Increased Survival Using Delayed Gamma Knife Radiosurgery for Recurrent High-Grade Glioma: A Feasibility Study

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Key words
- Anaplastic glioma
- Gamma knife radiosurgery
- GKRS
- Glioblastoma
- HGG, high-grade glioma
- Recurrent high-grade glioma
- WHO III
- WHO IV

Abbreviations and Acronyms
ARE: Adverse radiation effect
EBRT: External beam radiation therapy
GKRS: Gamma Knife radiosurgery
KPS: Karnofsky Performance Scale
LINAC: Linear accelerator
RPA: Recursive partitioning analysis
WHO: World Health Organization

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Citation: World Neurosurg. (2014) 82, 5:e623-e632. http://dx.doi.org/10.1016/j.wneu.2014.06.011

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

OBJECTIVE: **The current study retrospectively assessed delayed gamma knife radiosurgery (GKRS) in the management of high-grade glioma recurrences.**

METHODS: **A total of 55 consecutive patients with high-grade glioma comprising 68 World Health Organization (WHO) III and WHO IV were treated with GKRS for local recurrences between 2001 and 2007. All patients had undergone microsurgery and radiochemotherapy, considered as standard therapy for high-grade glioma. Complete follow-up was available in all patients; median follow-up was 17.2 months (2.5—114.2 months). Median tumor volume was 5.2 mL, prescription dose was 20 Gy (14—22 Gy), and median max dose was 45 Gy (30—77.3 Gy).**

RESULTS: **The patients with WHO III tumors showed a median survival of 49.6 months with and a 2-year survival of 90%. After GKRS of the recurrences, these patients showed a median survival of 24.2 months and a 2-year survival of 50%. The patients with WHO IV tumors had a median survival of 24.5 months with a 2-year survival of 51.4%. After the recurrence was treated with GKRS, the median survival was 11.3 months and a 2-year survival: 22.9% for the WHO IV patients.**

CONCLUSION: **The current study shows a survival benefit for high-grade glioma recurrences when GKRS was administered after standard therapy. This is a relevant improvement compared with earlier studies that had had not been able to provide a beneficial effect timing radiosurgery in close vicinity to EBRT.**

INTRODUCTION

In the treatment of malignant glioma (World Health Organization [WHO] III and IV), the use of modern microsurgery and chemotherapy have led to increased survival rates. Historically, the survival for patients with glioblastoma was 9—12 months, with modern chemotherapy survival rates up to 19 months can be achieved and recurrences can be significantly delayed (2, 10, 19, 23, 29, 34, 35, 42, 44-47). However, as promising and encouraging these developments may be, overall survival still is limited. When radiosurgery is applied in a logical time frame and embedded into established therapy concepts, Gamma Knife radiosurgery (GKRS) may represent a promising additional treatment option (Table 7) (8, 9, 11, 22, 24, 26, 30, 34, 36, 43).

PATIENTS AND METHODS

Between January 2001 and July 2007, a total of 347 patients with WHO grade III + IV gliomas were treated at the Karolinska University Hospital Stockholm.

These patients comprised 55 consecutive patients with 68 histopathologically confirmed tumor recurrences who had previously been treated with microsurgery, external beam radiation therapy (EBRT), and chemotherapy and subsequently underwent gamma knife radiosurgical treatments for these recurrences.

Standard Therapy

All patients initially were treated with conventional microsurgery followed by fractionated EBRT. Patients who had experienced tumor recurrences after this standard treatment were considered for stereotactic radiosurgery. A histopathologic diagnosis was available in all cases. All patients had been treated with upfront standard fractionated radiotherapy (EBRT) and optionally either with adjuvant or concomitant carmustine or temozolomide therapy. As an initial conventional radiation modality, EBRT consisted of single fractions $\leq$2 Gy amounting to total dose of 60 Gy.

Surgical Treatment

There were 27 women (49.1%) and 28 men (50.9%) harboring a total of 68 gliomas, with 36.4% of the patients (n = 20) being

Table 1. Histopathologic Characteristics

Tumor Grade	Patients, n (%)	Tumors, n (%)
WHO grade III	20 (36.4)	21 (30.9)
WHO grade IV	35 (63.6)	47 (69.1)

WHO, World Health Organization.

classified as WHO III and 63.6% (n = 35) as WHO IV. Of the 68 tumors 30.9% (n = 21) were diagnosed as WHO III and 69.1% (n = 47) as WHO IV (Table 1). A total of 8 patients (9.1%) had undergone biopsy, 23 patients (41.8%) partial resection, and 27 patients (49.1%) gross total resection of the initial glioma. Of the 20 patients with WHO grade III gliomas, 30% (n = 6) were diagnosed after a biopsy and 70% (n = 14) after a conventional microsurgical resection. Of the 35 patients with WHO grade IV gliomas, 6% (n = 2) had been diagnosed after a biopsy and 94% (n = 33) after a conventional microsurgical resection (Tables 2 and 3). All patients had experienced tumor recurrences after the described standard therapy. Radiosurgery was considered when no other surgical option was considered available.

Exclusion

The following patients were not considered suitable for stereotactic radiosurgery: 1) patients with a Karnofsky Performance Scale (KPS) score <70, patients with large multifocal recurrences; and 2) patients with leptomeningeal dissemination or patients with tumors locations within 5 mm of the optic chiasm. Patient age was not part of the exclusion criteria. The median patient age was 51.1 years (17.0–81.1 years).

Table 2. Surgical Modalities

Tumor Grade	Biopsy, n (%)	Resection, n (%)
WHO grade III	6 (30%)	14 (70%)
WHO grade IV	2 (5.7%)	33 (94.3%)

Table 3. Number of Resections

Tumor Grade	Resection × 1	Resection × 2	Resection × 3
WHO grade III	14 (70%)	4 (20%)	0
WHO grade IV	13 (37.1%)	8 (22.9%)	2 (5.7%)

WHO, World Health Organization.

Radiosurgical Procedure

The radiosurgical treatment was performed using a Leksell Gamma Knife 4C (Elekta, Stockholm, Sweden) at the Karolinska University Hospital Stockholm by 5 alternating neurosurgeons. The patients were stratified according to recursive partitioning analysis (RPA) classes (20, 21, 25, 37). Tumor definition was based on stereotactic magnetic resonance imaging as performed at the day of the Gamma Knife treatment with fluid-attenuated inversion recovery and T1- and T2-weighted studies without and with gadolinium. The contrast enhancing area was delineated as a target with no margins added.

Treatment Parameters

The median prescription dose was 20 Gy (14–22 Gy). Median maximum dose was 45.4 Gy (30.0–77.3 Gy). The median prescription isodose was 44% (range 30%–61%). The median 10 Gy volume was 25.8 mL (0.2–213.8 mL). The applied median prescription doses were not significantly different (20 Gy). The resulting median 10 Gy volumes were 31.2 mL (2.3–63.0 mL) and 24.0 mL (0.2–213.8 mL) for the WHO III and WHO IV tumors, respectively. (Table 4)

Tumor Volume

At diagnosis of the recurrence, a multidisciplinary team consisting of neurosurgeons, neurologists, neuroradiologists, neuropathologists, and neuro-oncologists assessed all cases. The indication for radiosurgery was based on the decision from the multidisciplinary conference that no other treatment option was preferable. Patients with tumor recurrences up to a volume of 10 mL were considered suitable for radiosurgery. However, several tumors showed an increased volume at the actual time of the treatment and were not declined for treatment. Hence, 10 patients were treated with tumor volumes of 10.8–17.6 mL. One patient with a tumor volume of 38.1 mL had been treated on compassionate grounds and was included in the current series. The median overall volume of the recurrent tumors was 5.2 mL (range 0.03–38.1 mL) for the entire group and 4.8 mL (range 0.03–38.1) for glioma WHO IV and 5.9 mL (0.3–17.6 mL) for glioma WHO III.

Survival

Survival was measured from an initial histopathologic diagnosis of the glioma, and further differentiation was made by reporting the survival after diagnosis of the recurrence. Three patients initially had been diagnosed with glioma WHO grade III but experienced further malignant transformation. These patients were classified as glioblastoma, with survival being measured starting at the histologic diagnosis of the malignant transformation and hence diagnosis of the glioblastoma. The

Table 4. Radiosurgery Parameters

Tumors	WHO IV	WHO III	Combined
Median volume, mL	4.80 (0.03–38.10)	5.9 (0.3–17.6)	5.20 (0.03–38.10)
Median prescription dose, Gy	20 (14–22)	20 (15–22)	20 (14–22)
Maximum dose, Gy	46.5 (30.0–66.7)	45 (33.9–77.3)	45.4 (30.0–77.3)
Median prescription isodose, %	43 (33–61)	44 (30–60)	44 (30–61)
Median 10-Gy Volume, mL	24.0 (0.2–213.8)	31.2 (2.3–63.0)	25.8 (0.2–213.8)

WHO, World Health Organization.