Neuroendocrinology Letters Volume 39 No. 4 2018
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Gamma knife radiosurgery for local recurrence of glioblastoma

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Submitted: 2018-05-25 *Accepted: 2018-09-22* *Published online: 2018-10-20*

Key words: **gamma knife radiosurgery; recurrent glioblastoma; safe palliative treatment; survival after gamma knife radiosurgery; tumor regression**

Neuroendocrinol Lett 2018; **39**(4):281–287 **PMID:** 30531701 NEL390418A02 © 2018 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVE: Local recurrence of glioblastoma is observed in most patients after standard oncologic treatment (surgery, chemotherapy and radiotherapy). Stereotactic radiosurgery with the Leksell Gamma Knife (SRS with LGK) was used to treat recurrent tumors in selected cases, and retrospective analysis of treatment outcome was performed.

METHODS: Altogether 126 patients were treated for glioblastoma at our center from 1992–2014. Sixty-nine patients (55%) were male and 57 (45%) female, with a median age of 56 years (range 17–80 years). Prior to LGK radiosurgery, 123 (98%) underwent surgery, 126 (100%) radiotherapy and 116 (92%) chemotherapy. The median Karnofsky score before LGK radiosurgery was 90% (range 50–100), and the median time from GBM diagnosis to LGK radiosurgery was 12 months (range 1–96 months). The median tumor volume was 3.75 cm^3 (range 0.04–37.10 cm^3). LGK radiosurgery was performed in a single fraction with a median minimal tumor dose of 12 Gy (range 10–25 Gy) on a median 50% (range 40–86%) isodose line. Two and more LGK radiosurgeries were performed in 19 (15%) cases, a median interval of 9.6 months (range 2–45 months) from the initial LGK radiosurgery. The median prescribed dose in these patients was 12.6 Gy (range 10–15 Gy), and the median volume 5.8 cm3 (range 0.1–13.7 cm^3).

RESULTS: The median survival from GBM diagnosis was 20 months (range 6–237 months). The median survival after LGK radiosurgery was 7 months (range 1–223 months). The one year survival after LGK radiosurgery was 27%, 2 years 8%, and more than 3 years 4%.

Tumor regression on MR images was observed in 17% of patients at a median interval of 7 months. The median interval to tumor progression on MR images after LGK treatment was 8.5 months. No treatment-related radionecrosis with expansive behaviour was detected after radiosurgery.

CONCLUSION: We show that LGK radiosurgery is a safe palliative treatment modality in patients with recurrent GBM.

ORIGINAL ARTICLE

INTRODUCTION

Glioblastoma multiforme (GBM) is the most widespread and most aggressive malignant tumor of the brain in adults. Despite the latest achievements in neuroimaging, surgical methods and conservative therapy such as chemotherapy and radiotherapy, the prognosis in GBM remains poor with local recurrence in more than 80% of patients (Stupp *et al.* 2005; 2009). Surgery, chemotherapy and fractionated radiotherapy play an important role in the management of recurrent disease (Nieder *et al.* 2000). Surgical treatment of local recurrence can also be employed for control of tumor growth (Stummer & Kamp 2009; Park *et al.* 2007), but this procedure can be carried out only in a small subpopulation (Barbagallo *et al.* 2008). Reirradiation with conventional external-beam radiotherapy provides only a modest benefit in most patients, and in many situations the risks outweigh the potential benefits (Krex *et al.* 2007). Options are limited by previous high doses of radiotherapy applied after the primary diagnosis, tumor volume and location at the time of recurrence (Pichler & Marosi 2011). The use of systemic chemotherapy in patients with recurrent GBM improves survival with a median range of 4 to 7 months (Stupp & Weber 2005; Chamberlain & Tsao-Wei 2004; Chua *et al.* 2004). Stereotactic radiosurgery with the Leksell Gamma Knife (SRS with LGK) is a logical complement to all treatment methods for recurrent GBM, due to its ability to provide high doses of radiation in a focal objective, is non-invasive and well tolerated by patients, and can be repeated (Romanelli *et al.* 2009). The purpose of SRS with LGK in the treatment of recurrent GBM is to increase survival and preserve an acceptable quality of life. SRS with LGK, due to steep fall of the dose and zonal effects, allows minimal influence of irradiation dose to healthy surrounding tissues. The main limit for SRS is volume, so LGK was used to treat recurrent GBM in selected cases suitable for single session irradiation and retrospective analysis of treatment results was performed.

METHODS AND MATERIALS

One hundred and twenty-six patients were treated for GBM between 1992–2014 at our institution and analyzed in the present study, including 69 (55%) male and 57 (45%) female patients with a median age of 56 years (range 17–80 years). From this group, 123 patients (98%) underwent surgery, 126 (100%) radiotherapy and 116 (92%) chemotherapy prior to LGK radiosurgery. The median Karnofsky score before SRS with LGK was 90% (range 50–100) and the median time from GBM diagnosis to LGK radiosurgery was 12 months (range 1–96 months). The median tumor volume was 3.75 cm^3 (range 0.04–37.10 cm^3). LGK radiosurgery was performed in a single fraction with a median minimal tumor dose of 12 Gy (range 10–25 Gy) on a median 50% (range 40–86%) isodose line. Repeated SRS with LGK was performed in 19 (15%) cases a median 9.6 months (range 2–45 months) from the initial LGK radiosurgery. Some patients (28%) underwent PET prior to SRS with LGK, which was later used during planning. The main characteristics of patients are provided in Table 1.

Tab. 1. Main characteristics of a total number of 126 patients treated for glioblastoma in this study.

Parameter	Total number	Range	Median
Sex	Male 69 (55%) Female 57 (45%)	–	–
Age	–	17–80 years	56 years
Surgery before LGK	123 (98%)	–	–
Radiotherapy before LGK	126 (100%)	–	–
Chemotherapy before LGK	116 (92%)	–	–
Time from diagnosis to LGK	–	1–96 months	12 months
Karnofsky score before LGK	–	50–100	90
Tumor location	Temporal 45 (36%) Frontal 31 (25%) Parietal 21 (17%) Occipital 12 (9%) Other 17 (13%)	–	–
Tumor volume	–	0.04–37.10 cm^3	3.75 cm^3
Minimal tumor dose	–	10–25 Gy	12 Gy
Prescription isodose	–	40–86%	50%
2nd LGK treatment	19 (15%)	–	–
Survival since LGK treatment	–	1–223 months	7 months
Survival since diagnosis	–	6–237 months	20 months

Description of radiosurgery treatment

Treatment was carried out by Leksell Gamma Knife (Elekta Instrument AB, Stockholm, Sweden). Fixation of the Leksell stereotactic frame was performed under local anesthesia. Magnetic Resonance Imaging (MRI) was conducted with contrast-enhanced T1-weighted spin echo sequences. Irradiation planning was carried out on the peripheral isodose line (covering at least 99% target volume) from 40 to 86% (median 50%). At the median, the prescribed dose was 12 Gy (from 10 to 25 Gy). The median volume was 3.75 cm^3.

The patients were evaluated every 3–5 months after LGK radiosurgical treatment, including contrast-enhanced brain MRI and neurological examination. In the event of neurological deterioration, unscheduled evaluation was performed. Dynamic MRI changes were qualified as volumetric regression or progression. FDG PET was used to help differentiate between tumor progression and pseudoprogression and was performed in 29% of cases (see Figure 1).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics version 20. Kaplan-Meier curves were used to plot survival from diagnosis and LGK treatment. The following parameters and values were tested as potential prognostic factors for survival from diagnosis: sex (male/female), age (50 years), Karnofsky (80) and volume (4 cm^3). Three tests were used to evaluate statistical significance: Log-rank, Breslow and Tarone-Ware. Significance was set at $p<0.05$.

RESULTS

Median patient survival from GBM diagnosis was 20 months (range 6–237 months). Median patient survival after LGK radiosurgery was 7 months (range 1–223 months). One year survival after LGK radiosurgery was achieved in 27% of patients, 2 year survival in 8% of patients, and more than 3 years survival in 4% of patients. A patient with two subsequent LGK treat-

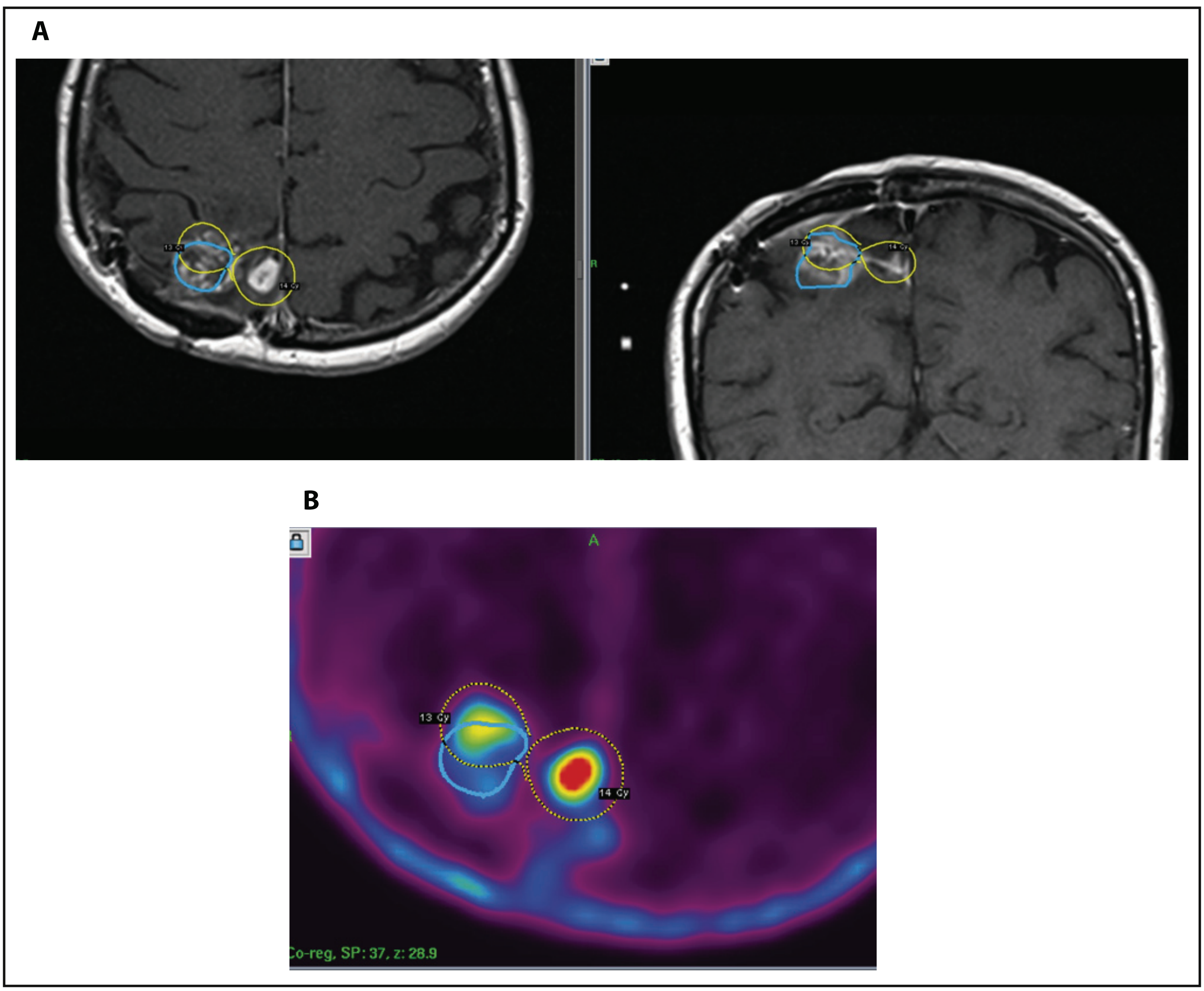

Fig. 1. Example of PET imaging used for tumor targeting together with MR imaging. FDG PET imaging was used for the differential diagnosis between the continued growth of the tumor and the possible formation of post-irradiation necrosis. PET imaging was performed in 29% cases in this study.

ments and survival of 38 months is shown in Figure 2. Kaplan-Meier survival from LGK treatment and diagnosis is provided in Figure 3. Kaplan-Meier survival for sex, age group, Karnofsky score and volume is shown in Figure 4. Only age was found to be statistically significant, where better survival was observed for patients 50 years of age and younger.

Tumor regression on MRI was observed in 17% of patients after a median interval of 7 months. The median time to tumor progression on MRI after LGK treatment was 8.5 months. No treatment-related radionecrosis with expansive behavior was detected after radiosurgery.

DISCUSSION

In current practice, SRS is applied in the event of recurrence after standard radiotherapy and chemotherapy. The effect of postoperative SRS followed by conventional external beam radiation therapy with chemotherapy was evaluated in a randomised study by Souhami and colleagues (2004). They reported no significant differences in survival or quality of life when boost SRS was performed before standard radiotherapy and chemotherapy.

In our study, we present the use of SRS with LGK as a salvage therapy following recurrence of GBM after stan-

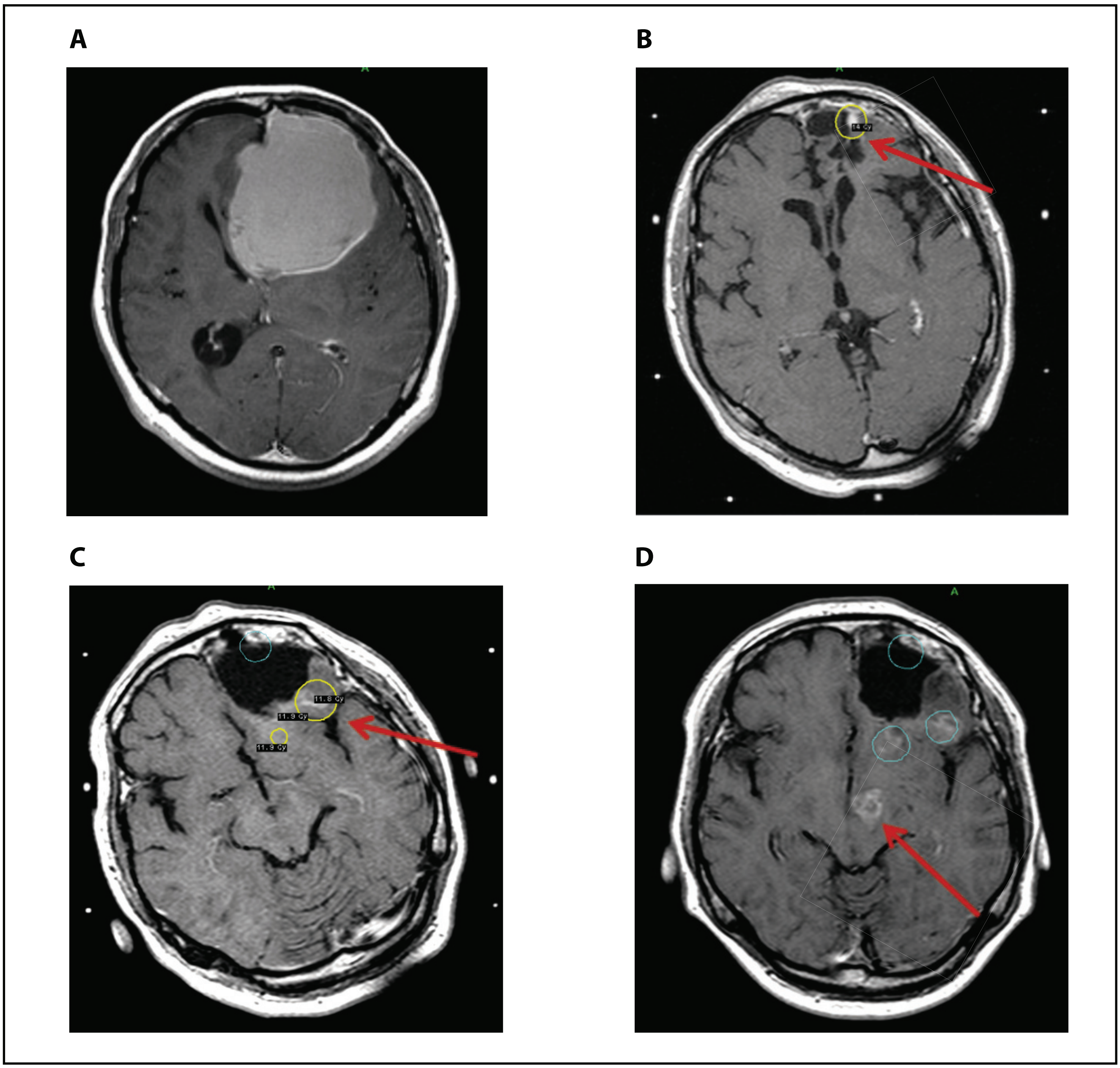

Fig. 2. Example of glioblastoma patient – male 36-year old at the time of diagnosis. A) Patient diagnosed with GBM followed by surgery, chemotherapy and radiotherapy (11/2004), B) Tumor recurrence and the first LGK treatment (05/2006), C) New tumor recurrence and the second LGK treatment (07/2007), D) Another tumor recurrence after which patient underwent chemotherapy (11/2007). Patient died in 01/2008 after 38 months since GBM diagnosis.

dard first-line therapy. Although radiation is proven to be effective in the treatment of GBM, a second course of radiotherapy is generally applied reluctantly with conventional techniques, as treatment outcome outweighs the risk of treatment-related side effects. In fact, the 60 Gy dose typically applied in first-line treatment generally hampers the application of a second full-dose radiotherapy course. Barani IJ[1] and Larson DA noted that re-irradiation strategies concurrently employ bevacizumab to limit treatment-related injury while still permitting the delivery of meaningful doses. These clinical trials are ongoing and the merits of these strategies are not yet clear, although they appear promising (Barani & Larson 2015).

A lack of prospective, randomized trials and the high probability of selection bias in single-arm studies increases concerns about safety and efficacy at recurrence after initial irradiation.

The use of SRS with LGK as a salvage therapy following GBM recurrence after standard first-line therapy has been linked to improved median overall survival (Murovic & Chang 2012; Nieder *et al.* 2000), with reported average life expectancies from 7.5 to 30 months after treatment (Combs *et al.* 2005; Hsieh *et al.* 2005; Niranjan *et al.* 2015; Larson *et al.* 1996; Mahajan *et al.* 2005; Shrieve *et al.* 1995; Biswas *et al.* 2009).

Frischer and colleagues (2016) reported a median survival of 9.6 months after SRS with LGK in 42 patients with recurrent GBM and radiological progression mainly occurred beyond the GKRS-irradiated area.

Niranjan A and colleagues (2015) retrospectively evaluated factors that affected overall survival and progression-free survival, and reported 30% of a heterogeneous cohort of GBM patients eligible for SRS had an overall survival of 2 years. Radiosurgery at the time of tumor progression was associated with a median survival of 21.8 months.

Fetcko K. and colleagues (2017) analysed twenty-nine studies published between 1992 and 2016 that reported the use of SRS for recurrent GBM. The pooled estimates of median progression-free survival and overall survival for recurrent GBM were 5.42 months (3–16 months) and 20.19 months (9–65 months), respectively. The results suggested that SRS holds promise as a relatively safe treatment option for GBM.

Many studies have analysed the role of prognostic factors in patients with recurrent GBM. Larson *et al.* (1996) found the positive factors for prolonged survival after radiosurgery to be: younger age, higher Karnofsky score, smaller tumor volume and unifocal tumor in gliomas of all grades (189 patients). Gorlia and colleagues (2012) performed a pooled analysis of European Organization for Research and Treatment of Cancer (EORTC) trials on recurrent GBM to validate existing clinical prognostic factors, identify new markers, and derive new predictions for overall survival and progression free survival (data from 300 patients with recurrent GBM). The median survival after SRS with LGK was 7 months, which is comparable with the majority of previous research. Only age was found to be statistically significant, where better survival was observed for younger patients.

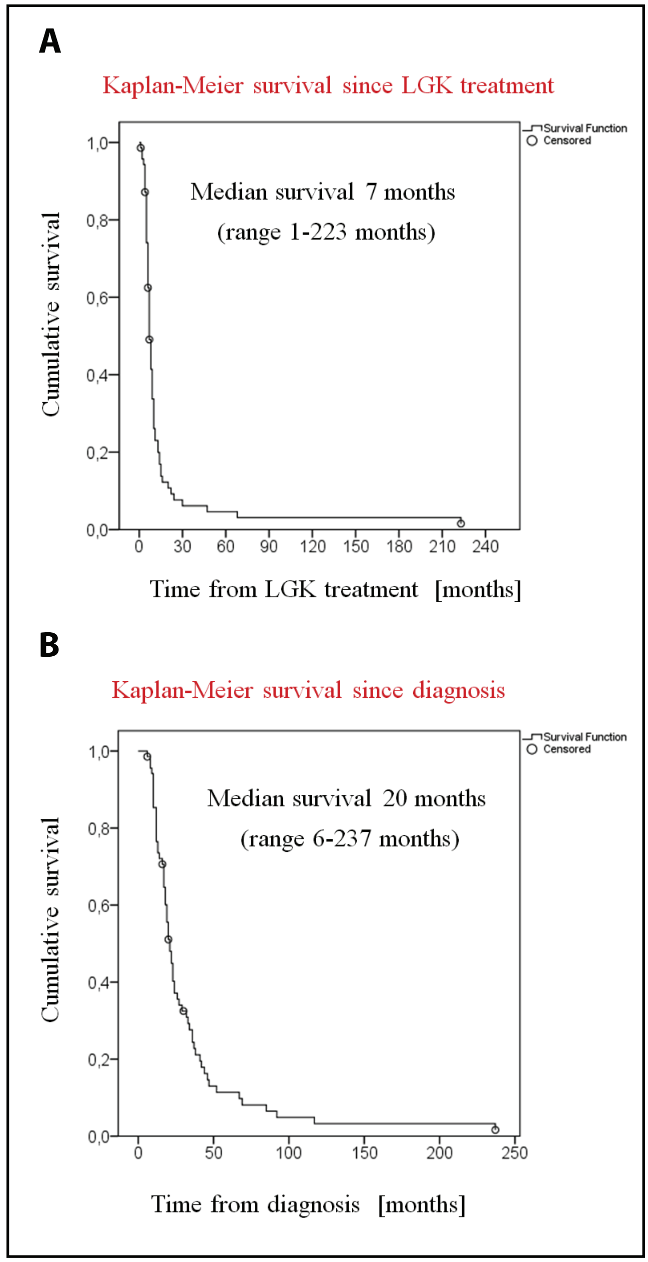

Fig. 3. Kaplan-Meier survival. A) Kaplan-Meier survival since LGK treatment. Median survival was 7 months. B) Kaplan-Meier survival since diagnosis. Median survival was 20 months.

Bokstein and colleagues (2016) presented a retrospective review of 55 Stereotactic Radiosurgery (SRS) procedures performed in 47 consecutive patients with high-grade glioma (HGG). They noted that SRS may be considered an effective salvage procedure for selected patients with small volume, recurrent high-grade gliomas. Long-term radiological control was observed in more than 50% of the patients.

The benefit of salvage SRS with LGK can potentially be increased by combination with bevacizumab and

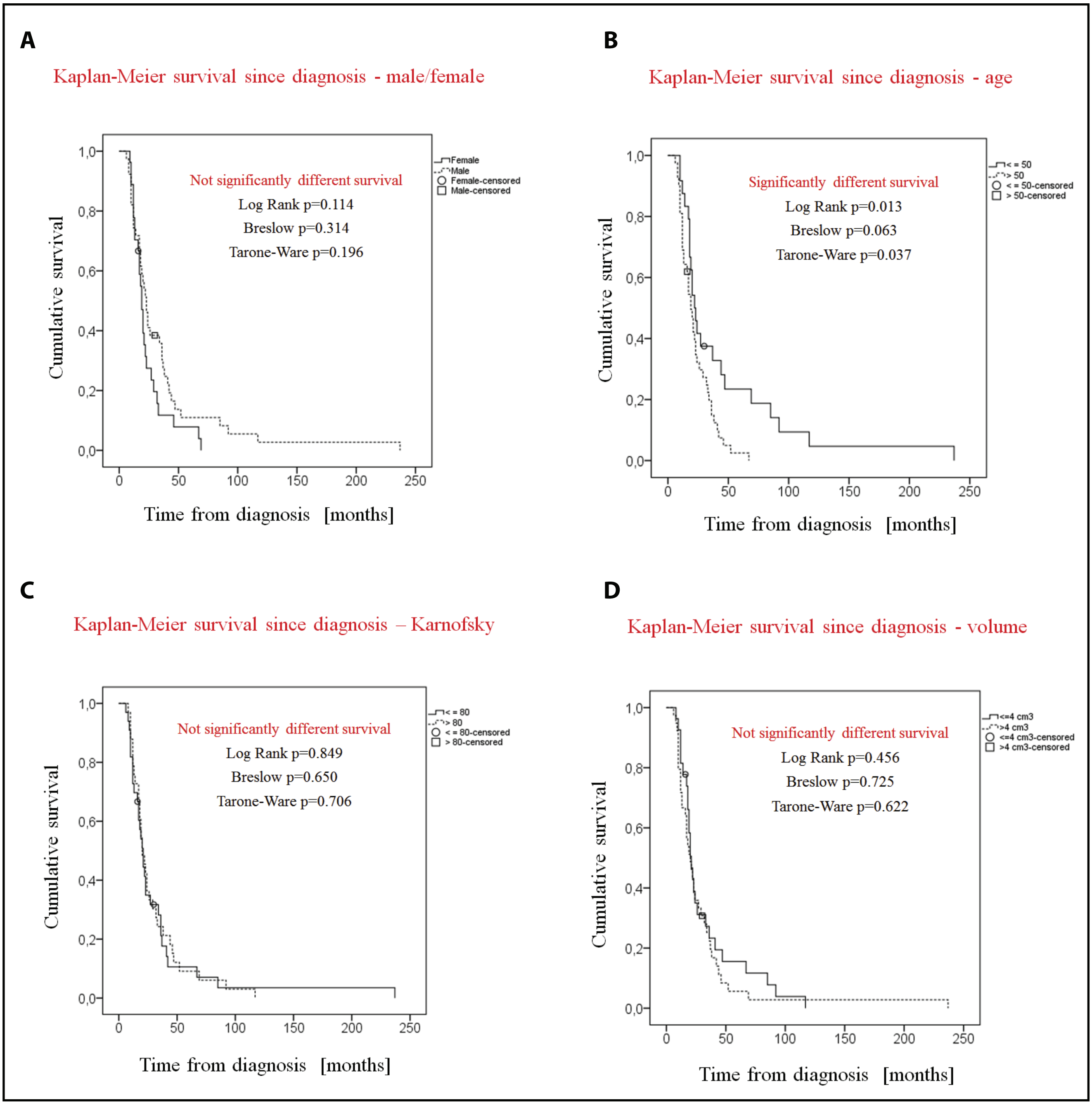

Fig. 4. Kaplan-Meier survival. A) Different Kaplan-Meier survival for male and female was not statistically significant. B) Kaplan-Meier survival for patients 50 years old and younger was better and statistically significant. C) Different Kaplan-Meier survival for Karnofsky 80 and better was not statistically significant. D) Different Kaplan-Meier survival for volume 4 cm^3 and smaller was not statistically significant.

chemotherapy with a little additional risk, as presented by Park KJ and colleagues in a small group of patients (n=11) with progressive GBM (Park *et al.* 2012).

CONCLUSION

We have shown that Gamma Knife radiosurgery is a safe palliative treatment modality for the treatment of recurrent glioblastoma, well tolerated by patients. Radiosurgery is limited to the tumor volume, and considering the infiltrative nature of recurrent GBM is mostly indicated as a complementary treatment after open surgery if repeated resection is not indicated for any reason or if open surgery is too risky due to tumor localization.

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