

# Treatment of recurrent glioblastoma with stereotactic radiotherapy: long-term results of a mono-institutional trial

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## ABSTRACT

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**Aims and background.** Few clinical data exist concerning normal brain tissue tolerance to re-irradiation. The present study evaluated long-term outcome of 22 recurrent glioblastoma patients re-irradiated with radiosurgery or fractionated stereotactic radiotherapy.

**Methods.** Twenty-two patients were treated with radiosurgery (13, 59%) or fractionated stereotactic radiotherapy (9, 41%) for 24 lesions of recurrent glioblastoma. The male/female ratio was 14:8, median age 55 years (range, 27-81), and median Karnofsky performance status 90 (range, 70-100). The majority of the cases (77%) was in recursive partitioning analysis classes III or IV. Radiosurgery or fractionated stereotactic radiotherapy was chosen according to lesion size and location.

**Results.** Median time between primary radiotherapy and re-irradiation was 9 months. Median doses were 17 Gy and 30 Gy, whereas median cumulative normalized total dose was 141 Gy and 98 Gy for radiosurgery and fractionated stereotactic radiotherapy, respectively. All patients submitted to radiosurgery had a cumulative normalized total dose of more than 100 Gy, whereas only a few (44%) of fractionated stereotactic radiotherapy patients had a cumulative normalized total dose exceeding 100 Gy. Median follow-up from re-irradiation was 54 months. At the time of analysis, all patients had died. After re-irradiation, 1 (4%) lesion was in partial remission, 16 (67%) lesions were stable, and the remaining 7 (29%) were in progression. Median duration of response was 6 months, and median survival from re-irradiation 11 months. Three of 13 (23%) patients submitted to radiosurgery developed asymptomatic brain radionecrosis. The cumulative normalized total dose for the 3 patients was 122 Gy, 124 Gy, and 141 Gy, respectively. In one case, the volume of the lesion was large (14 cc), and in the other 2 the interval between the first and second cycle of radiotherapy was short (5 months).

**Conclusions.** Re-irradiation with radiosurgery and fractionated stereotactic radiotherapy is feasible and effective in recurrent glioblastoma patients. Apart from the importance of an accurate patient selection, cumulative radiotherapy dose and a correct indication for radiosurgery or fractionated stereotactic radiotherapy must be taken into account to avoid brain toxicity. Free full text available at [www.tumorionline.it](http://www.tumorionline.it)

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## Introduction

The standard treatment of glioblastoma multiforme (GBM) is surgery followed by chemoradiotherapy<sup>1,2</sup>. Despite this therapeutic approach, overall survival remains poor. The vast majority of GBM (about 90% of cases) recurs within or adjacent to the original tumor bed<sup>3-5</sup>.

Treatment options for recurrent GBM are limited and include re-resection, chemotherapy and/or radiotherapy. Owing to the infiltrative nature of GBM, optimal

**Key words:** fractionated stereotactic radiotherapy, glioblastoma multiforme, radiosurgery, re-irradiation.

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Received May 13, 2010; accepted September 6, 2010.

re-resection is often associated to morbidity<sup>6,7</sup>. Systemic chemotherapy can be applied using regimens including carmustine or temozolomide, or drug combinations (e.g., prednisone, carmustine, vincristine), with a modest benefit limited only to a few patients<sup>8-10</sup>.

There is no standard protocol for re-irradiation. A large variety of irradiation treatment schemes are used with regard to total dose, size and number of fractions. Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) are attractive options because of their ability to precisely deliver high doses of irradiation to a defined target volume in a single – SRS, or more fractions – FSRT, with an expected lower incidence of treatment-related morbidity<sup>3,4,11-13</sup>. In the last 10 years, some authors have used SRS or FSRT to treat recurrent gliomas with promising results<sup>14-18</sup>.

Currently, the tolerance dose for the brain to a single course of radiation is estimated at 50-60 Gy in 2 Gy daily fractions<sup>19,20</sup>. Few clinical data exist concerning normal brain tissue tolerance to a second course of radiation. Less is known about regeneration after radiation and, hence, the tolerance to a second course of radiation. *In vivo* radiobiological data suggest a repair of central nervous system radiation damage after an initial course of irradiation<sup>21,22</sup>. The magnitude of recovery depends on total dose and fractionation regimen in the first course and on the interval between treatments. A recent review, using the linear quadratic model to derive information on the cumulative biologic effective tolerance dose ( $BED_{cumulative}$ , which results from  $BED_{initial} + BED_{re-irradiation}$ ), and equivalent doses in 2-Gy fractions (normalized total doses,  $NTD_{cumulative}$ , which results from  $NTD_{initial} + NTD_{re-irradiation}$ ), showed that radiation-induced brain tissue necrosis occurs at an  $NTD_{cumulative} > 100$  Gy<sup>23</sup>.

The present study evaluated long-term outcome of 22 patients with recurrent GBM re-irradiated with SRS or FSRT according to a phase II trial.

## Patients and methods

### Eligibility criteria

All cases were preliminarily discussed in a multidisciplinary meeting with radiation oncologists, neurosurgeons, neuroradiologists, medical oncologists, and pathologists to define the clinical indications.

To be eligible, patients must have received partial brain fractionated external beam radiotherapy  $\geq 5$  months before re-irradiation for GBM. Magnetic resonance imaging (MRI) of the brain with contrast evidence of a recurrence and/or progression of disease, patient Karnofsky performance status (KPS)  $\geq 70\%$ , and a life expectancy  $\geq 3$  months were also required.

No concomitant chemotherapy was admitted during re-irradiation. Informed consent was obtained according to the rules of our Institution.

### Protocol treatment

For SRS, a 3D-line stereotactic frame was applied under local anesthesia for head fixation during MRI and at the time of treatment. For FSRT, a non-invasive head-mask system was used to immobilize the patient. A fiducial system was used for stereotactic coordination definition. Target volume was delineated on a post-double-contrast MRI; target and critical structures were outlined on contiguous 3-mm separated slices. Gross tumor volume (GTV) consisted of the radiographically evident, contrast-enhancing, gross disease in T1-weighted sequences, and no expansion was done for clinical target volume (CTV). For SRS procedure, planning target volume (PTV) was considered equivalent to GTV/CTV, whereas for FSRT, a 3-mm isotropic margin was added to GTV/CTV to define the PTV. Treatment plans were produced on an Ergo 3D-line treatment instrument. Patients were treated with a 5-MV linear accelerator fitted with a commercial dynamic micro-multileaf collimator. Dose was prescribed to the isocenter, and the stereotactic plan was optimized so that at least the 90% isodose line encompassed the target volume.

FSRT was reserved for tumors with a diameter of more than 30 mm (otherwise, a volume of more than 14 cc) and/or located close to or at critical brain structures (e.g., brain stem, optic chiasm, etc.), whereas SRS was applied for other tumors. Considering SRS, doses were chosen according to maximum diameter of the tumor as suggested by RTOG Protocol 90-05 (i.e., 24 Gy, 18 Gy, and 15 Gy for tumors  $\leq 20$  mm, 21-30 mm, and 31-40 mm, respectively)<sup>13</sup>. Regarding FSRT, the maximum  $BED_{cumulative}$  accepted was 210 Gy, as suggested by Cho *et al.*<sup>15</sup>, and the number of fractions was conditioned by the tumor size (i.e., the smaller the lesion, the higher the number of fractions).

Only patients submitted to SRS received both 8 mg of dexamethasone and H2-antihistamines for gastric ulcer prophylaxis 1 h before and 12 h after the treatment. Dexamethasone was administered for another 7 days after SRS and was then tapered off. In FSRT patients, corticosteroids were administered on an as-needed basis.

### Follow-up and toxicity

For all 22 patients, the median  $BED$ ,  $BED_{cumulative}$ , and  $NTD_{cumulative}$  values were calculated. The  $BED$  values were calculated with the linear quadratic model, according to the following relationship:  $nd(1 + d/\alpha/\beta)$ , with  $d$  = fraction dose (Gy),  $n$  = number of fractions,  $nd$  =  $D$  = total physical dose (Gy), and  $\alpha/\beta$  = tissue repair capacity (Gy). Selecting an  $\alpha/\beta$  ratio of 2 Gy, the  $BED_2$  represents the biologic dose of high-dose-rate irradiation on the late-responding normal brain. The  $BED$  values were converted to  $NTD$  values, with  $NTD$  being defined as the total dose delivered in 2-Gy fractions at an  $\alpha/\beta$  ratio of 2 Gy<sup>23</sup>.

Acute and chronic toxicity were assessed according to the Radiation Therapy Oncology Group (RTOG) Scoring Criteria.

Patients were seen for follow-up 4 weeks after the end of re-irradiation, then at 3-month intervals or as needed. During the follow-up, MRI was performed every 3 months or when clinical worsening developed, whereas additional diagnostic procedures, such as MRI spectroscopy or single-photon emission computed tomography (SPECT-CT), were scheduled when there was a need to differentiate between radiotherapy-induced necrosis or tumor progression.

Failure was defined as follows: 1) an increase in volume of at least 25%, 2) the reappearance of a lesion that was in complete response, or 3) the appearance of any new lesion. Relapse was defined "in-field" when more than 95% of the recurrence volume was within the original 50% isodose, and "out-of-field" in the other cases.

### Statistical evaluation

Survival and progression-free survival were analyzed using the Kaplan-Meier method. Survival was calculated from first surgery to death, as well as from re-irradiation (i.e., the day of SRS or the date of first fraction of FSRT) to death. Progression-free survival after re-irradiation was also calculated until tumor progression or death. Univariate analysis was performed using the log-rank test. Variables compared were gender, age ( $\leq 50$  vs  $> 50$  years), KPS, ( $\leq 80$  vs  $> 80$ ), recursive partitioning analysis classes (RPA,  $< IV$  vs  $\geq IV$ )<sup>24</sup>, extent of first surgery (total versus subtotal), previous re-operation (yes versus no), previous history of chemotherapy (concomitant and adjuvant versus adjuvant), treatment volume ( $\leq 8$  vs  $> 8$ cc), previous radiotherapy doses ( $< 60$  vs  $\geq 60$  Gy), and interval from diagnosis to recurrence ( $\leq 10$  vs  $> 10$  months).

## Results

Between November 2001 and October 2008, 22 patients were treated with SRS or FSRT for 24 lesions of recurrent GBM. At the time of first diagnosis, all patients underwent neurosurgical resection, which was total in 19 (86%). Histology was in all cases GBM (i.e., WHO grade IV gliomas). The first external beam radiotherapy was in all cases conformal, with a median dose of 60 Gy (range, 42-66) delivered in a median number of 30 fractions (range, 14-35). Eighteen (82%) patients received chemotherapy, which was in 14 (78%) both concomitant and adjuvant to radiotherapy according to Stupp's treatment and in the remaining 4, only adjuvant<sup>1,2</sup>.

Fourteen (64%) patients were male and 8 (36%) female; median age was 55 years (range, 27-81), and median KPS was 90 (range, 70-100). According to RPA, 6 (27%) patients were class III, 11 (50%) class IV, and re-

maining 5 (23%) class V. The median time between primary radiotherapy and re-irradiation for tumor recurrence was 9 months (range, 5-25). At the time of re-irradiation, every patient presented evidence of disease localized within the former high-dose radiotherapy fields. Thirteen patients (59%) – 11 with 1 lesion and 2 with 2 lesions – received SRS; the remaining 9 (41%), each with only 1 lesion, received FSRT.

Before re-irradiation, 5 (23%) patients underwent re-resection; thereafter, 4 received SRS and 1 FSRT. Median volume of re-irradiated tumors was 5.3 cc (range, 0.6-14) and 44 cc (range, 1.4-151) in SRS and FSRT groups, respectively. Median dose was 17 Gy (range, 14-22) and 30 Gy (range, 15-45) in SRS and FSRT groups, respectively.

For the 9 FSRT patients, median number of fractions was 10 (range, 5-15), with daily 3 Gy per fraction, 5 times a week. In 8 patients, total doses varied between 15 Gy, 30 Gy, and 36 Gy in 3, 3, and 2 cases, respectively, with a  $BED_{cumulative} \leq 210$  Gy. The remaining patient, receiving 45 Gy in 15 fractions with a  $BED_{cumulative} > 210$  Gy, was the only one who exceeded the protocol cutoff dose. Median  $NTD_{cumulative}$  was 141 Gy (range, 116-186) and 98 Gy (range, 71-116) in SRS and FSRT groups, respectively. It is noteworthy that all (100%) patients submitted to SRS had an  $NTD_{cumulative}$  of more than 100 Gy, whereas only a few of those treated with FSRT had an  $NTD_{cumulative}$  exceeding 100 Gy (4/9, 44%).

Treatment was well tolerated by all patients. No acute toxicity of more than grade II was observed. Headache and nausea/vomiting were registered in 4 (18%) patients (2 for each group), symptoms regressed in 1 month with medium doses of steroids. In these patients, MRI performed 3 months after re-irradiation showed stable disease without surrounding edema. Only FSRT patients presented skin erythema and alopecia, which were restricted to small areas and were fully reversible in all cases. Three of 13 (23%) patients submitted to SRS developed brain radionecrosis. The volume of the lesions was 5 cc, 8 cc and 14 cc, and dose administered was 14 Gy, 15 Gy and 17 Gy, respectively. All 3 patients had received conformal radiotherapy as first treatment, with a median dose of 60 Gy (range, 60-66). For each patient,  $BED_{cumulative}$  was 244 Gy, 248 Gy and 282 Gy, and  $NTD_{cumulative}$  was 122 Gy, 124 Gy and 141 Gy, respectively. In all cases, MRI revealed local changes of the lesions characterized by irregular contrast enhancement associated to surrounding edema without mass effect. A diagnosis of radionecrosis was made using also MRI spectroscopy, which evidenced a low peak of choline, and SPECT-CT, in which no lesion uptake was registered. For these patients, who had neither subjective nor clinical symptoms or objective signs, no medical therapy was required. Three months after the diagnosis of radionecrosis, MRI assessed a reduction of edema in all cases. At follow-up, all 3 patients presented stable disease for a median of 7 months (range, 6-11) and died for an "out-of-field" relapse of disease.

Three months after re-irradiation, 1 (4%) lesion was in partial remission, 16 (67%) lesions were stable, and the remaining 7 (29%) lesions progressed, 3 “in-field”, 3 “out-of-field” and one both “in-field” and “out-of-field”. The total response rate was thus 71%, and median duration of response was 6 months (range, 3-11). After re-irradiation, only 3 (14%) patients received chemotherapy: 2 patients were treated with temozolomide 9 and 15 months after SRS because of disease progression, and the other one underwent adjuvant targeted therapy with bevacizumab 4 weeks after SRS.

At the time of analysis, all patients had died, all but one (95.5%) for brain progression of disease and one (4.5%) for myocardial infarction. Median overall survival calculated from first surgery to death was 26 months (Figure 1). After re-irradiation, median overall survival was 11 months for both SRS and FSRT patient groups (Figure 2). At 6 and 12 months after re-irradiation, survival rates for all patients were  $77 \pm 9\%$  and  $36 \pm 10\%$ , respectively. No statistically significant differences were observed in the two treatment groups ( $P = 0.5$ ; Figure 3). Median progression-free survival was 4 months. Progression-free survival at 6 months after re-irradiation was  $33 \pm 9\%$  and at 12 months was  $4 \pm 4\%$ . Sixteen (73%) patients maintained the KPS defined before re-irradiation.

The median BED of the first course of radiotherapy was the same in the two patient groups (120 Gy), whereas the median BED of re-irradiation was higher in the SRS group than in the FSRT group (162 *vs* 75). Consequently, comparing SRS and FSRT doses, median cumulative BED was 282 Gy (range, 232-373) and 195 Gy (range, 143-233), and median cumulative NTD was 141 Gy (range, 116-186) and 98 Gy (range, 71-116), respectively.

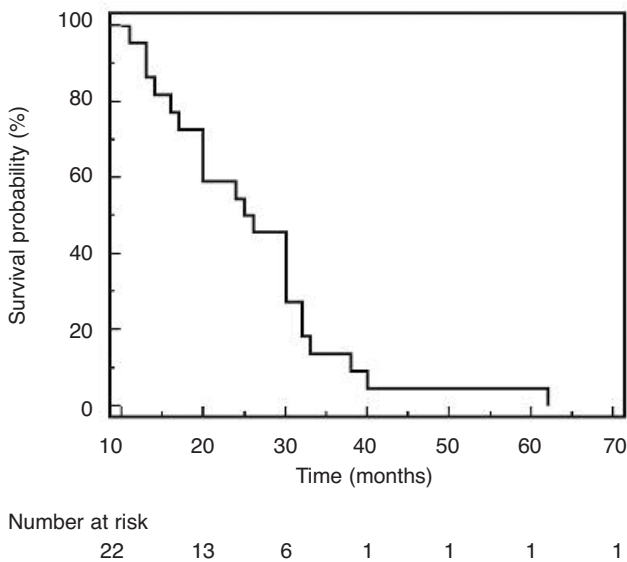


Figure 1 - Kaplan-Meier probability plot of overall survival as a function of months after first diagnosis. Number of patients at risk at 0, 10, 20, 30, 40, 50, 60 and 70 months is also presented.

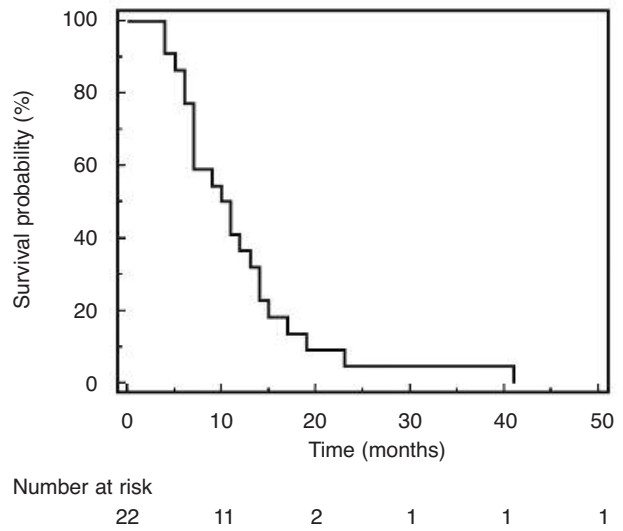


Figure 2 - Kaplan-Meier probability plot of overall survival for all patients as a function of months after re-irradiation. Number of patients at risk at 0, 10, 20, 30, 40 and 50 months is also presented.

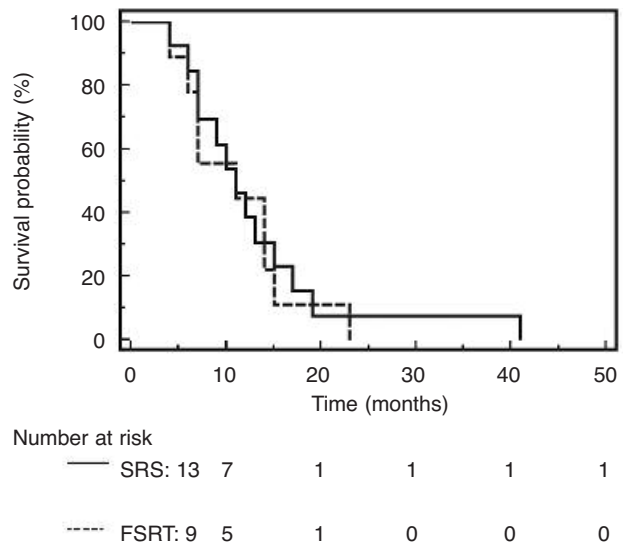


Figure 3 - Kaplan-Meier probability plot of overall survival for stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) regimen subgroups as a function of months after re-irradiation. Number of patients at risk at 0, 10, 20, 30, 40 and 50 months is also presented.

No significant prognostic factors for overall and progression-free survival were found, including gender, KPS, age, RPA class, previous re-operation, chemotherapy, treatment volume, radiotherapy doses, and interval from diagnosis to recurrence.

**Discussion**

The main goal in the treatment of gliomas is the achievement of local control. Combined treatment with

neurosurgical resection and radiochemotherapy (conformal radiotherapy plus temozolomide) is the standard approach for GBM<sup>1,2</sup>. In spite of this treatment, most patients develop recurrences “at” or “in close proximity to” the original site of the tumor, and a salvage therapy can be considered<sup>3,5</sup>.

Treatment outcomes of recurrent GBM are disappointing. Chemotherapy, the most frequent salvage treatment adopted in clinical practice, gives a low median survival (about 20 weeks)<sup>8-10</sup>. Surgical salvage can be done only in selected patients because of the infiltrative nature of the disease<sup>6,7</sup>. Generally, brain re-irradiation is rarely performed because of possible cumulative radiation-induced toxicity, and there are few clinical data regarding efficacy<sup>25-27</sup>. Bauman *et al.*<sup>20</sup> and Veninga *et al.*<sup>19</sup> treated with conventional radiotherapy and various dose fractionations 34 and 42 recurrent GBM patients, with a survival from re-irradiation of 2.8 and 5.9 months, respectively. In the study of Veninga *et al.*<sup>19</sup>, 3 cases of late toxicity were documented, i.e., brain radionecrosis in one patient retreated with a cumulative BED of 236 Gy and cognitive decline in 2 other patients retreated with a cumulative BED of more than 204 Gy.

SRS and FSRT are appealing because of their ability to precisely deliver high doses of irradiation to a defined target volume in a single or more fractions with a steep dose gradient around the target. Due to the potential toxicity associated with the single dose, SRS is generally limited to patients with small lesions and FSRT is reserved for large lesions. Cho *et al.*<sup>15</sup> treated 42 recurrent high-grade glioma patients, 27 with SRS and 15 with FSRT. Median dose was 17 Gy and 37.5 Gy with a median cumulative BED of 274.4 and 198.4 Gy for the two groups, respectively. Median survival was 7.1 months in all cases. Four patients in the SRS group and 1 patient in the FSRT group developed deterioration of neurological functions due to brain necrosis. In two different publications, Combs *et al.*<sup>3,17</sup> reported a median survival of 8 and 10 months, reached without toxicity, for 53 and 32 patients with recurrent GBM treated with FSRT and SRS and cumulative BED of 186 and 285.5 Gy, respectively.

To identify normal brain tissue tolerance dose, Mayer *et al.*<sup>23</sup> reviewed 21 studies of re-irradiation with conventional radiotherapy, FSRT or SRS. The incidence of radiation-induced brain tissue necrosis was analyzed using BED<sub>cumulative</sub> and NTD<sub>cumulative</sub> values. It was noted that BED<sub>cumulative</sub> and NTD<sub>cumulative</sub> increased when more precise irradiation techniques, such as FSRT or SRS, were adopted. Radionecrosis was reported after a NTD<sub>cumulative</sub> between 105 to 135 Gy and between 111 and 137.2 Gy in FSRT and SRS series, respectively. The authors concluded that with an  $\alpha/\beta$  ratio of 2 Gy, radiation-induced normal brain tissue necrosis was found to occur at BED<sub>cumulative</sub> >200 Gy and NTD<sub>cumulative</sub> >100 Gy<sup>23</sup>.

In our series, re-irradiation was well tolerated with no important acute toxicity or symptomatic late toxicity. However, MRI and SPECT-CT showed asymptomatic

brain radionecrosis in 3 patients. These patients, who were all in the SRS group, were at risk of radionecrosis because they had received high NTD<sub>cumulative</sub> doses, 122, 124 and 141 Gy. The fact that cumulative dose plays an important role in conditioning late toxicity is supported by the absence of brain radionecrosis in our FSRT group of patients, who had received median NTD<sub>cumulative</sub> doses of less than 100 Gy. Apart from this reason, the observed late brain toxicity could be due to the short interval (5 months) between the first and the second cycle of radiotherapy (in 2 cases) and the relatively large volume (14 cc) of the lesion (in one case). Anyway, it is noteworthy that radiotherapy-induced neurological impairment was not registered in any patient and that all 3 patients had a radiological normalization of radionecrosis signs 3 months after the diagnosis.

In our trial, 71% of patients obtained local control of disease, with a median duration of response of 6 months and a median survival from re-irradiation of 11 months, values which are close to the best published in the literature<sup>3,15,17</sup>. Local control and median survival were the same in both SRS and FSRT groups and did not seem to be conditioned by delivered dose. Most of the patients maintained the performance status defined before re-irradiation. Although, the relatively small number of patients entered in the study does not allow us to draw definitive conclusions, patient selection and adequate radiotherapy doses could have played an important role in obtaining the results. In fact, selection based on time between primary radiotherapy and re-irradiation (median, 9 months), good KPS (median 90), good RPA class ( $\leq$ IV in 77% of the cases), life expectancy ( $\geq$ 3 months) and administered doses (median values, 30 Gy for FSRT and 17 Gy for SRS) could have positively conditioned disease control and survival.

In conclusion, our data suggest that re-irradiation with SRS and FSRT is feasible and effective in recurrent GBM patients. The results were obtained thanks to an accurate patient selection based on adequate time between the first radiotherapy cycle and re-irradiation ( $\geq$ 5 months), good patient KPS ( $\geq$ 70%), and a life expectancy  $\geq$ 3 months. Brain toxicity may be limited taking into account cumulative radiotherapy dose (i.e., NTD<sub>cumulative</sub> doses less than 100 Gy) and choosing SRS or FSRT according to tumor size and location.

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