Journal of Clinical Neuroscience 92 (2021) 98–102

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Short communication

# Gamma Knife radiosurgery as salvage therapy for gangliogliomas after initial microsurgical resection

Constantin Tuleasca [a,b,c,d,*], Iulia Peciu-Florianu [a], Vauleon Enora [e], Nicolas Reyns [a]

[a] Centre Hospitalier Regional Universitaire de Lille, Roger Salengro Hospital, Neurosurgery and Neurooncology Service Lille, France
[b] Lausanne University Hospital (CHUV), Department of Clinical Neurosciences, Neurosurgery Service and Gamma Knife Center, Lausanne, Switzerland
[c] University of Lausanne (Unil), Faculty of Biology and Medicine (FBM), Switzerland
[d] Signal Processing Laboratory (LTS 5), Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland
[e] Centre Hospitalier Regional Universitaire de Lille, Roger Salengro Hospital, Neurooncology Service, Lille, France

ARTICLE INFO

*Article history:*
Received 6 March 2021
Accepted 29 July 2021

*Keywords:*
Gangliogliomas
Radiosurgery
Gamma Knife
Microsurgery

ABSTRACT

*Introduction:* Gangliogliomas (GG) are considered WHO grade I rare tumors. While they commonly manifest as temporal lobe epilepsy, they can be located anywhere in the brain. Primary treatment is complete microsurgical resection. Remnant or recurrent GG can benefit from radiation therapy. Here, we present a series of GG who received Gamma Knife radiosurgery (GKR) after initial microsurgery.
*Methods:* Between October 2009 and February 2020, four patients benefitted from such approach. The median age at surgery was 16 years (mean 17, 11–25) and at the time of GKR was 22.5 years (mean 23, 19–28). Initial clinical symptom was epilepsy in 3 cases and incidental in one. Biopsy was firstly performed in one case. One patient had stereotactic electroencephalography. The respective anatomical locations were right parieto-occipital, sylvian, left paraventricular and left inferior parietal.
*Results:* Gamma Knife radiosurgery was performed after a median time of 3.5 years after initial gross total microsurgical resection (GTR). The median follow-up after GKR was 54 months (mean 58.5, 6–120). The median marginal dose was 18 Gy (mean 17.5, 16–18). The median target volume was 0.5 mL (mean 0.904, 0.228–2.3). The median prescription isodose volume was 0.6 mL (mean 0.9, 0.3–2.4). At last follow-up, GG majorly decreased in 3 patients, remained stable in one.
*Conclusion:* Gamma Knife radiosurgery is safe and effective for remnant GG after GTR. Primary treatment remains microsurgical resection, especially in cases with symptomatic mass effect or with epilepsy. Single fraction GKR can be a valuable option for remnant or recurrent tumors after initial resection.


## 1. Introduction

Gangliogliomas (GG) are rare, while accounting for approximately 1% of all central nervous system (CNS) neoplasms [1]. They are considered World Health Organization (WHO) grade I tumors, although in approximately 5% of cases can exhibit aggressive behavior and anaplastic histological features (WHO grade III). Classical anatomical location is temporal lobe (approximately 85%), but they can occur anywhere in the brain. Hence, temporal lobe epilepsy is a common clinical manifestation [2].

Primary treatment in cases with symptomatic mass effect or epilepsy is complete microsurgical resection [2]. Radiation therapy has been described as a valuable option, for remnant, recurrent or malignant tumors, after surgical treatment, associated or not with chemotherapy [3]. Up-to-date, only one series described, among a surgical approach, the use of Gamma Knife radiosurgery (GKR) in single fraction for GG, including four cases [4]. However, dosimetric details were not presented.

Here, we present our experience in a series of 4 consecutive cases of GG exhibiting radiological progression after initial gross total resection (GTR). We detail our dose regimens, as well as patient's outcome after long-term follow-up.

## 2. Materials and methods

### 2.1. Type of study

This is a retrospective historical cohort study, non-randomized.

### 2.2. Participants

Between October 2009 and February 2020 four patients benefitted from GKR for progressive GG after initial GTR.

* Corresponding author at: Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Faculty of Biology and Medicine (FBM), Lausanne, Switzerland.
*E-mail address:* constantin.tuleasca@chuv.ch (C. Tuleasca).

https://doi.org/10.1016/j.jocn.2021.07.059
0967-5868/

All cases have been treated in Lille University Hospital (Roger Salengro Hospital), France.

### 2.3. Baseline and follow-up monitoring

The baseline assessment included clinical examination and brain magnetic resonance imaging (MRI). After GKR, patients were evaluated at 6 months, 12 months, and further on annual basis, respectively.

### 2.4. Description of the GKR technique

Leksell Model G stereotactic frame (Elekta Instruments AB, Sweden) under local anesthesia was applied in all cases. Patients underwent stereotactic MRI study with multiple sequences, including T1 with and without Gadolinium injection (1-mm slices) and T2 Fiesta (0.6 mm slices). Bone computed tomography (CT)-scan routinely supplements the stereotactic assessment.

Leksell Gamma Knife 4C was used Perfexion until 2016 and the Leksell Gamma Knife ICON afterwards (Elekta Instruments, AB, Sweden).

### 2.5. Basic demographic data (Table 1)

The median age at surgery was 16 years (mean 17, 11–25) and at the time of GKR was 22.5 years (mean 23, 19–28). Initial clinical symptom was epilepsy in 3 cases and incidental in one, which further developed epilepsy due to tumor progression.

The respective anatomical locations were right parieto-occipital, sylvian, left paraventricular and left inferior parietal.

Biopsy was firstly performed in one case, followed by GTR 4 years later. The second patient had subtotal surgical resection followed by GTR. The third case had initial stereotactic electroencephalography (SEEG) and further GTR. Last patient underwent GTR.

### 2.6. Basic dosimetric data (Table 2)

The median follow-up after GKR was 54 months (mean 58.5, 6–120).

Gamma Knife radiosurgery was performed after a median time of 3.5 years after initial GTR.

The median marginal dose was 18 Gy (mean 17.5, 16–18).

The median target volume was 0.5 mL (mean 0.904, 0.228–2.3). The median prescription isodose volume was 0.6 mL (mean 0.9, 0.3–2.4).

## 3. Results

### 3.1. Clinical follow-up

No patient experienced an acute or subacute clinical adverse radiation effect after GKR.

The epilepsy remained stable in all cases presenting one at the time of radiosurgery.

### 3.2. Radiological follow-up

At last follow-up, GG volume majorly decreased in 3 patients and remained stable in one. (please see illustrative cases in Fig. 1 and Fig. 2).

## 4. Discussion

To the best of our knowledge, this is the first study focusing exclusively on the post radiosurgical outcome after single fraction GKR for GG, after initial GTR. We consider this pathology as an indication for surgery, especially in patients with temporal lobe epilepsy. Radiosurgery was performed in case of tumor progression after postoperative remnants, using marginal doses between 16 and 18 Gy. At last follow-up, three GG majorly decreased in size, while one remained stable.

Up-to-date, only one series described the use of Gamma Knife radiosurgery (GKR) in single fraction for GG, including four cases, treated with marginal doses of 12, 13, 15 and 18 Gy respectively [4]. Tumors were considered controlled at last follow-up [4]. In the present series, the median marginal dose was 18 Gy (mean 17.5, 16–18). In other recent series discussing radiosurgery for such pathology, the median marginal dose was 15 Gy (ranging between 12 and 20 Gy) [5]. Other authors also considered a cut-off of 15 Gy as related to a good outcome and local control [6,7]. Limitations for prescribing a certain marginal dose might come from eloquent structures presence such as brainstem glioma, anterior optic pathway hypothalamic glioma etc [6].

Microsurgery remains the gold standard for GG and is a curative option, when complete removal is feasible [2]. In cases close to or within critical structures, particularly the brainstem, radiation or

**Table 1**
Basic demographic data.

| | Age at diagnosis | Initial surgery | Anatomical location | Symptom | Further surgery | WHO grade | Adjuvant treatment | Recurrence | Further treatment | Age at GK |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient #1 | 12 | Biopsy | R parieto-occipital | - Incidental - Epilepsy (2 years after discovery) | Gross total resection (4 years after biopsy) for volumetric increase | I | None | 3 years after surgery | Gamma Knife | 19 (normal neurological exam) |
| Patient #2 | 11 | Complete surgical resection | R sylvian | Partial motor seizures | Gross total resection (4 years after first surgery) for recurrence | I | None | 4 years after second surgery | Gamma Knife | 19 (normal neurological exam) |
| Patient #3 | 20 | SEEG | L paraventricular | Partial complex seizures | Gross total resection after SEEG | I | None | 6 years after surgery | Gamma Knife | 26 (normal neurological exam) |
| Patient #4 | 25 | Gross total resection | L inferior parietal | Partial seizures | – | I | None | 3 years after surgery | Gamma Knife | 28 (normal neurological exam) |

**Table 2**
Dosimetric data.

| | Dose (Gy) | Isodose | Target volume (mL) | Prescription isodose volume (mL) | Coverage | Selectivity | Gradient index | Duration of follow-up | Tumor at last follow-up |
|---|---|---|---|---|---|---|---|---|---|
| Patient #1 | 18 | 50% | 2.3 | 2.4 | 96% | 92% | 2.84 | 6 months | stable |
| Patient #2 | 18 | 60% | 0.228 | 0.351 | 100% | 65% | 2.72 | 12 months | decrease |
| Patient #3 | 18 | 50% | 0.662 | 0.737 | 95% | 87% | 2.92 | 96 months | decrease |
| Patient #4 | 16 | 50% | 0.426 | 0.425 | 88% | 89% | 3.37 | 120 months | decrease |

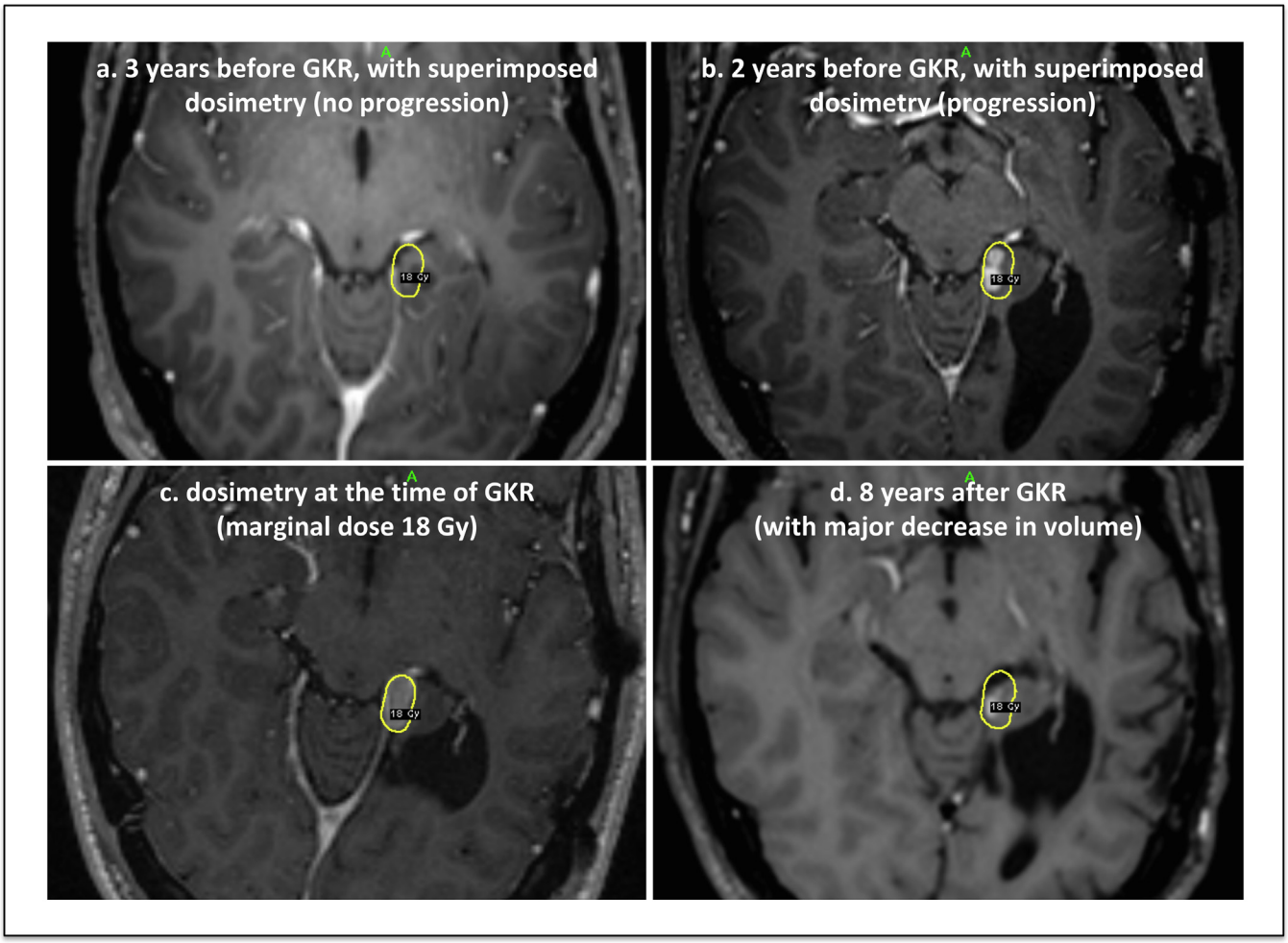


**Fig. 1.** a- 3 years after GKR, with superimposed dosimetry, showing no progression after surgery; b- 2 years before GKR, with superimposed dosimetry, showing tumor progression; c- dosimetry at the time of GKR; d- 8 years after GKR, with major decrease in volume;

chemotherapy can be used as potential alternatives or complementary treatments [4]. Luyken et al. [8] reported a surgical series of 184 patients, harboring supratentorial GG. The reported recurrence rates were 1% among patients with no residual tumor and 8% among cases showing residual tumor. Of note, the WHO grade is also considered a prognostic factor. However, here we only included cases with WHO grade I GG. Symptomatic improvement of epilepsy (Engle I) varies between 76 and 88% after surgery [2,4,8].

With regards to radiation, there is currently no consensus regarding the need of radiotherapy in patients with residual or recurrent GG. The median dose of radiotherapy (RT) is 54 Gy [9]. In a recent series of 7 patients with recurrent low grade GG, the overall local control rate after RT was 75% [9]. Other authors reported up to 90% local control after GTR plus RT [10]. It has been previously suggested that GKR might be more beneficial to GG as compared with classical RT [4]. The explanation would reside in a differential radiobiological effect, as RT could induce malignant changes in benign or normal cells [4]. Moreover, it is currently considered that the estimated risk of an intracranial secondary malignancy or malignant transformation of a benign tumor in patients treated with stereotactic radiosurgery remains low after long-term follow-up and is similar to the risk of the general population to have a primary CNS tumor [11]. This aspect is of particular importance for the pediatric and young adult population.

Our study has several inherent limitations. One is related to the number of treated patients. Such results should be validated in larger cohorts. The second is the retrospective nature, with all that implies.

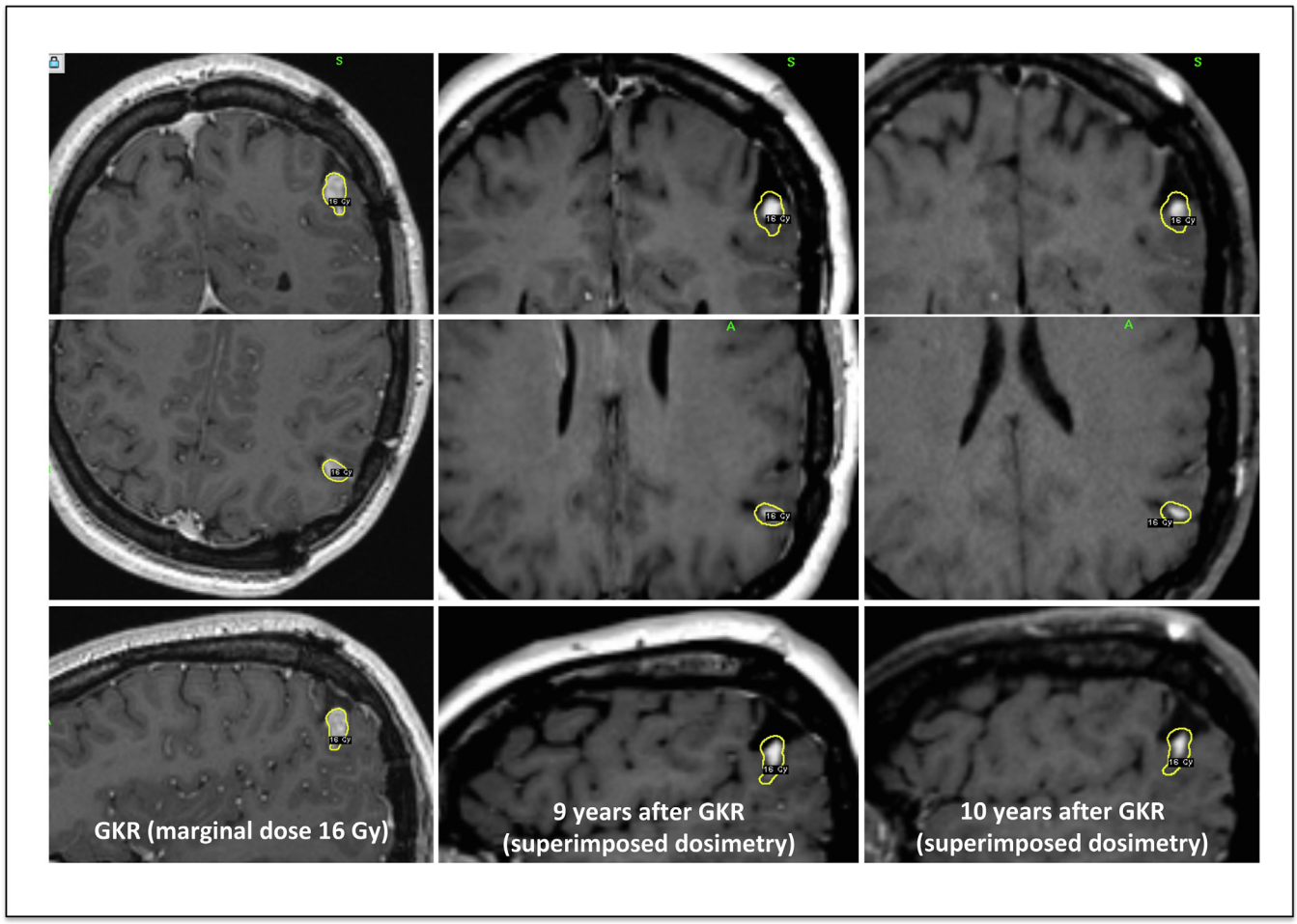


**Fig. 2.** From top to bottom, MRI reconstruction in coronal, axial and sagittal plane of T1 w MRI; from left to right: left- illustration of the GKR with the dosimetry (yellow line); center- 9 years after GKR, with superimposed dosimetry and further tumor decrease; right- 10 years after GKR, with superimposed dosimetry and further tumor decrease as compared to previous.

## 5. Conclusion

Single fraction radiosurgery and particularly GKR, in our experience, has been proven safe and effective for local progression after GTR of GG. We recommend using marginal doses between 16 and 18 Gy depending on the treated volume. At last follow-up, all tumors were controlled.

## Compliance with ethical standards

Yes.

## Funding

Constantin Tuleasca gratefully acknowledges receipt of a 'Young Researcher in Clinical Research Grant' (Jeune Chercheur en Recherche Clinique) from the University of Lausanne (UNIL), Faculty of Biology and Medicine (FBM) and the Lausanne University Hospital (CHUV).

## Acknowledgments

Lille and Lausanne University Hospital.

## Conflict of interest

All authors certify that they have no affiliations, with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained prior to the procedure.

## References

[1] Zhang D, Henning TD, Zou LG, Hu LB, Wen L, Feng XY, et al. Intracranial ganglioglioma: clinicopathological and MRI findings in 16 patients. Clin Radiol 2008;63(1):80–91.

[2] Zentner J, Wolf HK, Ostertun B, Hufnagel A, Campos MG, Solymosi L, et al. Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. J Neurol Neurosurg Psychiatry 1994;57(12):1497–502.
[3] Silver JM, Rawlings CE, Rossitch E, Zeidman SM, Friedman AH. Ganglioglioma: a clinical study with long-term follow-up. Surg Neurol 1991;35(4):261–6.
[4] Song JY, Kim JH, Cho YH, Kim CJ, Lee EJ. Treatment and outcomes for gangliogliomas: a single-center review of 16 patients. Brain Tumor Res Treat 2014;2(2):49–55.
[5] Gagliardi F, Bailo M, Spina A, Donofrio CA, Boari N, Franzin A, et al. Gamma knife radiosurgery for low-grade gliomas: clinical results at long-term follow-up of tumor control and patients' quality of life. World Neurosurg 2017;101:540–53.
[6] Deora H, Tripathi M, Tewari MK, Ahuja CK, Kumar N, Kaur A, et al. Role of gamma knife radiosurgery in the management of intracranial gliomas. Neurol India 2020;68(2):290–8.
[7] Hadjipanayis CG, Niranjan A, Tyler-Kabara E, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for well-circumscribed fibrillary grade II astrocytomas: an initial experience. Stereotact Funct Neurosurg 2002;79(1):13–24.
[8] Luyken C, Blümcke I, Fimmers R, Urbach H, Wiestler OD, Schramm J. Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. Cancer 2004;101(1):146–55.
[9] Liauw SL, Byer JE, Yachnis AT, Amdur RJ, Mendenhall WM. Radiotherapy after subtotally resected or recurrent ganglioglioma. Int J Radiat Oncol Biol Phys 2007;67(1):244–7.
[10] Rades D et al. The role of postoperative radiotherapy for the treatment of gangliogliomas. Cancer 2009;15(116):432–42.
[11] Wolf A, Naylor K, Tam M, Habibi A, Novotny J, Liščák R, et al. Risk of radiation-associated intracranial malignancy after stereotactic radiosurgery: a retrospective, multicentre, cohort study. Lancet Oncol 2019;20(1):159–64.