

## Case Series: Gamma Knife as Salvage Therapy for Recurrent Glioblastoma Multiforme

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### Abstract

**Objectives:** Glioblastoma multiforme is a highly malignant primary tumor of the brain. It has a dismal survival prognosis of 14-16 months following initial diagnosis. Despite aggressive upfront therapy, glioblastoma tends to recur in twelve months. Following this recurrence, some patients may benefit from Gamma Knife Radiosurgery (GKRS) treatment. This study analyzes survival outcomes in a case series by studying known prognostic indicators for glioblastoma patients.

**Methods:** 63 patients with recurrent glioblastoma were treated with GKRS as part of a multimodal treatment plan between 2002 and 2011. Overall survival (from date of diagnosis) was compared to expected survival times as indicated by updated RTOG recursive partitioning analysis (RTOG-RPA) Classes. Survival post-GKRS salvage was also investigated. Univariate and multivariate analyses were conducted to determine whether there were significant predictors of overall survival for patients undergoing GKRS salvage.

**Results:** Overall median survival from time of initial diagnosis was  $20.2 \pm 2.7$  months for the entire group. 46 patients were in RTOG-RPA Class IV with a median overall survival of  $20.2 \pm 2.6$  months (expected prognosis: 11.2 months). Median survival following GKRS salvage therapy was  $9.9 \pm 3.1$  months for all patients. Multivariate analysis indicated that KPS was a significant predictor of survival (Hazard Ratio 0.22 compared to a KPS of 80).

**Conclusions:** GKRS may be a safe and effective salvage therapy for selected recurrent glioblastoma patients, providing prolonged survival and quality of life compared to patients not receiving salvage treatment. Treatment options should be appropriately tailored to each patient's individual situation.

**Keywords:** Gamma knife; Radiosurgery; Recurrent glioblastoma

### Introduction

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults with an incidence of 3.005 per 100,000 in the United States [1] and is almost always uniformly fatal [2]. Classically, the best available therapeutic approach for most patients consists of gross total resection, temozolamide chemotherapy, and external beam radiation therapy (EBRT) [3-8]. Despite this regimen, these patients typically experience recurrence of GBM 6 months later with an overall total survival of 14-16 months. Stereotactic radiosurgery has not shown to provide a survival benefit when administered as upfront treatment in combination with EBRT, for newly diagnosed GBM [4,9]. Factors which historically predict a more favorable prognosis for GBM patients are age less than 50, Karnofsky Performance Status (KPS) of 90 or better, and achieving gross total resection [10-14]. Additional studies have shown an improved

prognosis for smaller volume tumors (<15cc), unifocal lesions, use of additional salvage therapies, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and Asian/Pacific Islander ethnicity [15-19].

Despite aggressive upfront therapy for newly diagnosed GBM, these tumors tend to recur within six months. This is due to the resistance of tumor cells to radiation and chemotherapy and the microscopic, infiltrative growth of tumor cells along white matter tracts up to 4 cm away from the original gross tumor location [20]. Treatment options for recurrent GBM (rGBM) are an area of interest. Primarily the aim of these treatments is to extend overall survival and improve quality of life. Some studies have focused on chemotherapeutic salvage options [5,13,21-23], but this relies on a patient's ability to tolerate repeat chemotherapy side effects [24]. Salvage surgical treatment, while effective in select cases [18,25,26], may not be an option for patients suffering from extensive tumors, or those affecting eloquent areas. Recovery from surgery may also be too challenging for a patient and their family during the terminal state of this illness. Repeated

conformal radiation therapy presents a high risk of radionecrosis or radiation-induced edema without providing substantial benefit [27,28]. Stereotactic radiosurgery therapies, such as Gamma Knife radiosurgery (GKRS), have the ability to deliver a high dose of radiation to a focal region while limiting the dose to surrounding healthy tissue, in many respects similar to the targeted second surgical resection of a GBM. Stereotactic radiosurgery has also shown to provide a survival benefit for those in which repeat surgical resection is not indicated [29]. Multiple studies have offered evidence to support a survival benefit for select rGBM patients who receive GKRS salvage treatment [15,16,18,30-35].

We present the results of 63 patients suffering from recurrence of histopathologically confirmed GBM who received between 1 and 5 salvage GKRS treatments at a single institution. The aim of this study was to retrospectively analyze survival outcomes relative to known clinical prognostic indicators.

## Materials and Methods

We examined the records 63 patients with a diagnosis of GBM between 2002 and 2011 who underwent GKRS salvage therapy. No patients were excluded. All patients were treated at Gamma Knife of Spokane using the Model C Leksell 60Co Gamma Knife (Elekta, Stockholm, Sweden). Prior to the GKRS procedure, local anesthetic was applied to facilitate placement of the stereotactic head frame. Gadolinium enhanced magnetic resonance imaging of the head within the coordinate frame was performed and then a neurological surgeon, radiation oncologist, and medical physicist concurrently planned the radiosurgery treatment. 47 patients received only one GKRS salvage treatment and 16 patients had two or more treatments. 13 patients had salvage resections, and 2 patients received bevacizumab salvage chemotherapy.

The patients were grouped by resection extent (biopsy, subtotal, or gross total as determined by postoperative MRI), by age at glioblastoma diagnosis (<50y, ≥50y), by KPS value (60, 70, 80, 90, 100, unknown), Gamma Knife treatment dose (<14Gy, 14-15Gy, 16Gy, >16 Gy), and by tumor volume (<15cc, ≥15cc). Table 1 shows number of patients in number of patients in these different defined groups.

Characteristic	Biopsy	Subtotal	GT	Total
	n=10	n=26	n=27	n=63
Age at diagnosis, median (range)	53 (28-85)	57 (28-85)	52 (23-76)	55 (23-85)
<50	3	10	6	19
≥50	7	17	20	44
KPS				
60	1	0	2	3
70	2	9	5	16
80	4	5	8	17

90	2	3	7	12
100	0	8	4	12
Unknown	1	1	1	3
GK Dose (Gy)				
<14	5	4	5	14
14-15	3	6	6	15
16	2	14	13	29
>16	0	2	3	5
Tumor volume (cc)				
<15	3	7	16	26
≥15	6	14	8	28
Unknown	1	5	3	9
Clinical Follow-Up, median (range)				8.9 (0.0-63.6)

**Table 1:** Patient population baseline characteristics, GT: Gross Total resection, KPS: Karnofsky Performance Status, GK: Gamma Knife

Survival curves were estimated using the Kaplan-Meier method and used to compare resection extent groups, KPS groups, Gamma Knife treatment dose groups, and tumor volume groups. Andersen 95% confidence intervals for the median survival time of the groups were constructed [36]. Log-rank tests were employed to determine if there is statistical evidence of differences between the survival curves of the groups. Finally, the Cox proportional hazard model was used in a multivariate analysis of the resection extent groups, age groups, KPS groups, Gamma Knife treatment dose groups, and tumor volume groups. All statistical analyses utilized StatsDirect Version 2.7.3 (StatsDirect Ltd., Altrincham, UK) and SigmaPlot Version 12.3 (SYSTAT Software, Inc., San Jose, CA).

## Results

The median survival of this cohort of patients was 20.2 months (±2.7 months) (Figure 1). This is better than the average survival predicted by historical studies using the conventional treatment regimen particularly for RTOG-RPA Class IV as shown in Table 2.

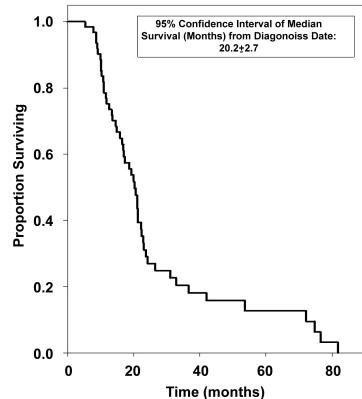
This may be in part due to GKRS salvage. Following GKRS salvage therapy, median survival was 9.9 months (±3.1 months) (Figure 2). There were no statistically significant differences in the Kaplan-Meier survival curves for resection extent groups, comparing biopsy, partial, and gross total resection (Figure 3). Patients with higher KPS scores tended to have longer survival (Figure 4).

There was no report of any complications or adverse radiation events due to GKRS for any patient in this study.

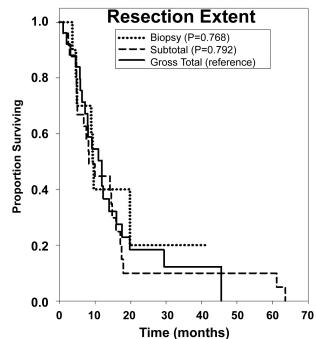
RTOG-RPA Class	Defining Variables	Li, et al. 2011	Present Study	# of patients	95% CI
III	age <50 y and KPS ≥90.	17.1	17.3	6	Not Significant

IV	age <50 y and KPS <90; age ≥50 y, KPS ≥70, resection, and working.	11.2	20.2	46	17.6-22.8
V	age ≥50 y, KPS ≥70, resection, and not working; age ≥50 y, KPS ≥70, biopsy only; age ≥50 y, KPS <70.	7.5	11	8	6.6-15.4

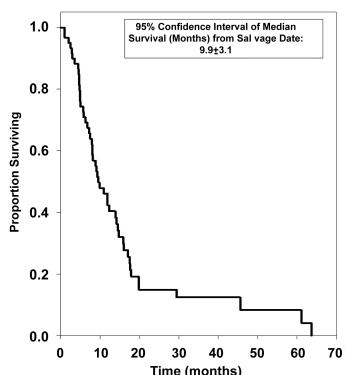
**Table 2:** Comparison of overall survival from diagnosis rates in updated RTOG-RPA Classes (months), RTOG-RPA: Radiation Therapy Oncology Group Recursive Partitioning Analysis, KPS: Karnofsky Performance Status



**Figure 1:** Overall survival from original diagnosis date



**Figure 3:** Overall survival curves based on extent of resection



**Figure 2:** Survival from date of first Gamma Knife salvage therapy for recurrent disease

Univariate median survival confidence interval and hazard ratio confidence intervals are included in Table 3. Within each category a reference group was selected (resection=GT, age<50y, KPS=80, dose=16Gy, tumor volume<15cc) against which the other groups' hazard ratios were tested.

The hazard ratio of the GT resection group was not found to be statistically different than the others. The hazard ratio of the ≥50 age group was not statistically different than the <50 reference group ( $P=0.221$ ). Both the KPS=60 and KPS=100 groups had hazard ratios different than the reference group of KPS=80 ( $P=0.021$  and  $P=0.034$ , respectively).

The analyses of the gamma knife treatment dose groups did not yield any statistically significant results. With respect to tumor volume, the ≥15 cc group's hazard ratio was determined to be statistically different from the <15 cc reference group ( $P=0.019$ ).

	Median Survival		Hazard Ratio		
	n	95% CI	Estimate	95% CI	P value**
<b>Resection extent</b>					
GT*	27	11.9 ± 4.4	reference		
Subtotal	26	9.9 ± 9.2	1.08	0.59-1.97	=0.792
Biopsy	10	9.6 ± 1.1	0.88	0.38-2.02	=0.768

Age at diagnosis					
<50*	19	12.3 ± 11.7	reference		
≥50	44	9.6 ± 2.4	1.44	0.81-2.54	=0.221
<b>KPS</b>					
60	3	3.0 ± 3.2	8.55	1.08-66.67	=0.021
70	16	5.7 ± 2.5	1.21	0.52-2.81	=0.699
80*	17	9.3 ± 2.1	reference		
90	12	11.9 ± 3.7	0.65	0.28-1.50	=0.308
100	12	17.9 ± 5.5	0.35	0.12-0.99	=0.034
Unknown	3	insufficient data	0.74	0.52-2.81	=0.699
<b>GK dose (Gy)</b>					
<14	14	9.6 ± 12.8	0.98	0.48-2.02	=0.966
14-15	15	7.9 ± 3.8	1.41	0.68-2.92	=0.314
16*	29	11.9 ± 2.8	reference		
>16	5	4.7 ± 4.5	0.78	0.24-2.51	=0.638
<b>Tumor volume (cc)</b>					
<15*	26	13.9 ± 4.2	reference		
≥15	28	7.2 ± 2.7	1.97	1.06-3.66	=0.019
Unknown	9	9.1 ± 4.0	1.61	0.61-4.35	=0.252

**Table 3:** Univariate median survival estimates (months) and hazard ratios, \*Reference group against which other groups' survival experience are compared. \*\*P value for log-rank testing the null hypothesis that the groups' survival experience is same as reference group, GT: gross total resection, KPS: Karnofsky Performance Status, GK: Gamma Knife

		Hazard Ratio		
		Estimate	95% CI	P value**
<b>Resection extent</b>				
GT*	reference			
Subtotal	0.97	0.44-2.15	0.941	
Biopsy	0.41	0.14-1.18	0.098	
<b>Age at diagnosis</b>				
<50*	reference			
≥50	1.38	0.67-2.85	0.383	
<b>KPS</b>				
60	8.09	3.69-17.78	<0.001	
70	1.47	1.35-1.61	<0.001	
80*	reference			
90	0.53	0.19-1.47	0.230	
100	0.22	0.15-0.33	<0.001	

Unknown	1.10	0.31-3.92	0.880
<b>GK dose (Gy)</b>			
<14	0.71	0.25-2.07	0.535
14-15	1.15	0.41-3.18	0.793
16*	reference		
>16	0.66	0.14-3.16	0.602
<b>Tumor volume (cc)</b>			
<15*	reference		
≥15	1.95	0.81-4.71	0.138
Unknown	3.68	1.08-12.58	0.038

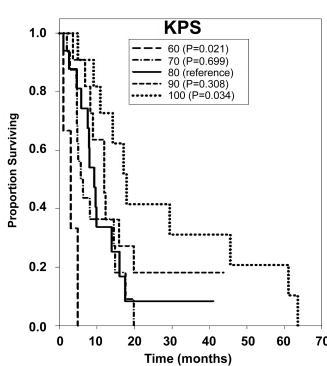
**Table 4:** Multivariate hazard ratios, confidence intervals, and P values, \*Reference group against which other groups' survival experience are compared. \*\*P value for test if groups' survival experience is same as reference group. GT: gross total resection, KPS: Karnofsky Performance Status, GK: Gamma Knife

The multivariate analysis hazard ratio estimates and confidence intervals are included in Table 4. The multivariate analysis utilized the same reference groups as the univariate analyses against which the other groups' hazard ratios were tested. The multivariate analysis did not find statistically significant differences in the resection extent, age, or gamma knife dose groups. Regarding KPS groups, the multivariate analysis indicated the KPS groups of 60, 70, and 100 all differed from the reference group of 80 (P-values <0.001).

Interestingly, the multivariate analysis indicated that tumor volume was not statistically significant ( $p=0.138$ ).

## Discussion

Almost all GBM patients will suffer a recurrence of their tumor and is incurable despite all available interventions [2]. In an effort to curb this dismal prognosis, it is imperative to study methods to treat this recurrence. This study aims to retrospectively analyze whether GKRS is effective as a salvage treatment option. Moreover, it is important to identify which patients are most likely to benefit from this treatment. To that end, overall survival outcomes from this study are compared to the updated RTOG recursive partitioning analysis (RTOG-RPA) described by Li et al. in 2010 which focused specifically on GBM histopathology [13]. The Li study identifies three RTOG-RPA classes: III, IV, and V with overall survival rates of 17.1, 11.2, and 7.5 months from initial diagnosis, respectively. Significant predictors of prognosis that they found are KPS, age, extent of resection, and neurologic function [13,37]. In the present study, RTOG-RPA Class was determined in 95% of patients with the greatest survival advantage appreciated by patients in Class IV: 20.2 months (Table 2) (Figure 4). In prior studies recently reviewed [38], median overall survival for all patients treated with salvage GKRS was from 16.7 to 33.2 months [15,16,18,30-35].



**Figure 4:** Overall survival curves based on Karnofsky Performance Status (KPS)

It is also informative to analyze which patient characteristics predict longer survival following salvage therapy. In this study, the most significant predictor of survival post-GKRS salvage was KPS score. This is based on the results from multivariate analysis and is consistent with other reports on GKRS salvage for rGBM. Elliott, et al. found improved outcomes for KPS  $\geq 90$  in their multivariate analysis [15]. The present study found no difference between KPS of 80 and 90 on multivariate analysis. Also, while patients with KPS scores of 60 and 70

faired significantly worse following GKRS salvage, comparing their survival rates to those in patients who do not receive salvage therapy may be worthwhile.

Evidence shows that patient age is a reliable predictor of overall survival following the initial diagnosis of GBM [10,11,19,30,39], but this study and others appear to suggest that it is not associated with survival differences following GKRS salvage (Tables 3 and 4) [15,18]. These data, along with the aforementioned RTOG-RPA comparison, suggest that older patients with favorable KPS scores are likely to appreciate similar post-salvage survival advantages as younger patients. Therefore, they ought to be considered as candidates. Likewise, this study did not find a post-salvage survival difference for patients who initially had gross total resection, subtotal resection, or biopsy as part of their adjuvant therapy following diagnosis of GBM (Tables 3 and 4) (Figure 3). This lack of statistical significance may be explained by the relatively small number of patients in each subgroup. An opposing view may be that regardless of initial extent of resection, it is important to continue to treat all visibly recurrent tumor tissue with radiosurgery as early as possible following detection on surveillance MRI. That said, salvage surgical resection, with or without GKRS, has been demonstrated to show a survival advantage for those patients who are eligible [18,25,40,41].

Multiple studies on salvage rGBM suggest that patients with smaller volume tumors seem to experience a greater survival advantage [15,16,18,38]. In the present study, multivariate analysis does not show significant survival difference when comparing tumors  $<15$  cc and those  $\geq 15$  cc (Table 4). This suggests that those patients suffering from a larger volume recurrence may still benefit from GKRS salvage.

This study is limited by its retrospective nature, without a control group. It may represent a selection bias in that those patients who are deemed eligible for Gamma Knife treatment could be in an advantageous position when it comes to rGBM survival. Also, some patients are deemed unfit for repeated resection, either by clinical assessment by the surgeon or the patient's ability to survive such an invasive procedure, or by patient preference. Until a randomized, controlled clinical trial is performed for GKRS for rGBM patients, this evidence has a limited scope for informing clinical practice [38,42]. However, the data from this study suggests a survival benefit independently of age, KPS score, and extent of resection including biopsy only.

Each rGBM patient and their family need to be counseled by the healthcare team to determine which surgical and medical options are available. An individually tailored, multimodal treatment plan based on tumor location and the patient's functional capacity should be offered in order to meet the individual's goals [43].

## Conclusions

GKRS salvage therapy for selected patients with rGBM showed overall median survival of 20.2 months and post-treatment survival of 9 months. When considering their RTOG-RPA classifications, these patients experienced longer survival than predicted. These results were independent of the size of the tumor and treatment dose. Those with better KPS scores tended to have longer post-GKRS survival.

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