ORIGINAL ARTICLE

Gamma Knife Radiosurgery for High Grade Glial Neoplasms: A Canadian Experience

F.A. Zeiler, A.M. Kaufmann, P.J. McDonald, D. Fewer, J. Butler, G. Schroeder, M. West

ABSTRACT: ***Object:*** To review our institutional experience with Gamma Knife (GK) stereotactic radiosurgery in treating focally recurrent high grade glial neoplasms of World Health Organization (WHO) grade III or IV. ***Methods:*** We conducted a retrospective cohort review of all patients treated with GK for focally recurrent high grade gliomas at our institution between November 2003 and April 2013. Data on age, sex, tumor volume, location and maximal diameter, presenting clinical status, complications and clinical outcome was recorded. ***Results:*** A total of 33 patients were identified. Four were lost to follow-up. Average post-GK and overall survival was 20.4 months (range: 3 – 72) and 63.3 months (range: 10 – 214) respectively. For WHO grade IV gliomas, the average post-GK and overall survival was 15.8 months (range: 3 – 77) and 40.1 months (range: 13 – 148) respectively. Similarily, for WHO grade III gliomas, the average post-GK and overall survival was 34.9 months (range: 6 – 72) and 136.4 months (range: 22 – 214) respectively. Twenty-two patients (75.9%) had post-GK edema, with 14 requiring dexamethasone and eight being asymptomatic. Four patients (13.8%) had imaging defined radiation necrosis. ***Conclusions:*** Gamma Knife SRS affords an extension of local tumor control, acceptable morbidity, and potentially prolonged survival, for highly selected patients with focally recurrent high grade glial neoplasms.

RÉSUMÉ: Radiochirurgie par scalpel gamma pour les néoplasies gliales de haut grade de malignité : une expérience canadienne. ***Objectif :*** Le but de l'étude était de revoir notre expérience institutionnelle de la radiochirurgie stétéotaxique par scalpel gamma (SG) pour traiter les récidives de néoplasies gliales de haut grade de malignité, soit de grade III ou IV de l'OMS. ***Méthode :*** Nous avons effectué une revue rétrospective de cohorte de tous les patients traités par SG pour une récidive focale d'un gliome de haut grade dans notre institution entre novembre 2003 et avril 2013. Nous avons recueilli les informations sur l'âge, le sexe, le volume de la tumeur, sa localisation et son diamètre maximal, l'état clinique du patient au moment de la consultation initiale, les complications et l'issue clinique. ***Résultats :*** Nous avons identifié 33 patients. Quatre ont été perdus au suivi. La survie moyenne post SG et la survie globale étaient de 20,4 mois (écart : 3 à 72 mois) et 63,3 mois (écart : 10 à 214) respectivement. La survie moyenne post SG et la survie globale étaient de 15,8 mois (écart : 3 à 77 mois) et 40,1 mois (écart : 13 à 148 mois) respectivement. Pour les gliomes de grade III de l'OMS, la survie moyenne post-SG et la survie globale étaient de 34,9 mois (écart : 6 à 72 mois) et 136,4 mois (écart : 22 à 214 mois) respectivement. Vingt-deux patients (75,9%) ont présenté un œdème post SG : 14 d'entre eux ont dû recevoir de la dexaméthasone et 8 étaient asymptomatiques. Quatre patients (13,8%) présentaient une radionécrose à l'imagerie. ***Conclusions :*** La radiochirurgie stétéotaxique par SG permet de prolonger le contrôle local de la tumeur avec une morbidité acceptable et une prolongation éventuelle de la survie chez des patients choisis avec soin qui présentent une récidive bien localisée d'une néoplasie gliale

Can J Neurol Sci. 2013; 40: 783-789

High grade glial neoplasms pose a significant challenge to neurosurgeons, neuro-oncologists, and radiation oncologists. Despite advances in medical and surgical treatment, the outcome for patients with high grade glial tumors remains poor. Surgical resection fails to obtain a cure, despite the most aggressive attempts. Numerous chemotherapeutic agents, with or without radiotherapy, have been trialed with mixed results on overall survival[1].

The aggressive treatment of patients with high grade glioma may be of benefit for patients who are young with good functional status at time of diagnosis, as these factors best predict success of treatment and overall survival[2,3]. As first line management in the newly diagnosed patient with high grade glioma, maximal cytoreductive surgical debulking is pursued. The extent of surgical resection is highly dependent on tumor location and pre-existing neurological deficits, leaving some patients with lesions in eloquent areas receiving biopsy only for pathological diagnosis to guide further chemotherapy and radiation treatment. Surgery is typically followed by fractionated

From the Section of Neurosurgery, Department of Surgery (FAZ, AMK, PJM, DF, MW); Department of Radiation Oncology (JB, GS), University of Manitoba, Winnipeg, Manitoba, Canada.

Received May 16, 2013. Final Revisions Submitted July 8, 2013.

Correspondence to: Frederick A. Zeiler, Section of Neurosurgery, University of Manitoba, Health Sciences Center, GB-1 820 Sherbrook Street, Winnipeg, Manitoba, R3A 1R9, Canada. Email: umzeiler@cc.umanitba.ca.

conformal radiotherapy with adjuvant chemotherapy consisting of temozolomide[4]. Despite these first line treatment strategies for high grade gliomas, the average two year survival for GBM remains at 27.3%, with a median overall survival of 14.6 months[1,4].

When it comes to discussing the treatment course of high grade gliomas, the current expectation is recurrence or progression. The timing of disease recurrence in relation to surgery, chemotherapy and radiation is difficult to predict. The typical pattern of recurrence is local, with up to 87% local failure despite aggressive treatment[5]. Current imaging limitations can make it difficult to discern recurrence from post-radiation changes[6].

Optimal salvage therapy for focal recurrent high grade glial neoplasms is not well defined. A wide array of second and third line chemotherapeutic agents have been utilized to varying degrees of success[1]. The use of stereotactic radiosurgery (SRS) for focal recurrence has been explored[7-13]. Souhami et al[14] demonstrated a lack of survival benefit of upfront SRS to the tumor resection cavity. As a result, the current focus of SRS for glioma is for focal recurrence, with the literature supporting a potential superior impact on survival compared to re-resection[15], with a median survival of 12 months and 6 months respectively.

The purpose of our study is to review our institutional experience with Gamma Knife (GK) SRS in the treatment of focally recurrent high grade glial neoplasms (World Health Organization (WHO) grade III and IV). The goal is to define tumor local control rate, pattern of failure, and the potential impact of GK on overall survival for WHO grade III and IV glial neoplasms.

Methods

We conducted a retrospective cohort review of all patients treated with GK for WHO grade III and IV glial tumors at our institution from November 2003 up to and including April 2013. Utilizing a prospectively maintained database of all GK treatments at our institution, we identified all those patients treated with GK for glial neoplasms. There were a total of 41 patients identified. We then screened these results for only those treated for high grade glial tumors, WHO grade III and IV. All data collection and chart reviews were conducted physically in the Section of Neurosurgery at Health Sciences Center, Winnipeg, Manitoba.

We recorded data on age, sex, histological diagnosis, WHO grade, tumor size, location and maximal diameter, presenting symptoms, Karnofsky Performance Score (KPS), pre-GK Radiation Oncology Therapy Group (RTOG) recursive partitioning analysis (RPA) for malignant glioma class[2,3], pre-GK treatments (surgery, radiation, and chemotherapy), GK treatment parameters, tumor local control, complications and survival. Post-radiosurgery assessments were conducted by the treating neurosurgeon involved with GK planning and treatment. Follow-up magnetic resonance imaging (MRI) post-GK occurred every three months, unless a change in clinical status prompted earlier examination. Post-treatment MRI interpretation was conducted by both neuro-radiology and the treating neurosurgeon. Telephone follow-up occurred via GK nursing staff in between in-person surgeon appointments. This study was approved by the Health Research Ethics Board at the University of Manitoba.

Results

Patient Demographics and Presentation

We defined high grade glioma as any glial neoplasm of WHO pathological grade III or IV. Reviewing our GK database for patients treated for recurrent high grade glial tumors, we identified a total of 33 patients, with four lost to follow-up, leaving a total of 29 patients included in the review and data analysis. Five patients (17.2%) have follow-up ongoing, as they continue to receive treatment for their malignancy. Demographics and presenting tumor data of those patients with follow-up can be seen in Table 1. For those lost to follow-up, their demographic data can be seen in Table 2.

Table 1: Demographic data for all high grade glioma patients with follow-up

Demographic Category		Patients with Follow-Up (n=29)	WHO Grade IV Tumors (n=22)	WHO Grade III Tumors (n=7)
Age (years)		50.2 (range: 15 – 75)	49.5 (range: 15 – 75)	52.1 (range: 33 – 57)
Sex	Male	21	16	5
	Female	8	6	2
Total GBM Patients		22	22	N/A
Total AA Patients		4	N/A	4
Total Oligo Patients		2	N/A	2
Total OA Patients		1	N/A	1
Avg Max Diameter (cm)		2.3 (range: 0.7 - 4.8)	2.5 (range: 1.04 – 4.8)	1.9 (range: 0.7 – 2.02)
Avg Max Volume (cm^3)		4.4 (range: 1.1 – 15.7)	5.2 (range: 1.3 – 15.7)	2.2 (range: 1.1 – 3.6)
Avg 50% Isodose (Gy)		17.5 (range: 12 – 24)	17.4 (range: 12 – 24)	17.8 (range: 12 – 24)
Avg Survival Post-GK (mon)		20.4 (range: 3 – 72)	15.8 (range: 3 – 77)	34.9 (range: 6 -72)
Avg Overall Survival from Diagnosis (mon)		63.3 (range: 10 – 210)	40.1 (range: 13 – 148)	136.4 (range: 22 – 214)

n = number, WHO = World Health Organization, Avg = average, cm = centimeter, Gy = gray, GBM = glioblastoma multiforme, AA = anaplastic astrocytoma, Oligo = oligodendroglioma, OA = oligoastrocytoma, mon = months.

https://doi.org/10.1017/S0317167100015894 Published online by Cambridge University Press

There were 21 males (72.4%) and 8 females (27.6%), with an average age of 50.2 years (range: 15 - 75). Twenty-seven (93.1%) of 29 patients had a previous surgical debulking of their tumor for histological diagnosis and cytoreduction. The average number of pre-GK surgical debulking procedures was 1.2 (range: 1 - 2) per patient, with seven (24.1%) undergoing two prior cytoreductive operations. Two (6.9%) patients had a biopsy as their only surgical procedure as a result of eloquent tumor location. No patients received surgery as preparation for GK treatment. All patients had received post-operative fractionated conformal radiotherapy (typically 60 Gy over 30 fractions), followed by chemotherapy. Pre-GK chemotherapy consisted of temozolomide in 17 (58.6%), temozolomide and cis-retinoic acid in 11 (37.9%), and procarbazine/lomustine/vincristine (PCV) in 1 (3.4%).

Overall, we had treated 22 (75.9%) patients for WHO grade IV tumors, histologically consisting of 5 (17.2%) GBM/oligodendroglioma mix and 17 (58.6%) GBM. As well, we treated seven (24.1%) patients for WHO grade III tumors, consisting of four (13.8%) anaplastic astrocytoma (AA), two (6.9%) oligodendrogliomas, and one (3.4%) oligoastrocytoma (OA).

Fourteen (48.3%) patients presented with a seizure as their primary symptom of intracranial malignancy. Other presentations included: headache in five (17.2%), right arm weakness in two (6.9%), left arm weakness in two (6.9%), visual field deficit in two (6.9%), ataxia in one (3.4%), dysphasia in one (3.4%), apoplexy in one (3.4%), and incidental in one (3.4%).

Tumor locations included: right frontal (10), left frontal (6), right temporal (6), left temporal (2), bifrontal (1), left parietal (1), left occipital (1), right insula (1), and brainstem (1).

The average pre-GK KPS for all patients was 85.2 (range: 60 -90), with only one patient (3.4%) with a KPS of 60 and two patients (6.9%) with KPS of 70 pre-GK. The average pre-GK KPS for WHO grade IV and III tumors was 84.5 and 87.1 respectively. Similarily, the average pre-GK RTOG malignant glioma RPA class[3,4] for all patients was 3.0 (range: 1 - 4), with the average for WHO grade IV and III lesions being 3.6 and 1.1 respectively. Overall, for WHO grade IV tumors we had 9 patients (31.0%) with a pre-GK RPA class of 3, and 13 patients (44.8%) with an RPA class of 4. Similarly, for WHO grade III tumors we had 1 patient (3.4%) with a pre-GK RPA class of 2, and 6 patients (20.7%) with a pre-GK RPA class of 1.

Tumor diameter and volume were determined from T1 images with gadolinium. Average tumor diameter treated with GK was 2.3 cm (range: 0.7 - 4.8 cm), with an average tumor volume of 4.4 cm^3 (range: 1.1 - 15.7 cm^3). The average tumor diameter and volume of the WHO grade IV lesions treated was 2.5 cm (range: 1.04 - 4.8 cm) and 5.2 cm^3 (range: 1.3 - 15.7 cm^3) respectively. Similarly, the average tumor diameter and volume of the WHO grade III lesions treated was 1.9 cm (range: 0.7 - 2.02 cm) and 2.2 cm^3 (range: 1.1 - 3.6 cm^3) respectively.

The average time from diagnosis to focal recurrence leading to GK was 43.0 months (range: 1 - 180 months), with the average for WHO grade IV and III lesions being 24.3 months (range: 1 - 135 months) and 101.6 months (range: 16 - 180 months), respectively. Of interest, the average time from diagnosis to GK for the GBM/oligodendroglioma mix and the GBM patients was 42.0 months (range: 1 - 135 months) and 19.2 months (range: 3 - 58 months) respectively.

Four (12.1%) of the total 33 patients with high grade gliomas identified from our GK database were lost to follow-up. Three of these patients had WHO grade IV tumors, with one being a GBM/oligodendroglioma mix and the other two being GBM. One patient lost to follow-up had a WHO grade III oligodendroglioma. All four of these patients were from out of province referral sources and returned to their respective home locations after GK treatment was completed. Attempts to establish follow-up via multiple phone calls failed. We suspect all have succumbed to their underlying malignancies at the time of this study.

GK Treatment Parameters

Treatment planning for GK utilized MRI in all patients. All GK treatments were for focally recurrent tumor only. Two patients had two GK treatments; both had WHO grade III glial tumors and had their repeat GK treatment within 12 months of the first for local in-field recurrence. Average 50% isodose line dose for all patients treated was 17.5 Gy (range: 12 - 24 Gy), with the average 50% isodose dose for WHO grade IV and III tumors being 17.4 Gy (range: 12 - 24 Gy) and 17.8 Gy (range: 12 - 24 Gy), respectively. The average total volume covered (TVC) for all patients was 4.8 cm^3 (range: 1.3 - 18.2 cm^3), with an average 98.9% (range: 94 - 100%) coverage.

Table 2: Characteristics of patients lost to follow-Up

Sex	Age	Histology	WHO Grade	Location	Disease Duration Up to Gamma Knife (Months)
M	54	GBM	IV	Lt Frontal	15
M	66	GBM	IV	Rt Temporal	Unknown
F	42	GBM/Oligo	IV	Lt Frontal	14
F	61	Oligo	III	Rt Frontal	121

M = male, F = female, Rt = right, Lt = left, GBM = glioblastoma multiforme, Oligo = oligodendroglioma, WHO = World Health Organization.

https://doi.org/10.1017/S0317167100015894 Published online by Cambridge University Press

Tumor Control and Patient Survival

Tumor control was defined as either stable size or decrease in size of the focally treated lesion on follow-up MRI. No tumor treated, either WHO grade IV or III lesion, demonstrated a decrease in tumor size post GK. The average time of local control of the treated lesion was 9.3 months (range: 1 - 72). All treatments eventually failed locally, resulting in recurrence within the tissue covered by the 50% isodose line. Seventeen (58.6%) patients also had distant recurrence, outside of the area treated with GK.

Average survival post-GK for all patients was 20.4 months (range: 3 - 72), with average overall survival (from diagnosis to death) of 63.3 months (range: 10 - 214). No deaths occurred from complications related to GK.

All patients received post-GK salvage chemotherapy for their recurrent high grade gliomas, which was started either immediately pre- or post-GK. Chemotherapeutic regimens included: temolzolomide only (20), thioguanine/procarbazine/lomustine/hydroxyurea (TPCH) (5), carboplatin (2), PCV (1), and lomustine (1). Only two patients (6.9%) received salvage surgical debulking, both had WHO IV astrocytomas. This occurred at 4 months post-GK in both patients due to significant disease progression on follow-up MRI.

For WHO grade IV gliomas treated with GK, the average local control was 7.2 months (range: 1 - 72), with GBM/oligodendroglioma and GBM subgroups displaying local control rates of 18 months (range: 2 - 72 months) and 4 months (range: 1 - 7 months) respectively. The average survival post-GK was 15.8 months (range: 3 - 77), with the GBM/oligodendroglioma and GBM subgroups displaying post-GK survival rates of 31.8 months (range: 13 - 77 months) and 11.1 months (range: 3 - 23 months) respectively. The average overall survival for WHO grade IV gliomas was 40.1 months (range: 13 - 148), with the GBM/oligodendroglioma and GBM subgroups displaying overall survival of 73.8 months (range: 16 - 148 months) and 30.2 months (range: 10 - 68 months) respectively.

Alternatively, WHO grade III gliomas treated with GK displayed an average local control of 16.0 months (range: 3 - 41). The average post-GK survival and overall survival for WHO grade III gliomas was 34.9 months (range: 6 - 72) and 136.4 months (range: 22 - 214) respectively.

In addition, for the WHO grade IV tumors reviewed, RPA class 3 and 4 patients displayed post-GK survival of 15.2 months (range: 10 - 40) and 16.2 months (range: 3 - 77 months) respectively. Furthermore, overall survival for RPA class 3 and 4 patients was 54.1 months (range: 10 - 148 months) and 30.4 months (range: 13 - 89 months) respectively. Similarly, for the WHO grade III tumors reviewed, RPA class 1 and 2 patients displayed post-GK survival of 35 months and 34.8 months (range: 6 - 72 months), respectively. While the overall survival for RPA class 1 and 2 patients was 112 months and 140.5 months (range: 22 - 214 months), respectively.

A summary of all survival data can be seen in Table 3.

Table 3: Survival outcome data for patients with follow-up

Demographic Category	Avg Survival Post-GK (Months)	Avg Overall Survival from Diagnosis (Months)
Total Population	20.4 (3 – 72)	63.3 (10 – 214)
WHO Grade IV	15.8 (3 – 77)	40.1 (13 – 148)
Tumors (n=22)		
RPA Class 3	15.2	54.1
RPA Class 4	16.2	30.4
GBM	11.1	30.2
GBM/Oligo	31.8	73.8
WHO Grade III	34.9 (6 – 72)	136.4 (22 – 214)
Tumors (n=7)		
RPA Class 1	34.8	140.5
RPA Class 2	35.0	112.0

n = number, Avg = average, cm = centimeter, Gy = gray, GK = Gamma Knife, WHO = World Health Organization, RPA = recursive partitioning analysis2,3, GBM = glioblastoma multiforme, Oligo = oligodendroglioma.

Complications

Permanent complications, referred to as adverse radiation effects (ARE), occurred in 26 of 29 patients (89.7%). Post-GK edema occurred in the field of treatment in 22 patients (75.9%), all within six months of GK. The remaining four patients (13.8%) had asymptomatic MRI defined radiation necrosis. The average RTOG toxicity grade[16] of all those with post-GK edema was 1.7 (range: 1 - 3). Of those patients with post-GK edema, 14 (48.3%) were dexamethasone dependant due to the symptomatic nature (RTOG radiation toxicity greater or equal to 2). The remaining 8 (27.6%) patients had asymptomatic post-GK edema (RTOG toxicity grade 1).

Only one patient met the criteria for RTOG toxicity of 3, requiring admission to hospital due to severe headache from cerebral edema and significant hyperglycemia secondary to dexamethasone usage. This individual was a 52-year-old male with history of previous resection, fractionated conformal radiotherapy and chemotherapy. He had a 3 cm diameter spherical recurrence in the resection cavity, treated with 18 Gy to the 50% isodose line.

No patient required operative intervention for edema or control of intracranial pressure. Similarily, no patient died as a result of their post-GK edema.

Comparing the average dose at the 50% isodose line for those with and without edema, there was no difference. The average dose at the 50% isodose line for those with RTOG toxicity grade 2 or higher was 16.8 Gy (range: 12 - 22 Gy), while the average dose for RTOG toxicity grade 1 patients was 18.2 Gy (range: 12 - 24 Gy). The Figure demonstrates post-GK edema six months post-treatment in a 63-year-old female, with a right temporal GBM previously treated with surgical debulking, fractionated conformal radiotherapy and temozolomide.

The four remaining ARE of the 26 described, were MRI described post-GK necrosis. None of the four cases described had pathological confirmation of necrosis. One patient had positron emission tomography (PET) of the brain indicating a hypometabolic lesion, suggestive of post radiation necrosis and not recurrence of the underlying neoplasm. All patients were asymptomatic.

Temporary complications occurred in 13 of the 29 patients (44.8%). All of these complications were temporary and resolved by one month post-GK. Temporary complications included: headache (9), pin site edema (3), and a single post-

https://doi.org/10.1017/S0317167100015894 Published online by Cambridge University Press

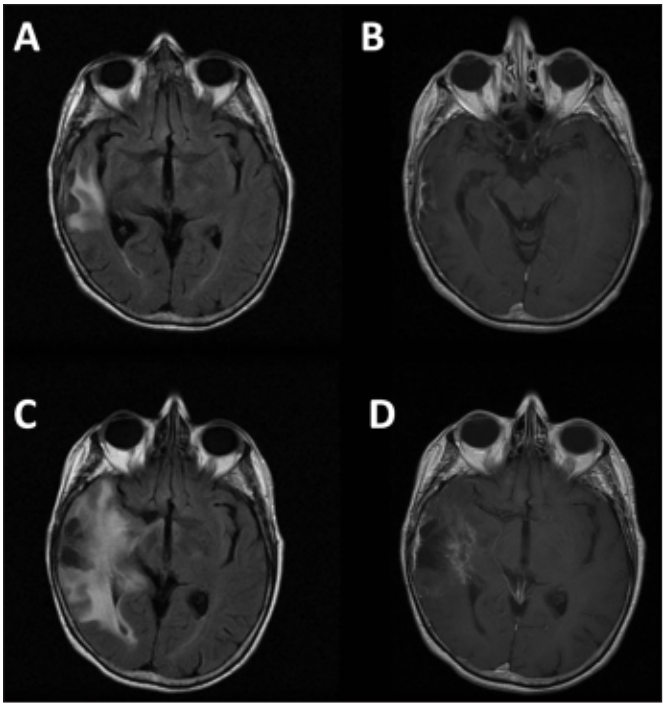

Figure: *Post-GK edema in 63-year-old female with GBM. A: Pre-GK right axial FLAIR image displaying right temporal lobe recurrent glioma with surrounding edema. B: Pre-GK axial T1 GAD enhanced image displaying right temporal lobe recurrent GBM. C: Six months post-GK axial FLAIR image displaying right temporal lobe worsening edema. D: Six months post-GK axial T1 GAD enhanced image displaying recurrent right temporal lobe GBM with post-radiation effect. Patient was started on dexamethasone due to symptomatic post-GK edema.*

GK sz (1). The patient with the post-GK seizure had a brief generalized tonic-clonic seizure on post-treatment day 2. This patient had initially presented with a generalized tonic-clonic seizure leading to the diagnosis of a right frontal GBM.

All 14 patients presenting with seizures leading to the diagnosis of their high grade glioma had stable seizure control post-GK, with no change in medications.

Discussion

The management of recurrent high grade gliomas is a challenging task. To date, there is no consensus treatment protocol for patients with recurrent high grade glial neoplasms. Those patients of young age and good functional status with recurrent high grade tumors are particularly discouraging, with the majority of all patients suffering from local failure upon recurence[5].

A variety of therapeutic options have been proposed for managing focal recurrent WHO grade IV and III glial neoplasms[1]. Repeat surgery alone provides an undetermined added survival benefit[17] in the setting of glioblastoma. Fear of radiation induced toxicity related to repeat conformal fractionated radiation in the setting of recurrence, has halted repeated treatment with this form of radiation[1]. A multitude of salvage chemotherapeutic agents have been tried with varying success. For example, temozolomide alone as salvage has displayed a 12 month survival rate post-progression of tumor approaching 25% in some studies[1,18].

Stereotactic radiosurgery has emerged as a potential salvage radiation modality for focally recurrent high grade gliomas, with some literature to date on dosing tolerance and toxicity in the setting of previously irradiated primary tumors[19]. Gamma Knife radiosurgery for focal recurrence has displayed improved survival over repeat resection in some series as well[15]. The timing of SRS in order to optimize survival is not clear. Early post-surgical SRS in addition to standard post operative fractionated radiotherapy and chemotherapy fails to provide survival benefit[14]. Souhami et al[14] displayed a 13.5 month median survival in the post-GK group compared to 13.6 months in the standard treatment group. However, GK has demonstrated improved survival, 17.4 months versus 15.1 months, when GK was reserved for recurrence, as opposed to on initial presentation[20].

To date, post-GK survival in the setting of focal treated recurrence has been described as 8.5 to 17.4 months for WHO grade IV and III gliomas[7-13]. Twelve-month actuarial survival post-GK for recurrent GBM and AA has been described at 37% and 80% respectively[12]. High grade oligodendrogliomas, WHO grade III, have been noted to have a mean survival post-GK of 28.3 months[21], though the literature to date is limited.

Our series of 29 patients with focal recurrent high grade glial neoplasms treated with GK SRS offers another look at the extension of local tumor control, potential effect on survival, and safety with GK for focally recurrent gliomas.

This series of WHO grade III and IV recurrent tumors displayed a post-GK survival of 20.4 months (range: 3 - 72), with average overall survival (from diagnosis to death) of 63.3 months (range: 10 - 214), which is slightly above that described in the literature to date[7-13]. The average survival post-GK was 15.8 months (range: 3 - 77), with the GBM/oligodendroglioma mix and GBM subgroups displaying post-GK survival rates of 31.8 months and 11.1 months respectively, comparable to the literature described post-GK survival of 8.4 to 16 months[7-13]. Of interest is the profound difference in GBM/oligodendroglioma mix survival and local control versus the standard GBM patients alone. We suspect that despite presentation with WHO IV pathological diagnosis, these tumors likely arose from lower grade oligodendrogliomas or mixed oligoastrocytomas, causing their natural history to vary from GBM irregardless of the treatment. The number of patients with GBM/oligodendroglioma mix in our study is small, yet the substantial difference in post-GK and overall survival and local control is notable.

Similarly, the average post-GK survival for WHO grade III gliomas was 34.9 months (range: 6 - 72), slightly longer than described in the literature. Unfortunately, given the small number of WHO grade III tumors treated in our series, we are unable to make any definitive statements about survival among AA, OA, and oligodendroglioma patient groups.

In our series, RTOG RPA malignant glioma class correlated well with overall survival. Recursive partitioning analysis class 1, 2, 3 and 4 patients displayed overall survival 140.5 months, 112.0 months, 54.1 months and 30.4 months respectively. This correlates to other series in the literature to date[7,9,10,12,14].

https://doi.org/10.1017/S0317167100015894 Published online by Cambridge University Press

Our permanent complications, or ARE, were significantly higher than those described in the literature. Twenty-six (89.7%) patients had ARE post-GK. Twenty-two patients had post-GK edema. Fourteen required dexamethasone (RTOG toxicity 2 or greater) due to symptoms and eight patients were asymptomatic (RTOG toxicity of 1). No correlation between marginal tumor dose and the presence of edema of RTOG toxicity 1 or higher was evident. Similarly, there was only a small difference in marginal dose for those with RTOG class 1 toxicity versus 2 or higher, with doses of 18.2 Gy versus 16.8 Gy respectively. It is possible that the increase in edema post-GK is related to tumor progression and not an effect of radiation, though it is likely a combination of both factors. The four patients with radiation necrosis (ARE), as defined by MRI, were asymptomatic. The lack of pathological confirmation of radiation necrosis raises the question as to whether these patients actually had radiation necrosis. Fortunately, of the entire group of ARE described in our series, no patient required surgical intervention or died as a result of these complications. One unfortunate patient suffered class 3 RTOG toxicity related to edema as previously described, with no identifiable cause upon further analysis of treatment characteristics.

Transient complications were also high in our series, with 13 patients in this category. The majority of these transient complications were minor and all had resolved by one month post-GK.

Overall, our results for post-GK survival were encouraging in the face of these aggressive malignancies. We believe similar survival times can be replicated by the following. First, we believed our patient selection may have contributed to our local control rates and survival post-GK. Decision to offer GK in the treatment of gliomas was made on an individual basis and was considered based on age, functional status, and size of focal tumor recurrence. The population of GBM patients treated with GK was a highly selected patient group, with less than 2% of all GBM patients over the last decade treated at our institution considered eligible for treatment. As outlined by the RPA malignant glioma classification[2,3], age and KPS are the most important determinants of outcome in any malignant glioma treatment. We postulate that our selection of young (average age 50.2 years) and highly functioning individuals (average KPS 85.2) with focal recurrence, is a major factor in our average post-GK survival time of 20.4 months, with a post-GK survival of 15.8 months and 34.9 months for WHO grade IV and III tumors respectively. Despite our average RPA class of 3.0 for the total population in our series, a large portion of those WHO grade IV tumors with RPA class 4 designations were due to age between 50 and 60, and not poor KPS. This is reflected in our similar post-GK survival times for RPA class 3 and 4 patients. Second, we maintained dosing within tolerance defined by Shaw et al[19], which potentially maximized the degree of local tumor control and prolonged survival. Finally, the management of focally recurrent high grade gliomas is not a single modality treatment. Our approach to recurrent malignant gliomas involves our multi-disciplinary neuro-oncology group and aggressive salvage chemotherapeutic regimens. Thus, our results for survival post-GK and overall survival are reflective of this.

We acknowledge our study has significant limitations. First, the retrospective nature of the study and small patient numbers make it difficult to generalize to all patients with focally recurrent high grade gliomas. Second, the heterogeneity in chemotherapeutic regimens both pre- and post-GK make it difficult to interpret the overall effect of GK on prolongation of survival. Third, the small number of WHO grade III tumors treated, and the heterogeneous histological subtypes make it difficult to generalize the outcome data for this group and make comments on outcome with GK SRS for focally recurrent AA, OA, and oligodendrogliomas. Fourth, the four patients lost to follow-up is a major concern, as all of these individuals may have completely failed to respond to the GK treatment or have had significant complications. Fifth, genetic variation within the gliomas treated likely impacted their response to both radiation and chemotherapy. Mutations in isocitrate dehydrogenase (IDH), O-6-methylguanine methyltransferase (MGMT) and 1p 19q codeletions may be significant factors in the survival times reported in our patient population. Given the restrospective nature of our study, small patient numbers, and absence of genetic tumor testing in the majority of cases, we are unable to comment on the impact of particular mutations on outcome post SRS. Finally, our ARE complications were quite high, limiting the satisfaction that can be drawn from the post-GK survival times we achieved. We were unable to identify any treatment related parameters to account for this. It is likely that the edema is a combination of tumor progression and post-radiation effects. Fortunately the majority of the ARE encountered were RTOG toxicity class 2 or less.

Our limited experience highlights important questions. What is the role for SRS in the treatment of mixed high grade gliomas? Our results with the few mixed GBM/oligodendroglioma patients were promising in terms of local control and post-GK survival. What is the role for SRS in the treatment of WHO grade III gliomas? The literature to date mainly focuses on GBM and to some extent AA. What about oligodendrogliomas? In light of the literature to date, the future of GK SRS for the treatment of high grade glial neoplasm is still uncertain. Further randomized control trials should be conducted.

Conclusions

In our experience GK SRS affords an extension of local control for highly selected focally recurrent high grade glial neoplasms, with acceptable morbidity. Large randomized control studies of SRS for focal recurrence of high grade gliomas are required in order to define possible benefit for individual histological subtypes of WHO grade IV and III glial tumors.

https://doi.org/10.1017/S0317167100015894 Published online by Cambridge University Press

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https://doi.org/10.1017/S0317167100015894 Published online by Cambridge University Press