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

Ernest Dodoo[1], Beate Huffmann[5], Inti Peredo[1], Hanne Grinaker[2], Georges Sinclair[1], Theofilos Machinis[6], Per Oyvind Enger[7], Bente Sandvei Skeie[7], Paal-Henning Pedersen[7], Marcus Ohlsson[1], Abiel Orrego[3], Thomas Kraepelien[2], Pierre Barsoum[2], Hamza Benmakhlouf[2], Lars Herrman[4], Mikael Svensson[1], Bodo Lippitz[1]

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

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

From the Departments of [1]Neurosurgery, [2]Medical Physics, [3]Pathology, and [4]Neuroradiology, Karolinska University Hospital, Stockholm, Sweden; [5]Department of Neurosurgery, Aachen University Hospital, Aachen, Germany; [6]Department of Neurosurgery, Virginia Commonwealth University, Richmond, Virginia, USA; and [7]Department of Neurosurgery, Haukeland University Hospital, Bergen, Norway

To whom correspondence should be addressed: Ernest Dodoo, M.D. [E-mail: ernest.dodoo@karolinska.se]

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

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

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

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

INTRODUCTION

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

PATIENTS AND METHODS

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

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

Standard Therapy

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

Surgical Treatment

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

Table 1. Histopathologic Characteristics

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

WHO, World Health Organization.

Table 3. Number of Resections

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

WHO, World Health Organization.

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

Exclusion

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

Table 2. Surgical Modalities

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

Radiosurgical Procedure

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

Treatment Parameters

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

Tumor Volume

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

Survival

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

Table 4. Radiosurgery Parameters

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

WHO, World Health Organization.

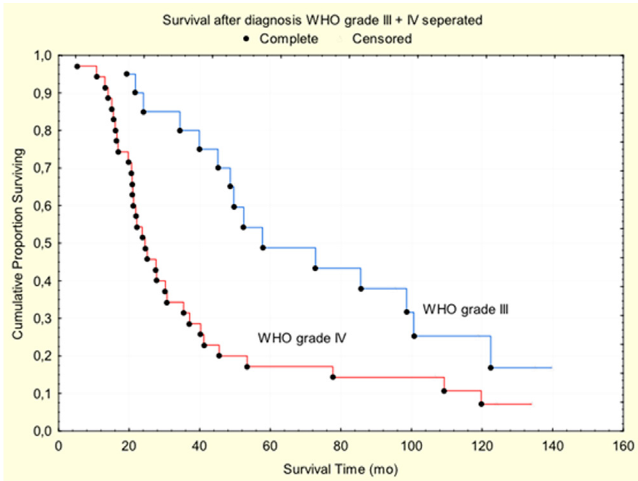

Figure 1. Survival after initial diagnosis for WHO grade III and IV. WHO, World Health Organization.

study end points were overall survival and survival after salvage GKRS.

Follow-Up Assessment

All cases had a complete follow-up, with a median of 17.2 months after GKRS (2.5–114.2 months). Follow-up investigations were performed as magnetic resonance imaging routinely in 3 monthly intervals. The maximum tumor diameter was assessed in axial and coronal planes. The patients' clinical status was assessed via the KPS in regular outpatient examinations.

RESULTS

After the tumor diagnosis, the 20 patients with WHO III glioma showed a median survival of 49.6 months (19.2–122.5 months) whereas the 35 WHO IV patients survived a median of 24.5 months (5.4–84.35 months) (Figure 1). After Gamma Knife treatment of the tumor recurrence, the 20 patients with WHO III glioma had a median survival of 24.2 months (5.0–68.1 months), with 8 patients alive at the study's conclusion date (21 July 2007), whereas the 35 WHO IV patients had median survival of 11.3 months (2.5–62.8 months) (Figure 2; Table 5).

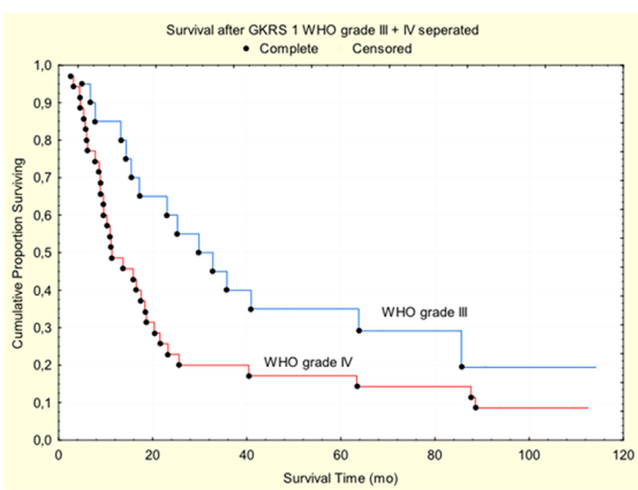

Figure 2. Survival after first GKRS for WHO grade III and IV. GKRS, Gamma Knife radiosurgery; WHO, World Health Organization.

Overall Survival in RPA Classes

Patients classified according to RPA class I (n = 11) at the time of their tumor recurrence had a median survival of 47.7 months (5–64 months) after their initial diagnosis and a 2-year survival rate of 45.5% (5 of 11 patients). The median survival in RPA class II was 61.2 months (7.8–40.9 months) with a 2-year survival of 50% (3 of 6 patients).

After the Gamma Knife treatment of the tumor recurrence, the median survival was 22.7 and 26.4 months in RPA class 1 and 2 and 14.1, 15.4, and 13.7 months in RPA classes 3, 4, and 5, respectively (Figure 3; Table 6).

Side Effects and Reoperations

There were secondarily increasing contrast enhancing lesions in 40% (n = 22) of all patients. Although components with progressive tumor recurrences could not be ruled out entirely, these reactions were considered as adverse radiation effects (AREs), and fluorodeoxyglucose-positron emission tomography examinations used for further differentiation, which generally is difficult both in imaging and histology.

In 37% of the ARE cases, the patients experienced clinical symptoms related to their anatomical tumor localization. Hence, a total of 25% (n = 14) of 55 treated patients were symptomatic as the result of AREs. Most of these patients symptoms were treated with corticosteroid medication, but 20% (n = 4) of patients with WHO grade III gliomas and 23% of patients with WHO grade IV gliomas (n = 8) underwent a second resection. Two glioblastoma patients underwent a third operation.

Table 5. Survival After Initial Diagnosis and After GKRS

Tumor Grade	Patients, n	Median Survival After Diagnosis, months	Median Survival After GKRS, months
WHO grade III	20	55.1	31.3
WHO grade IV	35	24.5	11.3
Combined	55	—	17.2

RPA, recursive partitioning analysis; GKRS, Gamma Knife radiosurgery; WHO, World Health Organization.

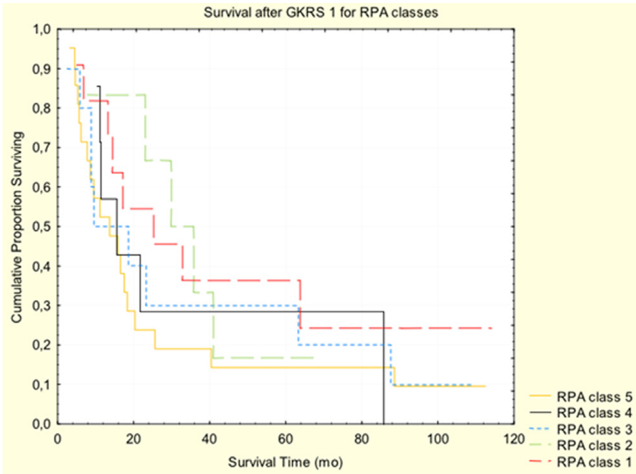

Figure 3. Survival after GKRS in RPA classes. GKRS, Gamma Knife radiosurgery; RPA, recursive partitioning analysis.

DISCUSSION

The current study demonstrates the results after GKRS of recurrent malignant glioma and glioblastoma. Gamma Knife treatment of tumor recurrence resulted in a median survival of 24.2 months for WHO III tumors and 11.3 months for glioblastoma, which appears as a promising option with regard to this otherwise highly complex situation, when no other surgical approach is available.

The current approach is based on the concept of a glioma as a long-term process rather than a confined mass, in which radiosurgery may constitute a potential late salvage therapy for tumor recurrences (22, 34, 36, 39). The present results offer a positive outlook even with regard to other historical series but the limitations attributed to the small sample size and the retrospective setting have to be considered (**Figures 4-6**).

The current study demonstrates the feasibility of GKRS for malignant glioma. Compared with several earlier studies, the timing of the Gamma Knife procedure plays a crucial role in this context. Although initial studies (22, 30) had published beneficial effects after radiosurgery using both Gamma Knife and linear accelerator (LINAC) techniques, the prospective randomized RTOG study 93-05 put an end to all radiosurgical treatment options in malignant glioma because no survival benefit could be achieved compared with standard fractionated radiotherapy. The patients randomized for radiosurgery had received a stereotactic boost immediately followed by fractionated radiotherapy. In this context, it is essential to highlight the differences in the approach between the current retrospective analysis and the prospective trial.

Because tumor recurrences occur almost invariably after standard treatment, the concept of the current study provides another option available when further conventional radiotherapy or surgery is unavailable. Although the RTOG study 93-05 (41) used radiosurgery together with fractionated radiotherapy as initial boost, the current protocol applied radiosurgery late in the event of a recurrence.

Hence the emphasis of the current radiosurgical study is the late and limited application of Gamma Knife. In this context the results of the current study appear to be promising. Several other retrospective studies using both single or multiple fraction regimes support the results of the current feasibility study in which we demonstrated benefit after radiosurgery in patients with high-grade glioma (**Table 7**) (8, 11, 22, 26, 34, 36).

Hence a consideration of late radiosurgery in a prospective trial for recurrent anaplastic glioma would be valuable because it would constitute a fundamentally different approach compared with the previous RTOG study. Microsurgery will always be considered as method of choice to reduce tumor mass effect, but stereotactic radiosurgery has a potential role in smaller recurrent glioma when further resections cannot be applied.

The application of the extreme precision of GKRS for a highly diffuse malignant glioma has been questioned, but it has to be taken into consideration that even a standard surgical resection is a extremely locally confined treatment and, like the more widespread fractionated radiotherapy, invariably results in local recurrences. Earlier studies have shown that malignant glioma typically recurs within a 2-cm margin of the initial tumor (4, 13, 21, 28, 31, 40).

The present study was performed to define the potential survival benefit in a clinically rather unselected cohort of patients with recurrent gliomas, where the decision of a multidisciplinary conference had been that no other therapy was preferable. Further evaluation will be made to define the dose volume criteria of AREs and

Table 6. Survival After Initial Diagnosis in RPA Classification

RPA class	Patients, n (%)	Median Survival After Diagnosis, Months	2-Year Survival After Diagnosis, Patients, n (%)	Median Survival After GKRS, Months	2-Year Survival After GKRS, Patients, n (%)
1	11 (20)	52.5	10 (90)	25.3	6 (54.5)
2	6 (10.9)	61.2	6 (100)	32.8	3 (50)
3	10 (18.2)	28.9	7 (70)	14.1	3 (30.3)
4	7 (12.7)	28.0	4 (57.1)	15.4	2 (28.6)
5	21 (38.2)	22.2	9 (42.9)	13.7	5 (23.8)
6	0				
Total	55 (100)			17.2	

RPA, recursive partitioning analysis; GKRS, Gamma Knife radiosurgery.

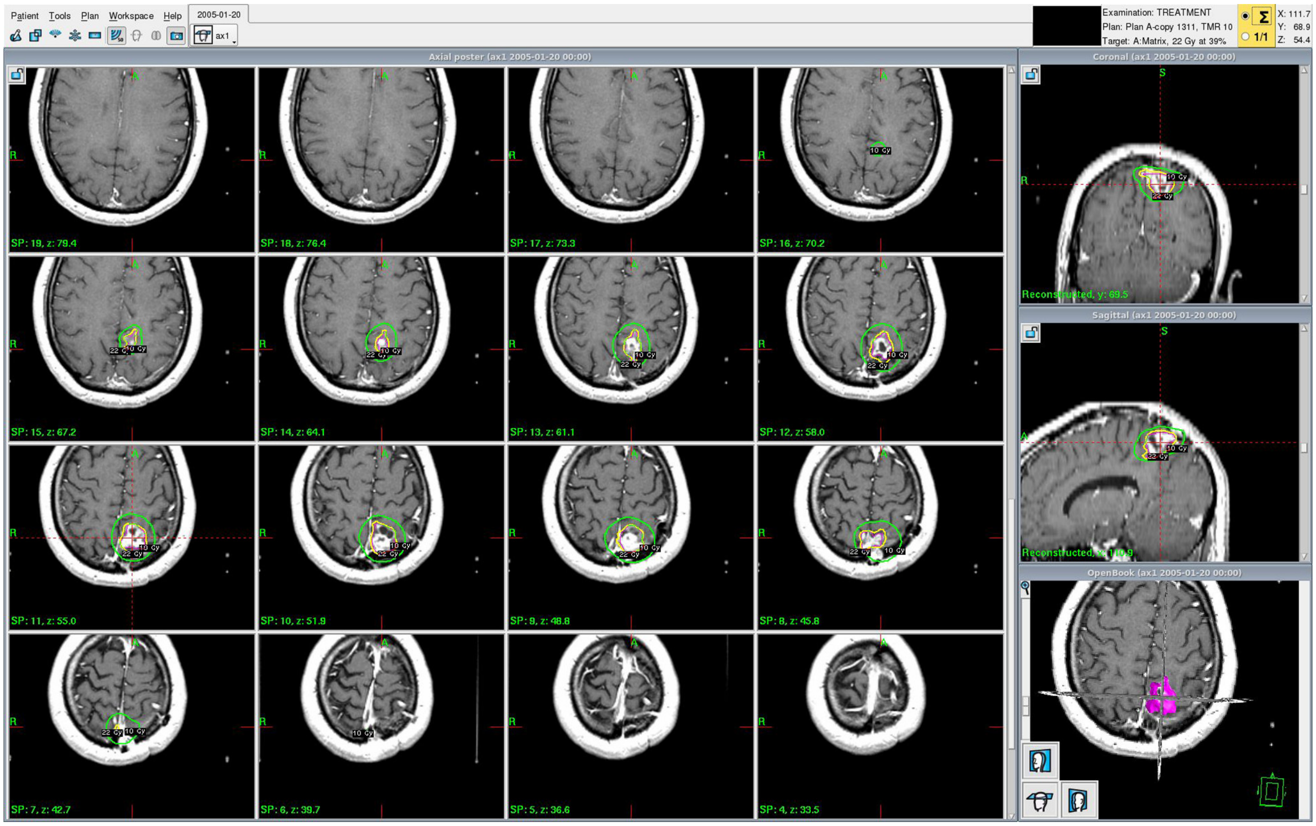

Figure 4. Dose plan of gamma knife treatment, January 2005.

associated side effects and will be published separately. The established selection criteria for GKRS potentially generate a bias towards patients with smaller tumors and better clinical condition (1, 6, 27, 32), which represents the qualitative cornerstones in radiosurgery. Although in the current study clinical criteria such as KPS, age, and tumor malignancy are considered in the applied RPA classification, the majority of tumor volumes were relatively small in the range between 0.03 and 7 mL. However, 20% of patients had tumor recurrences with volumes between 10.8 and 38 mL. It is possible that tumors could be smaller than in an unselected cohort of patients. Consequently, comparisons with unselected historical material might be skewed. However, the range of tumor volumes corresponds to other radiosurgical series in which authors applied stereotactic radiosurgery for glioblastoma recurrences for median tumor volumes of 10.4 mL (0.3–60.1) (33), 10.1 mL (2.2–83) (38), and 6.5 mL (0.88–31.2) (22). Only scarce data exist after radiosurgery of larger tumor volumes (21.6 mL) (20). Although the series with the largest tumors showed a 33% risk for AREs, the reported survival was relatively similar ranging between 10 and 14 months after treatment of the recurrence.

It is established that patients with tumor volumes smaller than 10 cm^3 show a better outcome, but detailed selection criteria for salvage radiosurgery have yet been insufficiently defined. Not surprisingly, Larson et al. (24) demonstrated that the outcome after stereotactic radiosurgery of glioma was dependent on specific selection criteria: younger patients (age <70) in good clinical condition (KPS >60) with smaller (<5 cm), unifocal, hemispheric, supratentorial, and subcortical tumors had a better prognosis. In a similar way, these selection criteria are reflected in the RPA classification. Curran et al. (12) established clinical prognostic classes through recursive partitioning analysis of 1578 patients from 3 consecutive RTOG trials. Patients younger than 50 years were categorized by histology (astrocytomas with anaplastic or atypical foci vs. glioblastoma multiforme) and subsequently by normal or abnormal mental status for patients with anaplastic or atypical foci and by performance status for those with glioblastoma multiforme. For patients 50 years of age or older, performance status was the most important variable, and in the poorer performance status group the mental status created the only significant split.

However, it has to be emphasized that these criteria only generate outcome classes for scientific comparison, not selection classes for differential treatment options. The present study used the RPA criteria to facilitate categorization and comparison of outcome. However, the reported number of patients represents 1 of the 3 largest cohorts of patients with recurrent malignant gliomas treated with stereotactic radiosurgery but is definitely too small to reliably define

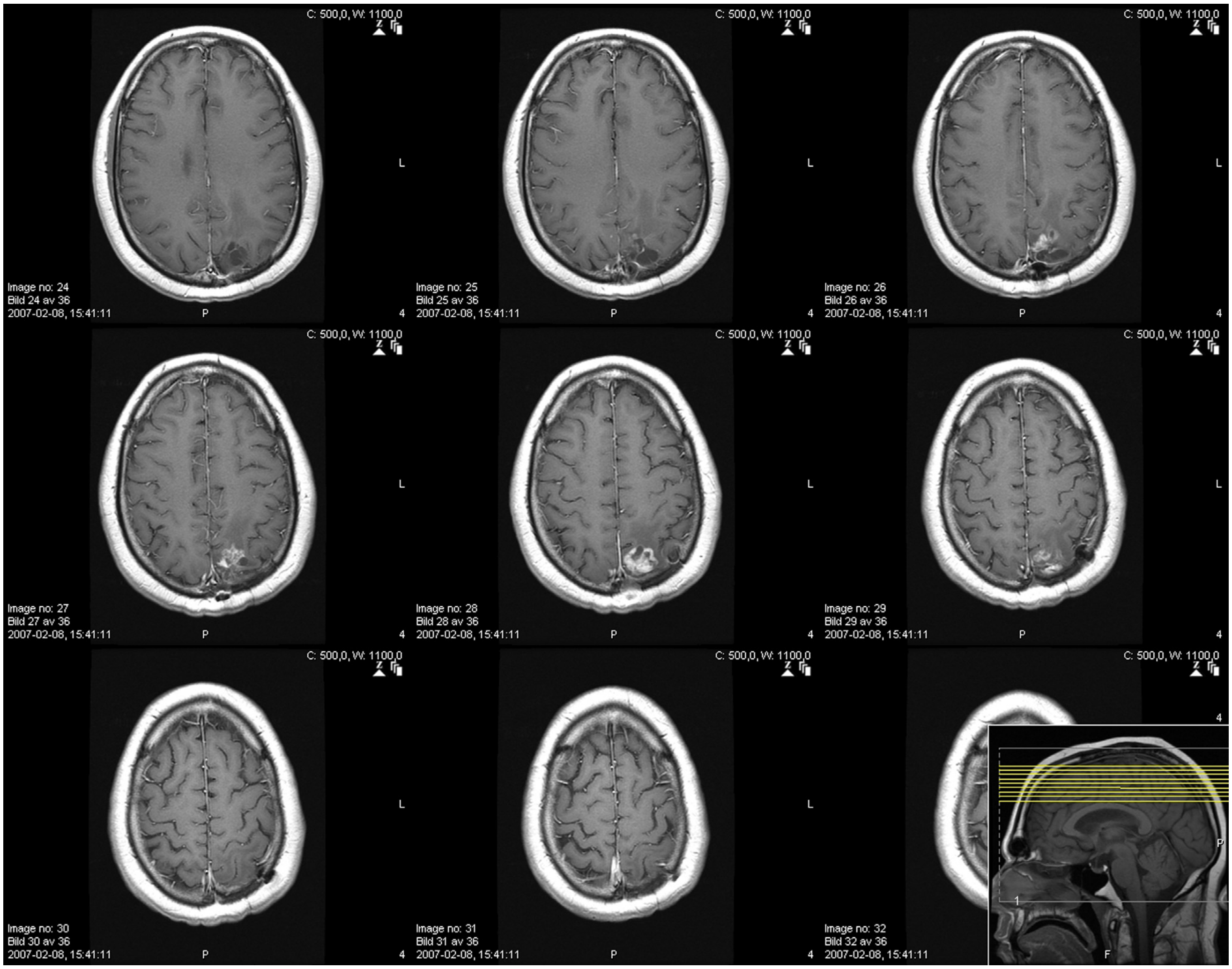

Figure 5. Follow-up magnetic resonance imaging; February 2007.

further selection criteria for clinical and prognostic subcategorization.

Independently, if patients with glioblastoma recurrences fulfill the various outcome criteria, tumor recurrences after standard treatment constitute a major therapeutic dilemma that cannot be solved by established therapies. The median survival time after reoperation of recurrent glioblastoma can be estimated with 3.5–9 months (8, 9, 22, 36), but the prerequisite for a reoperation is a good preoperative clinical condition (KPS > 60) (13). A study at the Memorial Sloan-Kettering Cancer Center with recurrent glioblastoma showed that the median overall survival after progressive disease on bevacizumab was 4.5 months (43). Repeated conventional fractionated radiotherapy is generally not feasible.

Hence the aim of the current study was rather to define the feasibility for radiosurgery of recurrent glioma as late salvage treatment and definition of criteria for radiosurgical options rather than the proof of superiority compared with other therapies.

The present outcome in terms of survival allows a promising prospect and would justify a prospective trial. Using a LINAC for a fractionated stereotactic conformal radiotherapy boost, Balducci et al. (2) showed promising results performing a salvage therapy treatment for patients with recurrences of high-grade glioma. Similarly, Biswas et al. (4) and Combs et al. (11) showed encouraging results with the use of LINAC-based concepts. A benefit for these patients seems achievable with various radiation treatment modalities and regimes and is clearly not exclusively reserved for stereotactic radiosurgery or GKRS.

In the present series, patients classified according to RPA 1 and 2 showed a highly interesting survival rate both after diagnosis and after the Gamma Knife procedure. RPA 1 with a median survival of 52.5 months after diagnosis and 25.3 months after GKRS and RPA 2 of 61.2 and 32.8 months, respectively. Stratification of patients according to the RPA classification system could prove as a valuable instrument for the selection of patients for

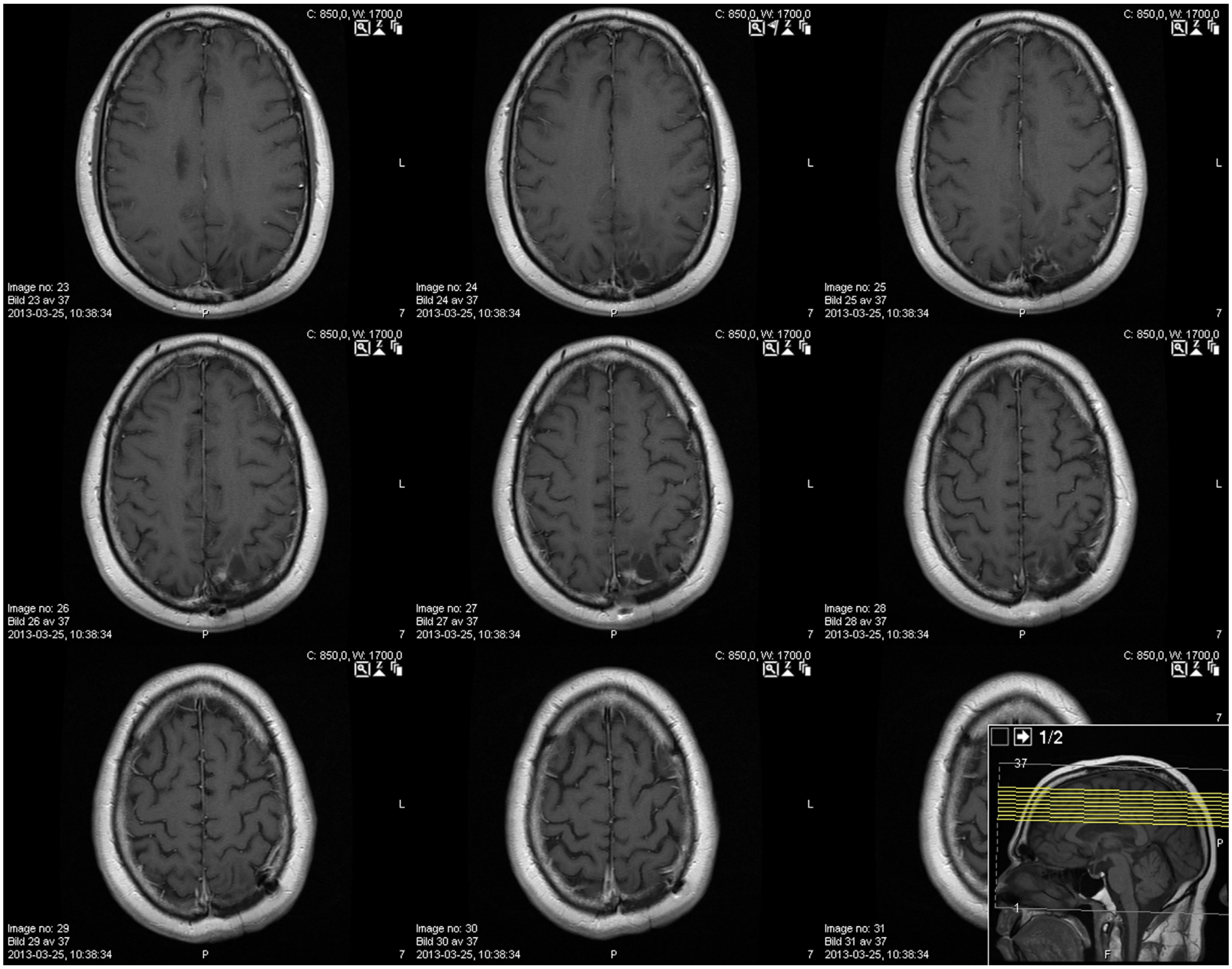

Figure 6. Follow up magnetic resonance imaging; March 2013.

delayed gamma knife surgery. Comparably with the present feasibility study, Hsieh et al. (20) demonstrated a significant survival benefit in patients with RPA class III and IV when they applied GKRS as an adjuvant therapy in glioblastoma recurrences compared with historical controls (36). The present study confirms a beneficial effect of GKRS in the treatment of malignant glioma WHO III and IV. A median overall survival from the initial diagnosis of 24.5 months for WHO grade IV patients and 49.6 months for grade III patients enable these results to range well within the promising results of further studies in which authors use radiosurgery in the treatment of high-grade glioma. The delayed timing of the radiosurgical procedure, as opposed to earlier studies as well as aiming specifically at local recurrences, plays a crucial role in administering GKRS.

The study's promising results must be interpreted with care because both its small patient population as well as its lack of a randomized setting requires larger and prospective study settings that may confirm these preliminary results. The current study shows a feasible way of integrating GKRS into established therapy strategies. The potential to induce AREs is a known phenomenon in radiosurgery (3, 5-7, 14-18) and has to be thoroughly assessed in the current indications. A total of 40% of all treated patients in this study developed AREs, representing a risk much greater than previously reported in other publications. The patients of the current study suffered clinical "impact," meaning symptoms related to their anatomical localization in 37% of the ARE cases. However, most of the patients' symptoms could be controlled with transitory low amounts of corticosteroids. Specifically, in view of these patients limited expected, survival the phenomenon of AREs plays an important role in the physician's discussion with the patient as well as in a quest for reducing the

Table 7. Overview of Various Studies in Which Authors Used Radiosurgery for High-Grade Glioma

Author	Modality	Pathology	Patients, n	Median Age, Years	KPS	Tumor, mL	Median Prescription Dose, Gy	Median OS from Diagnosis, Months	Median OS from Radiosurgery, Months
Skeie et al., 2012 (39)	GKRS	WHO IV	32	51	73	12.4	12.2	19	12
	GKRS + Re-Op		19	50	81	13.9	12.2	19	12
Pouratian et al., 2009 (34)	GKRS	WHO IV	48	61	80	14.4	—	16.2	—
Kong et al., 2008 (23)	SRS LINAC + GKRS	WHO IV	65	49	60	10.6	16 (SRS) 60 (initial)	23	13
		WHO III	49	49	60	10.6	16 (SRS) 60 (initial)	37.5	26
Hsieh et al., 2005 (20)	GKRS upfront	WHO IV	25	—	—	13.6	12	10	—
	GKRS at recurrence	WHO IV	26	—	—	13.6	12	16.7	—
Souhami et al., 2004 (41)	EBRT + BCNU	WHO IV	97	55.5 mean	> 60	4.0	—	—	13.6
	SRS upfront + EBRT + BCNU	WHO IV	89	56.4 mean	> 60	4.0	15, 18, 20	—	13.5
Nwokedi et al., 2002 (29)	EBRT	WHO IV	33	—	—	—	59	12	—
	EBRT + GKRS boost	WHO IV	31	—	—	18.5	17.1	25	—
Larson et al., 2002 (24)	GKRS	WHO IV	39	50	90	9.1	16	11	—
	GKRS + Marimastat	WHO IV	14	53	90	8.0	15	9.5	—
	GKRS	WHO III	15	35	90	6.0	17	14.8	—
	GKRS + Marimastat	WHO III	12	44	90	2.7	16.5	17	—
Kondziolka et al., 1997 (22)	GKRS	WHO IV	64	51	90	6.5 mean	15.5	26	21
	GKRS	WHO III	43	45	90	6.0 mean	15.2	32	16
Karolinska, 2014	GKRS	WHO IV	35	51.1	> 70	24	20	24.5	11.3
	GKRS	WHO III	20	51.1	> 70	31.2	20	55.1	31.3

KPS, Karnofsky Performance Scale; OS, overall survival; GKRS, Gamma Knife radiosurgery; Re-Op, reoperation; WHO, World Health Organization; SRS, stereotactic radiosurgery; LINAC, linear accelerator; EBRT, external beam radiation therapy; BCNU, *bis*-chloroethylnitrosourea.

probability of inducing this side effect. This very important factor of radiosurgery in the current context will be discussed at length elsewhere.

CONCLUSIONS

The present data indicate that GKRS could be feasible for a subset of patients with recurrent malignant gliomas in as addition to standard therapy when other treatment options appear unavailable. Rather than an alternative, Gamma Knife radiosurgery could have an integrated role in comprehensive treatment concepts. A promising outcome can be achieved if GKRS is used in combination with the classical standard management specifically timed and aimed at treating local recurrences. Further prospective studies will further identify the patient population that may benefit most in this context.

REFERENCES

1. Anker CJ, Hymas RV, Hazard LJ, Boucher KM, Jensen RL, Shrieve DC: Stereotactic radiosurgery eligibility and selection bias in the treatment of glioblastoma multiforme. J Neurooncol 98: 253-263, 2010.
2. Balducci M, Apicella G, Manfrida S, Mangiola A, Fiorentino A, Azario L, et al: Einarmige Phase-II-Studie zur konformalen Strahlentherapie mit Temozolomid plus fraktionierter stereotaktischer konformaler Boostbestrahlung bei höhergradigen Gliomen. Abschlussbericht. Strahlentherapie Und Onkologie 186:558-564, 2010.
3. Becker KP, Yu J: Status quo—standard-of-care medical and radiation therapy for glioblastoma. Cancer J 18:12, 2012.
4. Biswas T, Okunieff P, Schell MC, Smudzin T, Pilcher WH, Bakos RS, Vates GE, Walter KA, Wensel A, Korones DN, Milano MT: Stereotactic radiosurgery for glioblastoma: retrospective analysis. Radiat Oncol 4:11, http://dx.doi.org/10.1186/1748-717X-4-11, 2009.
5. Chamberlain MC, Barba D, Kormanik P, Shea WM: Stereotactic radiosurgery for recurrent gliomas. Cancer 74:1342-1347, 1994.
6. Chamberlain MC, Lassman AB, Iwamoto FM: Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. Neurology 74:1239-1241, 2010.
7. Chang JE, Khuntia D, Robins HI, Mehta MP: Radiotherapy and radiosensitizers in the treatment of glioblastoma multiforme. Clin Adv Hematol Oncol 5:894-902; 907-915, 2007.
8. Clavier JB, Voirin J, Kehrli P, Noël G: Systematic review of stereotactic radiotherapy for high-grade gliomas. Cancer/Radiothérapie 14:739-754, 2010.
9. Coffey RJ: Boost gamma knife radiosurgery in the treatment of primary glial tumors. Stereotact Funct Neurosurg 61:59-64, 1993.
10. Combs SE: Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. J Clin Oncol 23:8863-8869, 2005.
11. Combs SE, Gutwein S, Thilmann C, Debus J, Schulz-Ertner D: Reirradiation of recurrent WHO grade III astrocytomas using fractionated stereotactic radiotherapy (FSRT). Strahlenther Onkol 181:768-773, 2005.
12. Combs SE, Widmer V, Thilmann C, Hof H, Debus J, Schulz-Ertner D: Stereotactic radiosurgery (SRS). Cancer 104:2168-2173, 2005.
13. Costa BM, Caeiro C, Guimarães I, Martinho O, Jaraquemada T, Augusto I, Castro L, Osório L, Linhares P, Honavar M, Resende M, Braga F, Silva A, Pardal F, Amorim J, Nabiço R, Almeida R, Alegria C, Pires M, Pinheiro C, Carvalho E, Lopes JM, Costa P, Damasceno M, Reis RM: Prognostic value of MGMT promoter methylation in glioblastoma patients treated with temozolomide-based chemoradiation: A Portuguese multicentre study. Oncol Rep 23, 2010.
14. Crowley RW, Pouratian N, Sheehan JP: Gamma knife surgery for glioblastoma multiforme. Neurosurg Focus 20:E17, 2006.
15. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, As-bell SO, Krisch RE: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 85:704-710, 1993.
16. Dobelbower MC, Burnett OL III, Nordal RA, Nabors LB, Markert JM, Hyatt MD, Fiveash JB: Patterns of failure for glioblastoma multiforme following concurrent radiation and temozolomide. J Med Imaging and Radiat Oncol 55:77-81, 2011.
17. Einstein DB, Wessels B, Bangert B, Fu P, Nelson AD, Cohen M, Sagar S, Lewin J, Sloan A, Zheng Y, Williams J, Colussi V, Vinkler R, Maciunas R: Phase II trial of radiosurgery to magnetic resonance spectroscopy–defined high-risk tumor volumes in patients with glioblastoma multiforme. Int J Radiat Oncol Biol Phys 84:668-674, 2012.
18. 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 76:128-140, 2011.
19. Fiveash JB, Spencer SA: Role of radiation therapy and radiosurgery in glioblastoma multiforme. Cancer J 9:222-229, 2003.
20. Flickinger JC, Kano H, Niranjan A, Kondziolka D, Lunsford LD: Dose selection in stereotactic radiosurgery. In: Krayenbühl H, ed. Progress in Neurological Surgery, Vol. 27. Basel: Karger AG; 2012:49-57.
21. Fogh SE, Andrews DW, Glass J, Curran W, Glass C, Champ C, Evans JJ, Hyslop T, Pequignot E, Downes B, Comber E, Maltenfort M, Dicker AP, Werner-Wasik M: Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. J Clin Oncol 28:3048-3053, 2010.
22. Gorlia T, Stupp R, Brandes AA, Rampling RR, Fumoleau P, Dittrich C, Campone MM, Twelves CC, Raymond E, Hegi ME, Lacombe D, van den Bent MJ: New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: A pooled analysis of EORTC Brain Tumour Group phase I and II clinical trials. Eur J Cancer 48: 1176-1184, 2012.
23. 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 57:684-692, 2005.
24. Iwamoto FM, Abrey LE, Beal K, Gutin PH, Rosenblum MK, Reuter VE, DeAngelis LM, Lassman AB: Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. Neurology 73:1200-1206, 2009.
25. Kondziolka D, Flickinger JC, Bissonette DJ, Bozik M, Lunsford LD: Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasms. Neurosurgery 41:776, 1997.
26. Kong D-S, Lee J-I, Park K, Kim JH, Lim D-H, Nam D-H: Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. Cancer 112:2046-2051, 2008.
27. Larson DA, Prados M, Lamborn KR, Smith V, Sneed Penny K, Chang S, Nicholas KM, Wara WM, Devriendt D, Kunwar S, Berger M, McDermott MW: Phase II study of high central dose Gamma Knife radiosurgery and marimastat in patients with recurrent malignant glioma. Int J Radiat Oncol Biol Phys 54:1397-1404, 2002.
28. Li J, Wang M, Won M, Shaw Edward G, Coughlin C, Curran WJ Jr, Mehta MP: Validation and simplification of the radiation therapy oncology group recursive partitioning analysis classification for glioblastoma. Int J Radiat Oncol Biol Phys 81:623-630, 2011.
29. Loeffler JS, Shrieve DC, Alexander E: Radiosurgery for glioblastoma multiforme: the importance of selection criteria. Int J Radiat Oncol Biol Phys 30:731-733, 1994.
30. Lustig RA, Scott CB, Curran WJ: Does Stereotactic eligibility for the treatment of glioblastoma cause selection bias in randomized studies? Am J Clin Oncol 27:516-521, 2004.
31. Massey V, Wallner KE: Patterns of second recurrence of malignant astrocytomas. Int J Radiat Oncol Biol Phys 18:395-398, 1990.
32. Mirimanoff RO: Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. J Clin Oncol 24: 2563-2569, 2006.
33. Nwokedi EC, DiBiase SJ, Jabbour S, Herman J, Amin P, Chin LS: Gamma knife stereotactic

radiosurgery for patients with glioblastoma multiforme. Neurosurgery 50:41-47, 2002.

34. Oh J, Sahgal A, Sanghera P, Tsao MN, Davey P, Lam K, Symons S, Aviv R, Perry JR: Glioblastoma: patterns of recurrence and efficacy of salvage treatments. Can J Neurol Sci 38:621-625, 2011.

35. Pannullo SC, Fraser JF, Moliterno J, Cobb W, Stieg PE: Stereotactic radiosurgery: a meta-analysis of current therapeutic applications in neuro-oncologic disease. J Neurooncol 103:1-17, 2010.

36. Patel M, Siddiqui F, Jin J-Y, Mikkelsen T, Rosenblum M, Movsas B, Ryu S: Salvage reirradiation for recurrent glioblastoma with radiosurgery: radiographic response and improved survival. J Neurooncol 92:185-191, 2008.

37. Pouratian N, Crowley RW, Sherman JH, Jagannathan J, Sheehan JP: Gamma Knife radiosurgery after radiation therapy as an adjunctive treatment for glioblastoma. J Neurooncol 94: 409-418, 2009.

38. Rock K, Mcardle O, Forde P, Dunne M, Fitzpatrick D, O'Neill B, Faul C: A clinical review of treatment outcomes in glioblastoma multiforme—the validation in a non-trial population of the results of a randomised Phase III clinical trial: has a more radical approach improved survival? Br J Radiol 85:e729-e733, 2012.

39. Sarkaria JN, Mehta MP, Loeffler JS, Buatti JM, Chappell RJ, Levin AB, Alexander E 3rd, Friedman WA, Kinsella TJ: Radiosurgery in the initial management of malignant gliomas: survival comparison with the RTOG recursive partitioning analysis. Radiation Therapy Oncology Group. Int J Radiat Oncol 32:931-941, 1995.

40. Scott CB, Scarantino C, Urtasun R, Movsas B, Jones CU, Simpson JR, Fischbach AJ, Curran WJ Jr: 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 40:51-55, 1998.

41. Shrieve DC, Alexander E, Wen PY, Fine HA, Kooy HM, Black PM, Loeffler JS: Comparison of stereotactic radiosurgery and brachytherapy in the treatment of recurrent glioblastoma multiforme. Neurosurgery 36:275-282; discussion 282-284, 1995.

42. Skeie BS, Enger PØ, Brøgger J, Ganz JC, Thorsen F, Heggdal JI, Pedersen PH: Gamma Knife surgery versus reoperation for recurrent glioblastoma multiforme. World Neurosurg 78: 658-669, 2012.

43. Sneed PK, Gutin PH, Larson DA, Malec MK, Phillips TL, Prados MD, Scharfen CO, Weaver KA, Wara WM: Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. Int J Radiat Oncol Biol Phys 29: 719-727, 1994.

44. 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 60:853-860, 2004.

45. Stupp R, Hegi ME, van den Bent MJ, Mason WP, Weller M, Mirimanoff RO, Cairncross JG; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy GroupsNational Cancer Institute of Canada Clinical Trials Group: Changing paradigms—an update on the multidisciplinary management of malignant glioma. Oncologist 11:165-180, 2006.

46. Szeifert GT, Prasad D, Kamyrio T, Steiner M, Steiner LE: The role of the Gamma Knife in the management of cerebral astrocytomas. Prog Neurol Surg 20:150-163, 2007.

47. Wick W, Weller M, van den Bent M, Stupp R: Bevacizumab and Recurrent Malignant Gliomas: A European Perspective. J Clin Oncol 28:e188-e189, 2010.

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