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MINIREVIEWS

Clinical outcomes following salvage Gamma Knife radiosurgery for recurrent glioblastoma

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Abstract

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor with a survival prognosis of 14-16 mo for the highest functioning patients. Despite aggressive, multimodal upfront therapies, the majority of GBMs will recur in approximately six months. Salvage therapy options for recurrent GBM (rGBM) are an area of intense research. This study compares recent survival and quality of life outcomes following Gamma Knife radiosurgery (GKRS) salvage therapy. Following a PubMed search for studies using GKRS as salvage therapy for malignant gliomas, nine articles from 2005 to July 2013 were identified which evaluated rGBM treatment. In this review, we compare overall survival following diagnosis, overall survival following salvage treatment, progression-free survival, time to recurrence, local tumor control, and adverse radiation effects. This report discusses results for rGBM patient populations alone, not for mixed populations with other tumor histology grades. All nine studies reported median overall survival rates (from diagnosis, range: 16.7-33.2 mo; from salvage, range: 9-17.9 mo). Three studies identified median progression-free survival (range: 4.6-14.9 mo). Two showed median time to recurrence of GBM. Two discussed local tumor control. Six studies reported adverse radiation effects (range: 0%-46% of patients). The greatest survival advantages were seen in patients who received GKRS salvage along with other treatments, like resection or bevacizumab, suggesting that appropriately tailored multimodal therapy should be considered with each rGBM patient. However, there needs to be a randomized clinical trial to test GKRS for rGBM before the possibility of selection bias can be dismissed.

Key words: Gamma Knife radiosurgery; Malignant glioma; Glioblastoma; Salvage therapy; Stereotactic radiosurgery; Multimodal treatment

Core tip: Glioblastoma is the most common malignant primary neoplasm of the brain. Despite aggressive, upfront therapy, most patients will experience a recurrence of their tumor six months after treatment. This review article analyzes the outcomes of clinical trials that utilized Gamma Knife radiosurgery as salvage therapy for recurrent glioblastoma. Other modalities of radiosurgery were excluded from this study as there is variability in the targeting precision and radiation dos-

age fall off. Gamma Knife can be used to target tumors that are adjacent to eloquent brain tissue, thus allowing it to treat a wider population of patients, improving overall survival.

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INTRODUCTION

Glioblastoma multiforme (GBM) remains the most common malignant primary brain tumor in adults and is uniformly fatal[1]. Without treatment, most patients die within a few weeks after presentation of symptoms[2]. For newly diagnosed GBM, median survival can be extended to 14-16 mo using a standard treatment protocol that includes maximal surgical resection followed by temozolomide chemotherapy and 60 Gy of external beam radiation therapy (EBRT)[3,4].

Strong predictors of prognosis with these treatments for patients with GBM have been outlined by Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA). These include tumor histopathology, age, Karnofsky Performance Score (KPS), neurologic function, and initial treatments[5,6]. Patients with GBM histology are categorized in one of four groups, RPA Classes Ⅲ, Ⅳ, Ⅴ, and Ⅵ, with Class Ⅵ having the worst prognosis. In 2011, Li *et al*[7] analyzed the RTOG-RPA with a renewed focus on GBM alone. They suggest that there is not a significant difference between Classes Ⅴ and Ⅵ, and that these groups could be combined. They report median overall survival times for the updated classification as 17.1, 11.2, and 7.5 mo for patient populations in Classes Ⅲ, Ⅳ, and Ⅴ + Ⅵ, respectively[7]. Additional prognostic factors that may improve survival include small tumor volume, unifocal lesions, use of additional salvage therapies, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation[8-11] MGMT status, however, was either not known, or not reported for any of the studies reviewed herein.

Despite aggressive adjuvant therapy for GBM, tumors typically recur within 6 mo of treatment. This may be due in part to microscopic infiltrative growth up to 4 cm from visible tumor location along white matter tracts in normal brain tissue[12] as well as the resistance of the tumor to radiation and chemotherapy treatments. Salvage therapy for recurrent GBM (rGBM) is an area of current interest in order to extend overall survival beyond the aforementioned median survival of 17.1 mo for the most functional patients. Some patients may not be eligible for repeated surgery because of the location of the tumor in critical structures or its diffuse nature. Others may find that recovery from surgery is too burdensome during the terminal stage of illness. Salvage chemotherapy may be an option for patients who can tolerate the side effects. Repeated conformal radiation therapy comes with uncertain benefit and increased risk of adverse radiation effects including radionecrosis or radiation-induced edema. Stereotactic radiosurgery has shown not to be superior to standard EBRT for newly diagnosed GBM[13]. However, its role in rGBM is still under investigation.

There are multiple modalities of stereotactic radiosurgery; one of which often utilized for this recurrent disease is Gamma Knife radiosurgery (GKRS). GKRS is capable of delivering a high dose of radiation to a tumor while sparing healthy surrounding tissue. Its advantages in rGBM include the convenience of a single outpatient treatment, minimization of potential radiation necrosis to adjacent brain, and a cost benefit over open resection[14]. Its disadvantage includes the lack of treatment to regions of tumor not well visualized on magnetic resonance imaging. Therefore, its effect on both local tumor control and overall survival is unclear. Previous review articles on stereotactic radiosurgery for malignant gliomas have taken a broad approach, including gliomas of multiple grades or a variety of radiosurgery treatment modalities. These other articles have excluded some of the smaller studies of radiosurgery for rGBM. The present article reviews the outcomes of clinical studies which used GKRS alone or as part of multimodal treatment regimens as salvage therapy for rGBM. While other modalities, such as CyberKnife® or linear accelerator based systems may have similar outcomes, these radiosurgery modalities are not included in this review due to the differences in cost, conformity, homogeneity, maximum dose, treatment times, dose fall off, invasiveness, treatment planning, and beam properties[15-20]. Different radiosurgical delivery systems may be more appropriate for other tumor types and locations which are not discussed here[18,20].

RESEARCH

A PubMed search was performed to identify clinical studies that used GKRS salvage for treatment of rGBM between 2005 and 2013. Key words for this search included "Stereotactic Radiosurgery", "Gamma Knife", "Glioblastoma", "recurrent GBM", "Glioma", and "Glioma salvage therapy". To expand the search strategy, references from articles found in this search were also analyzed for inclusion in this review. Studies which treated World Health Organization Grade Ⅰ-Ⅲ Gliomas without treating Grade Ⅳ (GBM) were also excluded. Finally, studies which used Gamma Knife as upfront therapy only for newly diagnosed GBM were excluded.

The median overall survival outcomes as compared to RTOG-RPA prognostic indicators[7] were extracted and collated from these research studies. Other results were also analyzed including median survival post-GKRS salvage, progression-free survival, and time to repeat tumor recurrence. This article will discuss additional factors that may contribute to improved outcomes based on

Table 1 Characteristics of patients with newly diagnosed glioblastoma multiforme

Ref.	rGBM patients	Median age (range)	Median KPS (range)	Median tumor volume (mL) (range)
Skeie *et al*[9]	32	51	73	12.4
	19	50	81	13.9
Park *et al*[10]	11	62 (46-72)	90 (80-100)	13.6 (1.2-45.1)
	44	64 (41-77)	90 (70-100)	9.5 (1.5-48.9)
Koga *et al*[28]	9	43 (17-64)	90 (80-90)	NR
	9	53 (27-79)	90 (80-90)	
Elliott *et al*[11]	16	60 (35-69)	90 (80-100)	1.35 (0.37-6.2)
Pouratian *et al*[25]	26	60.7 (12.9-76.9)	80 (40-100)	21.3 (0.3-110.0)
Kida *et al*[21]	54	[Mean 52.4 (11-80)]	NR	(Mean: 29.0 mm) (7-48.3 mm)
[1]Kong *et al*[23]	65	NR	NR	NR
Kohshi *et al*[22]	11	NR	NR	NR
Hsieh *et al*[24]	26	(Mean 58.2)	(Mean: 70)	(Mean: 21.6)

[1]Kong *et al*[23] (2008) includes data from 0-5 cases treated with LINAC. rGBM: Recurrent glioblastoma multiforme; KPS: Karnofsky Performance Status; NR: Data not reported or not segregated for rGBM patients.

Table 2 Upfront treatment modalities for newly diagnosed glioblastoma multiforme

Ref.	rGBM patients	Initial surgery	Adjuvant rad	Adjuvant chemotherapy	Time to 1st recurrence (mo)
Skeie *et al*[9]	32	All GTR	93.5% of patients had EBRT	37% Temo, 19.9% PCV	11.0 (mean)
	19		(39-60 Gy)		10.4 (mean)
Park *et al*[10]	11	4 Bx, 7 GTR	All EBRT (54-60 Gy)	All Temo	NR
	44	NR	NR	NR	
Koga *et al*[28]	9	All resection	8 EBRT (48-80 Gy)	6 ACNU, 2 Temo, 1 CE	14.5 (median) (range, 1-51)
	9	2 Bx, 7 resection	All EBRT (60-80 Gy)	All Temo	12 (median) (range, 6-39)
Elliott *et al*[11]	16	NR	All EBRT (60 Gy)	All Temo	7.9 (median) (range, 2-84)
Pouratian *et al*[25]	26	2 Bx, 18 STR, 6 GTR	25 EBRT (dose NR)	16 had chemotherapy (type NR)	NR
Kida *et al*[21]	54	NR	NR	NR	NR
[1]Kong *et al*[23]	65	NR	All EBRT (54-70 Gy)	NR	4.3 (range, 1.5-27.0)
Kohshi *et al*[22]	11	All debulking	All EBRT (50-72 Gy)	All had chemotherapy (type NR)	NR
Hsieh *et al*[24]	26	NR	All EBRT (60 Gy)	NR	NR

[1]Kong *et al*[23] (2008) includes data from 0-5 cases treated with LINAC. rGBM: Recurrent glioblastoma multiforme; GTR: Gross total resection; STR: Subtotal resection; Bx: Biopsy; EBRT: External beam radiation therapy; Temo: Temozolomide; PCV: Procarbazine, lomustine, and vincristine; NR: Data not reported or not segregated for rGBM patients.

these combined results. Additionally, barriers to effective GKRS salvage treatment are considered. Some studies did not report segregated data for GBM versus Grade Ⅰ-Ⅲ gliomas[11,21-23] or salvage GKRS versus upfront GKRS[24,25] in all categories; however, we considered data as available.

RESULTS

Table 1 outlines the characteristics of patients from the various studies who were newly diagnosed with GBM. Table 2 shows which upfront treatment modalities were used for newly diagnosed GBM and the time until the first recurrence. In Table 3 we show the available details for salvage treatment modalities. Finally, Table 4 describes the outcomes of these salvage therapies.

Median overall survival from initial diagnosis compared to RPA prognosis

Primarily, salvage therapies for rGBM, such as GKRS, are designed to prolong the life of the patient. Taken as a whole, these studies showed an improved survival compared to classical results from the RTOG-RPA study. Considering the KPS scores and ages of patients in each study, it is expected that the majority of patients would be classified as RTOG-RPA Classes Ⅲ or Ⅳ with an expected overall median survival of 17.1 or 11.2 mo, respectively[7]. The longest median survival for these salvage studies was reported in the cohort of eleven patients studied by Park *et al*[10] in 2012 who were treated with both GKRS and bevacizumab as salvage: 33.2 mo (95%CI: 23.7-42.7 mo) survival after initial GBM diagnosis. These patients were matched to a group of 44 patients who were treated with GKRS salvage without bevacizumab resulting in median overall survival of 26.7 mo (95%CI: 21.8-31.6 mo). While the authors attributed this longer survival to selection bias (KPS scores ≥ 70), it is worth mentioning that four of the eleven patients in the bevacizumab treatment group would be classified in RPA Class Ⅴ + Ⅵ as they were older than 50 and received biopsy only when initially diagnosed, and thus their survival would have classically been very limited.

A 2012 study by Skeie *et al*[9] demonstrated a survival advantage in patients who received salvage GKRS with salvage gross total resection (median 21 mo) or without salvage gross total resection (median 18 mo). Improved

Table 3 Salvage treatment modalities and details for recurrent glioblastoma multiforme

Ref.	rGBM patients	Margin GK dose (range) Gy	Salvage resection	Salvage radiotherapy	Salvage chemotherapy
Skeie *et al*[9]	32	12.2 (8-20)	None	19 EBRT	3 Temo, 15 PCV
	19		All GTR	12 EBRT	1 Temo, 6 PCV
Park *et al*[10]	11	16 (13-18)	2 debulking	None	All BZ (9 w/irinotecan, 1 w/Temo)
	44	15 (10-20)	7 resection	1 EBRT	19 patients (no BZ)
Koga *et al*[28]	9	20	NR	NR	NR
	9	Extended field, 20	NR	NR	NR
Elliott *et al*[11]	16	15 (12-18)	14 GTR, 2 NTR	NR	NR
Pouratian *et al*[25]	26	6.0 (3.0-15.0)	NR	NR	NR
Kida *et al*[21]	54	14.7 (8-25)	NR	NR	NR
[1]Kong *et al*[23]	65	16 (12-50)	NR	NR	13 Temo or PCV
Kohshi *et al*[22]	11	22 (18-27) in 8 fractions followed by HBO therapy	2 patients	NR	NR
Hsieh *et al*[24]	26	12	NR	NR	NR

[1]Kong *et al*[23] (2008) includes data from 0-5 cases treated with LINAC. rGBM: Recurrent glioblastoma multiforme; GK: Gamma knife; HBO: Hyperbaric oxygen; GTR: Gross total resection; NTR: Near-total resection; EBRT: External beam radiation therapy; Temo: Temozolomide; PCV: Procarbazine, lomustine, and vincristine; BZ: Bevacizumab; NR: Data not reported or not segregated for rGBM patients.

Table 4 Outcomes following Gamma Knife salvage therapy for recurrent glioblastoma multiforme

Ref.	rGBM patients	Med. survival from diagnosis (mo)	Progression-free survival	Median survival after GK salvage (mo)	Time to recurrence, post-GK (mo)	Local tumor control	ARE
Skeie *et al*[9]	32	18.0 (95%CI: 16.7-30.8)	NR	9 (95%CI: 8.7-14.9)	6	18.8%	9.80%
	19 (salvage GTR)	21.0 (95%CI: 21.2-55.9)		15 (95%CI: 12.8-40.4)			
Park *et al*[10]	11 (salvage BZ)	33.2 (95%CI: 23.7-42.7)	14.9 (95%CI: 6.5-23.3)	17.9 (95%CI: 10.1-25.7)	All 6 tumors > 10 mL: 5.9 (95%CI: 1.8-10.0) 1 of 5 tumors < 10 mL: 9.5	NR	9.00%
	44	26.7 (95%CI: 21.8-31.6)	6.7 (95%CI: 5.6-7.8)	12.2 (95%CI: 8.1-16.3)	19 of 21 tumors > 10 mL: 5.1 (95%CI: 4.0-6.2) 21 of 23 tumors < 10 mL: 8.3 (95%CI: 4.2-12.4)	NR	46%
Koga *et al*[28]	9	24.0 (range, 14-57)	NR	10.5 (range, 3-29)	NR	47.0%	5.90%
	9 (EF GK)	21.0 (range, 15-51)		9 (range, 6-27)		93.0%	28.6%
Elliott *et al*[11]	16	26.1	NR	13 (range, 2.5-37.2)	NR	NR	18.8%
Pouratian *et al*[25]	26	17.4 (95%CI: 14.4-20.4)	7.1 (95%CI: 2.9-11.3)	9.4 (95%CI: 7.9-10.9)	NR	NR	0.0%
Kida *et al*[21]	54	27.0	NR	14.0	NR	NR	NR
[1]Kong *et al*[23]	65	23.0 (95%CI: 16.2-29.3)	4.6 (95%CI: 4.0-5.2)	13 (95%CI: 10.6-16.0)	NR	NR	NR
Kohshi *et al*[22]	11	21.0 (95%CI: 16-26)	NR	11 (95%CI: 4-12)	NR	NR	18.0%
Hsieh *et al*[24]	26	16.7	NR	10.0	NR	NR	NR

[1]Kong *et al*[23] (2008) includes data from 0-5 cases treated with LINAC. rGBM: Recurrent glioblastoma multiforme; GK: Gamma Knife; ARE: Adverse radiation effects; GTR: Gross total resection; BZ: Bevacizumab; NR: Data not reported or not segregated for rGBM patients.

survival was shown for salvage GKRS patients in all RPA Classes, the majority of whom were in Class Ⅳ. In 2011, Elliott *et al*[11] showed that salvage GKRS with repeat resection for rGBM patients resulted in 26.1 mo survival. This longer than average survival could be due, in part, to the relatively small volume tumors which were selected: median 1.35 mL (range, 0.37-6.2 mL).

There were two other studies which compared median overall survival outcomes to the RPA Classes of their patients: Hsieh *et al*[24] and Pouratian *et al*[25] reported 16.7 and 17.4 mo survival, respectively. Pouratian *et al*[25] showed that their patients who had GKRS as salvage had significantly longer survival than those who received upfront GKRS therapy and the group which received the greatest benefit were patients in RPA Class Ⅲ. Contrarily, the study conducted by Hsieh *et al*[24] found that patients in Class Ⅵ received the greatest survival benefit. It is worth mentioning that both of these studies used a relatively low median marginal dose for the GKRS therapy: 12 Gy in the Hsieh study and 6.0 Gy in Pouratian.

There have not been large studies assessing the number or frequency of repeated salvage GKRS for recurrent GBM. However there have been some reports that suggest that eligible patients may be offered as many repeated therapies as can be tolerated or are feasible with some initial promising results[26,27].

Other outcomes

Without treatment, the natural history of a recurrent GBM is grim[2]. It is expected that the same prognostic indicators mentioned previously are the best predictors of survival following recurrence. It is therefore useful when evaluating the efficacy of GKRS salvage therapy to consider the length of median overall survival after treat-

ment, length of progression-free survival, and time to repeat tumor recurrence post-GKRS salvage.

Median overall survival post-GKRS salvage ranged from 9-17.9 mo, and was reported for all nine of these studies (n = 322 patients)[9-11,21-25,28]. Longer survival was associated with a combination salvage treatment of bevacizumab[10], or repeated surgical treatment[9]. Those patient cohorts with a shorter post-salvage survival did not use these combined therapies, used a lower radiation dose for GKRS salvage, or did not report any information for other modes of rGBM salvage therapy[9,22,24,25,28].

Three of these studies reported progression-free survival data following salvage GKRS for their rGBM patients, which might be useful in counseling a patient on their treatment options[10,23,25]. Park *et al*[10] described 6.7 mo progression-free survival in the 44 patient cohort receiving GKRS salvage compared to 14.9 mo progression-free survival in the 11 patients who received GKRS + bevacizumab salvage (P = 0.035). Kong *et al*[23] reported only 4.6 mo median progression-free survival following GKRS salvage while their patients demonstrated promising median overall survival of 23 mo. Unfortunately, many of the other patient characteristics, treatment histories, and prognostic factors that they reported were grouped together with Grade Ⅲ gliomas. This makes it difficult to independently assess their rGBM patient population. Lastly, the smaller dosage GKRS study by Pouratian *et al*[25] showed median progression-free survival of 7.1 mo.

Only two of the reviewed studies reported the time to tumor recurrence following GKRS salvage[9,10]. Predicting the timeline of a second recurrence could be helpful in planning later salvage options. Skeie *et al*[9] indicated that the second recurrence was at a median of 6 mo after GKRS compared to 2 mo following repeat resection without GKRS (P = 0.009). The study by Park *et al*[10] found that the pattern of recurrence was dependent upon initial tumor volume. The tumors which were larger than 10 mL tend to recur in approximately 6 mo while smaller tumors did not recur until around 9 mo independent of the addition of bevacizumab treatment[10].

Factors contributing to outcomes

Due to the infiltrative nature of GBM, most tumors will recur locally, within 4 cm from the original resection bed[12]. In the hope of stopping or delaying this progression, it is important to develop a treatment strategy that will achieve local control. Skeie *et al*[9] assessed 98 of their treated patients and found that 18.8% of those treated with salvage GKRS achieved local control compared to only 2.0% of those receiving repeat resections only (P = 0.032). Koga *et al*[28] demonstrated 93% local control in their patients who received 20 Gy to a 0.5-1.0 cm extended field GKRS compared to 47% of patients who were treated with 20 Gy to the gadolinium-enhancing margin only.

Other strategies for delaying progression of GBM include radiosensitization methods such as bevacizumab[10], chloroquine[29], or hyperbaric oxygen therapy[22]. If the tumor tissue can be sensitized to radiation, it may be possible to prescribe a smaller dose of radiation while achieving the same therapeutic effect and reducing adverse side effects. This could open up GKRS salvage to a wider patient population: those with larger volume tumors and/or tumors in close proximity to eloquent brain areas (*e.g.*, basal ganglia, optic chiasm, and brainstem). Kohshi *et al*[22] used hyperbaric oxygen therapy combined with fractionated GKRS as salvage in an effort to sensitize the tumor while reducing adverse effects of radiation, resulting in a median survival of 21 mo in their rGBM patients. There has not yet been a randomized clinical trial to test these results so the benefits remain theoretical.

Barriers to effective GKRS salvage

Radionecrosis or radiation induced edema present a challenge for repeat conformal radiation treatment as well as aggressive GKRS salvage. In the studies reviewed, the highest rates of symptomatic radiation side effects were associated with the highest prescribed GK dose to the tumor margin. Koga *et al*[28] reported adverse radiation effects in 28.6% of patients who received 20 Gy to the extended margin, this suggests that achieving improved local tumor control may come with an increased risk of side effects. Park *et al*[10] demonstrated that bevacizumab not only prolonged survival but also reduced detectable adverse radiation effects from 46% to 9% (P = 0.037). Two studies reported 0% radiation side effects in their patients: Pouratian *et al*[25] used a median margin dose of 6.0 Gy while Kohshi *et al*[22] delivered 22 Gy in 8 fractions (2-3 Gy per fraction).

CONCLUSION

The benefits of salvage GKRS for rGBM appear to be promising in a selected group of patients. However selection bias is uncontrolled in these studies, and poses a significant limitation in these retrospective studies. Without a randomized clinical trial, it is unclear whether these salvage therapies truly prolong survival. A future randomized trial is necessary to demonstrate that radiosurgery is beneficial for rGBM. Future studies should evaluate which RPA Classes benefit most from salvage GKRS.

In our center, Gamma Knife of spokane, each case of rGBM undergoes a multi-disciplinary review followed by individualized treatment. Temozolomide and EBRT are used as upfront therapy and bevacizumab upon recurrence of GBM. When identifying patients for salvage GKRS *via* surveillance magnetic resonance imaging, treatment is typically offered to those with a KPS of 60 or better, at any age. In patients who are candidates for GKRS, we typically treat rGBM to a marginal dose of 16 Gy. The median tumor volume treated has historically been 16.2 cc (range 0.6-52.2 cc).

REFERENCES

1 **Goodenberger ML**, Jenkins RB. Genetics of adult glioma.

Cancer Genet 2012; **205**: 613-621 [PMID: 23238284 DOI: 10.1016/j.cancergen.2012.10.009]

2 **Hou LC**, Veeravagu A, Hsu AR, Tse VC. Recurrent glioblastoma multiforme: a review of natural history and management options. *Neurosurg Focus* 2006; **20**: E5 [PMID: 16709036 DOI: 10.3171/foc.2006.20.4.2]

3 **Krex D**, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M, Sabel M, Steinbach JP, Heese O, Reifenberger G, Weller M, Schackert G. Long-term survival with glioblastoma multiforme. *Brain* 2007; **130**: 2596-2606 [PMID: 17785346 DOI: 10.1093/brain/awm204]

4 **Stupp R**, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO, European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 2009; **10**: 459-466 [PMID: 19269895 DOI: 10.1016/S1470-2045(09)70025-7]

5 **Curran WJ Jr**, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Krisch RE. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 1993; **85**: 704-710 [PMID: 8478956 DOI: 10.1093/jnci/85.9.704]

6 **Scott CB**, Scarantino C, Urtasun R, Movsas B, Jones CU, Simpson JR, Fischbach AJ, Curran WJ. Validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: a report using RTOG 90-06. *Int J Radiat Oncol Biol Phys* 1998; **40**: 51-55 [PMID: 9422557 DOI: 10.1016/S0360-3016(97)00485-9]

7 **Li J**, Wang M, Won M, Shaw EG, Coughlin C, Curran WJ, Mehta MP. Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. *Int J Radiat Oncol Biol Phys* 2011; **81**: 623-630 [PMID: 20888136 DOI: 10.1016/j.ijrobp.2010.06.012]

8 **Gorlia T**, van den Bent MJ, Hegi ME, Mirimanoff RO, Weller M, Cairncross JG, Eisenhauer E, Belanger K, Brandes AA, Allgeier A, Lacombe D, Stupp R. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol* 2008; **9**: 29-38 [PMID: 18082451 DOI: 10.1016/S1470-2045(07)70384-4]

9 **Skeie BS**, Enger PØ, Brøgger J, Ganz JC, Thorsen F, Heggdal JI, Pedersen PH. γ knife surgery versus reoperation for recurrent glioblastoma multiforme. *World Neurosurg* 2012; **78**: 658-669 [PMID: 22484078 DOI: 10.1016/j.wneu.2012.03.024]

10 **Park KJ**, Kano H, Iyer A, Liu X, Niranjan A, Flickinger JC, Lieberman FS, Lunsford LD, Kondziolka D. Salvage gamma knife stereotactic radiosurgery followed by bevacizumab for recurrent glioblastoma multiforme: a case-control study. *J Neurooncol* 2012; **107**: 323-33 [PMID: 22057917 DOI: 10.1007/s11060-011-0744-9]

11 **Elliott RE**, Parker EC, Rush SC, Kalhorn SP, Moshel YA, Narayana A, Donahue B, Golfinos JG. Efficacy of gamma knife radiosurgery for small-volume recurrent malignant gliomas after initial radical resection. *World Neurosurg* 2011; **76**: 128-140; discussion 61-62 [PMID: 21839964 DOI: 10.1016/j.wneu.2010.12.053]

12 **Silbergeld DL**, Chicoine MR. Isolation and characterization of human malignant glioma cells from histologically normal brain. *J Neurosurg* 1997; **86**: 525-531 [PMID: 9046311 DOI: 10.3171/jns.1997.86.3.0525]

13 **Souhami L**, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, Schultz CJ, Sause W, Okunieff P, Buckner J, Zamorano L, Mehta MP, Curran WJ Jr. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys* 2004; **60**: 853-860 [PMID: 15465203 DOI: 10.1016/j.ijrobp.2004.04.011]

14 **Tatter SB**. Recurrent malignant glioma in adults. *Curr Treat Options Oncol* 2002; **3**: 509-524 [PMID: 12392640 DOI: 10.1007/s11864-002-0070-8]

15 **Griffiths A**, Marinovich L, Barton MB, Lord SJ. Cost analysis of Gamma Knife stereotactic radiosurgery. *Int J Technol Assess Health Care* 2007; **23**: 488-494 [PMID: 17937838 DOI: 10.1017/S0266462307070584]

16 **Blamek S**, Grządziel A, Miszczyk L. Robotic radiosurgery vs micro-multileaf collimator: a dosimetric comparison for large or critically located arteriovenous malformations. *Radiat Oncol* 2013; **8**: 205 [PMID: 23968165 DOI: 10.1186/1748-717X-8-205]

17 **Stieber VW**, Bourland JD, Tome WA, Mehta MP. Gentlemen (and ladies), choose your weapons: Gamma knife vs. linear accelerator radiosurgery. *Technol Cancer Res Treat* 2003; **2**: 79-86 [PMID: 12680787]

18 **Plowman PN**, Doughty D. Stereotactic radiosurgery, X: clinical isodosimetry of gamma knife versus linear accelerator X-knife for pituitary and acoustic tumours. *Clin Oncol* (R Coll Radiol) 1999; **11**: 321-329 [PMID: 10591820 DOI: 10.1053/clon.1999.9074]

19 **Dutta D**, Balaji Subramanian S, Murli V, Sudahar H, Gopalakrishna Kurup PG, Potharaju M. Dosimetric comparison of Linac-based (BrainLAB®) and robotic radiosurgery (CyberKnife®) stereotactic system plans for acoustic schwannoma. *J Neurooncol* 2012; **106**: 637-642 [PMID: 21892741 DOI: 10.1007/s11060-011-0703-5]

20 **Perks JR**, St George EJ, El Hamri K, Blackburn P, Plowman PN. Stereotactic radiosurgery XVI: Isodosimetric comparison of photon stereotactic radiosurgery techniques (gamma knife vs. micromultileaf collimator linear accelerator) for acoustic neuroma--and potential clinical importance. *Int J Radiat Oncol Biol Phys* 2003; **57**: 1450-1459 [PMID: 14630285]

21 **Kida Y**, Yoshimoto M, Hasegawa T. Radiosurgery for intracranial gliomas. *Prog Neurol Surg* 2009; **22**: 122-128 [PMID: 18948724 DOI: 10.1159/000163387]

22 **Kohshi K**, Yamamoto H, Nakahara A, Katoh T, Takagi M. Fractionated stereotactic radiotherapy using gamma unit after hyperbaric oxygenation on recurrent high-grade gliomas. *J Neurooncol* 2007; **82**: 297-303 [PMID: 17120158 DOI: 10.1007/s11060-006-9283-1]

23 **Kong DS**, Lee JI, Park K, Kim JH, Lim DH, Nam DH. Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. *Cancer* 2008; **112**: 2046-2051 [PMID: 18338759 DOI: 10.1002/cncr.23402]

24 **Hsieh PC**, Chandler JP, Bhangoo S, Panagiotopoulos K, Kalapurakal JA, Marymont MH, Cozzens JW, Levy RM, Salehi S. Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. *Neurosurgery* 2005; **57**: 684-692; discussion 684-692 [PMID: 16239880 DOI: 10.1227/01.NEU.0000175550.96901.A3]

25 **Pouratian N**, Crowley RW, Sherman JH, Jagannathan J, Sheehan JP. Gamma Knife radiosurgery after radiation therapy as an adjunctive treatment for glioblastoma. *J Neurooncol* 2009; **94**: 409-418 [PMID: 19330482 DOI: 10.1007/s11060-009-9873-9]

26 **Larson EW**, Peterson HE, Fairbanks RK, Lamoreaux WT, Mackay AR, Call JA, Demakas JJ, Cooke BS, Lee CM. Long-Term Survival and Improved Quality of Life following Multiple Repeat Gamma Knife Radiosurgeries for Recurrent Glioblastoma Multiforme: A Case Report and Review of the

Literature. *Case Rep Oncol Med* 2013; **2013**: 431857 [PMID: 24175106 DOI: 10.1155/2013/431857]
27 **Thumma SR**, Elaimy AL, Daines N, Mackay AR, Lamoreaux WT, Fairbanks RK, Demakas JJ, Cooke BS, Lee CM. Long-term survival after gamma knife radiosurgery in a case of recurrent glioblastoma multiforme: a case report and review of the literature. *Case Rep Med* 2012; **2012**: 545492 [PMID: 22548078 DOI: 10.1155/2012/545492]
28 **Koga T**, Maruyama K, Tanaka M, Ino Y, Saito N, Nakagawa K, Shibahara J, Todo T. Extended field stereotactic radiosurgery for recurrent glioblastoma. *Cancer* 2012; **118**: 4193-4200 [PMID: 22180028 DOI: 10.1002/cncr.27372]
29 **Cerniglia GJ**, Karar J, Tyagi S, Christofidou-Solomidou M, Rengan R, Koumenis C, Maity A. Inhibition of autophagy as a strategy to augment radiosensitization by the dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor NVP-BEZ235. *Mol Pharmacol* 2012; **82**: 1230-1240 [PMID: 22989521 DOI: 10.1124/mol.112.080408]

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