.1. Re-S + adjuvant treatment

Similar to treatment for newly diagnosed cases, at recurrence, surgery may be offered in combination with other therapy modalities (Ening et al., 2015). The combination of local treatments (Re-S + Re-RT) may be an option for rec-GBM. The first existing paper that argued in favour of this strategy was published by Straube et al. (Straube et al., 2017). The authors assessed the patterns of relapse in 26 patients receiving GTR for rec-GBM: since exclusive local failure was the predominant pattern (70 %), they concluded that giving re-RT after re-S could be beneficial. Based on the analysis of failure patterns and on the review of the literature, they also generated recommendations for target volume definition in this setting.

In 2017, Combs et al. (Combs et al., 2018) published the first report on Re-RT following Re-S, including 108 patients with recurrent high grade gliomas who were treated with a EQD2 ranging from 25 to 57 Gy. Most patients received 36 Gy in 2 or 3 Gy per fraction. Median survival of 12 months was obtained without any severe toxicity. At multivariate analysis the extent of surgery, MGMT-methylation, interval time between first and second course of RT and KPS were strong prognostic factors for survival.

Lee et al. (Lee et al., 2018) reported 25 cases of recurrent GBM who were operated and, then, treated with hypofractionated radiotherapy with a simoultaneous integrated boost technique (37.5 Gy and 45 Gy in 15 fractions). Median PFS and 1-year PFS were 13 months and 51.4 %, respectively; median OS and 1-year OS were 16 months and 60 %, respectively. Of note, 33 % of patients were hospitalized for radionecrosis. The gross tumor volume at re-RT (surgical cavity and any residual contrast-enhanced lesion) >100 mL was the only independent prognostic factor confirmed at multivariate analysis.

Local treatment intensification was described also in a series from Chun et al. (Chun et al., 2018):at recurrence, 84 patients with high grade gliomas received a second course of RT after Re-S for a median EQD2 of 42.8 Gy and cumulative median EQD2 of 99.3 Gy. The addition of RT to reoperation was related to a significant benefit in terms of PFS (mPFS was 3.5 and 9.0 months for Re-S alone and Re-S + Re-RT, respectively). Of note, a case of right middle artery stroke occurred during re-RT but no cases of radionecrosis were observed. The authors also defined three risk categories according to the presence of one, two or three of the most significant prognostic risk factors (age ≥50, WHO grade IV and unmethylated MGMT promoter).

Since these results were obtained in series were patients who were initially diagnosed with lower grade gliomas, it will be important that the positive results are validated by the GlioCave study, an ongoing phase II trial that investigates early reirradiation (46 Gy in 2 Gy-fractions or 36 Gy in 3 Gy-fractions) after surgical resection for rec-GBM (Straube et al., 2018).

Another combined option to consider is the administration of systemic therapy after Re-S. The addition of systemic therapy after Re-S for relapsing GBM has been reported as a significant factor for a better survival in several articles (De Bonis et al., 2013; McNamara et al., 2014; Sastry et al., 2018). De Bonis et al. (De Bonis et al., 2013) showed that patients treated with postoperative chemotherapy had a significant survival advantage (mOS = 14 months), if compared with patients treated with Re-S alone (mOS = 6 months). The addition of chemotherapy to Re-S was an independent prognostic factor affecting OS on multivariate analysis, in the series published by Mc Namara et al. (McNamara et al., 2014). In a large German multicenter study including 503 patients operated for relapsing GBM (Ringel et al., 2016), adjuvant treatment (primarily chemotherapy) was the strongest factor for survival: patients receiving chemotherapy had a median survival equal to 13.4 months, whereas patients treated with Re-S alone and had a median OS of 8.5 months.

The positive impact of adding postoperative treatment to Re-S was confirmed by a recently published retrospective series of 300 patients with rec-GBM, who were treated in two centers in the Netherlands (van Linde et al., 2017). Four different treatment strategies were used: best supportive care, systemic treatment, Re-RT alone and Re-S followed by adjuvant treatment (systemic treatment and/or Re-RT). Patients in the Re-S + adjuvant therapy group had the longest median OS (11 months) and PFS (9.0 months). Similarly, Azoulay et al. (Azoulay et al., 2017) found that the addition of chemotherapy and/or re-RT (30−35 Gy in 10 fractions) to Re-S provided significant survival benefit (median OS 10 months), compared to other treatment options (Re-S alone or chemotherapy or Re-RT).

Combined treatment may be considered even in elderly patients, as shown by Chen et al. (Chen et al., 2018) who reported a large cohort of patients older than 65, included in the Surveillance, Epidemiology, and End Results (SEER) Medicare database: re-RT, TMZ or re-RT + TMZ were associated with significantly improved survival when combined with re-S.

10.2. Re-RT + systemic therapy

At the moment of recurrence, the addition of systemic therapy to Re-RT may also be an option considering the existence of several series where systemic treatment improved reirradiation outcomes (Grosu et al., 2005; Flieger et al., 2014; Niyazi et al., 2012; Cuneo et al., 2012). The potential advantage of adding systemic treatment to the second course of irradiation was investigated in a secondary analysis of NRG Oncology/RTOG Trial 0525: although the difference is not statistically significant, the subgroup of patients treated with both systemic therapy and Re-RT had the best outcome in terms of survival (median OS: 12.2 months) as compared to radiation therapy only (median OS: 8.21 months) or systemic treatment alone (median OS: 10.5 months) (Shi et al., 2018b).

11. Conclusions

In conclusion, herein we proposed a four-step decision tree that originated by the analysis of the existing literature. Patients with a relatively good life expectancy (>3 months) and with a circumscribed disease should be considered for local treatment. Confirmation of need of a local strategy and, in that case, the choice between second surgery and repeat irradiation should be based on a careful pretreatment assessment of the prognostic factors and of the expected toxicity. The opportunity of a combined strategy should be taken into account, considering the growing evidence in favour of combination treatment. Noteworthy, a multidisciplinary discussion for every single case remains essential before any therapeutic decision is made. Of course, skilled neurosurgeons and expert radiation oncologists are needed. In addition, involving the patient in the final decision is crucial, after a deep discussion about the risks and benefits of the existing treatment options (Siminoff, 2013).

Declaration of Competing Interest

The authors report no declarations of interest.

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Nothing to declare.

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