Efficacy of Gamma Knife Radiosurgery for Small-Volume Recurrent Malignant Gliomas After Initial Radical Resection

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Key words
- Anaplastic astrocytoma
- Anaplastic oligoastrocytoma
- Glioblastoma
- Malignant glioma
- Radiosurgery
- Recurrence

Abbreviations and Acronyms
AA: Anaplastic astrocytoma
AMOA: Anaplastic mixed oligoastrocytoma
CI: Confidence interval
EBRT: External-beam radiation therapy
GBM: Glioblastoma multiforme
Gd: Gadolinium
GKR: Gamma Knife radiosurgery
GTR: Gross total resection
HGG: High-grade glioma
HR: Hazard ratio
IDL: Isodose line
KPS: Karnofsky Performance Status
LC: Local control
MRI: Magnetic resonance imaging
NTR: Near-total resection
OS: Overall survival
PET: Positron emission tomography
PFS: Progression-free survival
RPA: Recursive partitioning analysis
RTOG: Radiation Therapy Oncology Group
SRS: Stereotactic radiosurgery
TMZ: Temozolomide
WHO: World Health Organization

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OBJECTIVE: **To review the authors' experience with Gamma Knife radiosurgery (GKR) for small recurrent high-grade gliomas (HGGs) following prior radical resection, external-beam radiation therapy (EBRT), and chemotherapy with temozolomide (TMZ).**

METHODS: **The authors retrospectively analyzed 26 consecutive adults (9 women and 17 men; median age 60.4 years; Karnofsky Performance Status [KPS] ≥70) who underwent GKR for recurrent HGGs from 2004–2009. Median lesion volume was 1.22 cc, and median treatment dose was 15 Gy. Pathology included glioblastoma multiforme (GBM; $n = 16$), anaplastic astrocytoma (AA; $n = 5$), and anaplastic mixed oligoastrocytoma (AMOA; $n = 5$). Two patients lost to follow-up were excluded from radiographic outcome analyses.**

RESULTS: **Median overall survival (OS) for the entire cohort from the time of GKR was 13.5 months. Values for 12-month actuarial survival from time of GKR for GBM, AMOA, and AA were 37%, 20% and 80%. Local failure occurred in 9 patients (37.5%) at a median time of 5.8 months, and 18 patients (75%) experienced distant progression at a median of 4.8 months. Complications included radiation necrosis in two patients and transient worsening of hemiparesis in one patient. Multivariate hazard ratio (HR) analysis showed KPS 90 or greater, smaller tumor volumes, and increased time to recurrence after resection to be associated with longer OS following GKR.**

CONCLUSIONS: **GKR provided good local tumor control in this group of clinically stable and predominantly high-functioning patients with small recurrent HGGs after radical resection. Meaningful survival times after GKR were seen. GKR can be considered for selected patients with recurrent HGGs.**

INTRODUCTION

The treatment of high-grade gliomas (HGGs) is one of the most challenging and frustrating issues in neuro-oncology. Despite significant improvements in neuroimaging, volumetric surgical techniques, functional mapping, intraoperative magnetic resonance imaging (MRI), and chemotherapy, survival for patients with HGGs remains universally poor (50, 57, 58). Although recent randomized trials have shown improved survival with temozolomide (TMZ) and external-beam radiation therapy (EBRT) in patients with newly diagnosed glioblastoma multiforme (GBM), the magnitude of the improvement is small (increase in survival from 12 months to 14 months) (57, 58). Despite "complete resection," tumor recurrence and progression invariably occur and are responsible for death in nearly all patients. At the present time, few effective treatments exist for recurrent HGGs, and the median survival is 3–6 months after recurrence (4, 33, 65). The role of aggressive, multimodality salvage therapy remains disputed (26).

Treatment options at recurrence include local and systemic therapies, but the decision to treat depends heavily on tumor size, tumor location, and overall functional status of the patient. The mainstay of treatment at recurrence is systemic chemotherapy, which routinely has toxic side effects (36). Small series have shown incremental benefits of chemotherapy regimens including TMZ, nitrosoureas, PCV (procarbazine, carmustine, vincristine), irinotecan, and, more recently, bevacizumab (7, 8, 10, 18, 19, 43). Reoperation may also be beneficial to some high-functioning patients but can be

associated with increased neurologic morbidity and with increased postoperative complications after chemotherapy and radiation (1, 3, 23, 28). Retreatment with standard EBRT regimens exposes the brain to an unacceptably high risk of radiation injury and necrosis and is usually avoided (64).

Given the highly invasive nature of HGGs and risk of standard EBRT or surgery at recurrence, attempts at local control (LC) of rapidly growing areas that spare the surrounding brain have come into vogue. Some authors argue that LC is paramount to improved survival given that most patients die of recurrent disease at the margins of the previous resection (14, 34, 54). Minimally invasive treatments aimed at LC of disease consist of brachytherapy (35, 53), stereotactic radiosurgery (SRS) (27, 31, 53), and fractionated stereotactic radiotherapy (14, 15) for tumor recurrence. Although numerous small, nonrandomized series have shown improved survival compared with historical controls using these treatment modalities, no prospective, randomized studies have confirmed these results in patients with recurrent HGGs.

We report on our experience using Gamma Knife radiosurgery (GKR) to treat a select population of highly functioning patients with small-volume (<12 cc) recurrences after aggressive initial surgery of HGGs. Univariate and multivariate risk factor analysis was performed to determine predictors of treatment success.

METHODS

Between April 2004 and March 2009, 26 consecutive adults underwent GKR for recurrent HGGs at New York University Langone Medical Center. Following approval by the New York University institutional review board, data were retrospectively collected by reviewing office and inpatient records; preoperative, postoperative, and last follow-up computed tomography and MRI studies; and operative and pathology reports. Patient characteristics, prior treatments, imaging features, extent of surgical resection, time to progression and recurrence, symptoms at recurrence, and other oncologic treatments were recorded. Long-term follow-up information was obtained in 2009 by contacting patients, families, and referring physicians and from office records. Dates of death were obtained from a Social Security Death Index. Patients were classified using standard recursive partitioning analysis (RPA) typically used for newly diagnosed HGGs and the 7-tiered grading scale by Carson et al. (12) specific to recurrent HGGs.

The goal of initial surgery was gross total resection (GTR) of the contrast-enhancing lesion, accomplished in all but two patients (near-total resection [NTR] in both, defined as ≥95% of contrast-enhancing volume). Following initial resection and diagnosis of HGG, all patients received concurrent chemoradiotherapy with EBRT with a median 60 Gy over 30 fractions and TMZ. Postoperative imaging was obtained every 3 months after surgery.

Only three patients had stereotactic biopsy to confirm recurrent HGG. Imaging findings alone were used to define recurrence in the remaining patients. All lesions at time of recurrence had high relative cerebral blood volume on perfusion MRI compared with contralateral white matter and increased relative cerebral blood volume compared with the prior study. Criteria for GKR included Karnofsky Performance Status (KPS) 70 or greater and small-volume tumor recurrence (<12 cc). HGG pathology types included anaplastic astrocytoma (AA), World Health Organization (WHO) III/IV; anaplastic mixed oligoastrocytoma (AMOA), WHO III/III; and GBM, WHO IV/IV. All AMOA tumors had pseudopallisading necrosis on histopathologic examination.

Radiosurgery Technique

All patients underwent outpatient radiosurgery using a nonrelocatable Leksell stereotactic head frame that was applied under local anesthesia and mild sedation. A standard MRI protocol was performed after injection of gadolinium (Gd) and acquisition of contiguous 1-mm magnetization prepared rapid gradient echo T1-weighted axial images.

Radiosurgery was performed with a Leksell GKR unit (Elekta Instruments, Atlanta, Georgia, USA). The target volume consisted only of the discrete, contrast-enhancing lesion, and no surrounding brain parenchyma or nonenhancing, hyperintense T2 signal volume was included in the treatment. The median dose administered was 15 Gy to the 50% isodose line (IDL; range 10–18 Gy), and the median maximal dose was 30 Gy (range 20–36 Gy). Determination of treatment dose was at the discretion of the multidisciplinary treating team and was based on lesion size, location, and prior EBRT field.

Follow-up

Patients were followed clinically and with serial MRI scans at 6 weeks and then at 8- to 12-week intervals thereafter. Two patients (7.7%) did not have follow-up at our center, and post-treatment imaging was unavailable for review. These patients are included in survival analysis but not LC or distant progression analyses. LC was defined as stabilization or decrease of lesion size or enhancement on imaging and lack of consistently increased surrounding T2 signal changes on serial examinations. Local failure of all lesions treated with GKR was defined as persistent increase in size of the contrast-enhancing lesion (>20% volume increase) or new contiguous areas at the margin of treatment and concomitant T2 signal change. Distant failure was defined as the development of noncontiguous areas of contrast enhancement outside of the treatment volume including parenchymal, subependymal, and leptomeningeal disease. Toxicity was graded as per the Radiation Therapy Oncology Group (RTOG) toxicity scale (52). Radiation necrosis was determined on a clinical basis using radiographic findings or via histopathologic confirmation after surgical resection. Imaging features used to diagnose radiation necrosis consisted of initial response to GKR (loss of central enhancement, increase in peripheral enhancement, decrease or stabilization in size) with or without corresponding changes on diffusion-weighted imaging.

Endpoints and Statistical Analysis

Primary endpoints included local progression-free survival (PFS), distant PFS, and overall survival (OS). OS times from diagnosis of HGG and from recurrence (time of GKR) were measured from the date of surgery and from time of GKR to time of death. Local and distant PFS were measured from the time of GKR to local failure (progression of treatment volume) and distant failure (progression of HGG outside of the