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Gamma Knife Stereotactic Radiosurgery as Salvage Therapy After Failure of Whole-Brain Radiotherapy in Patients With Small-Cell Lung Cancer

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Abstract

Purpose—Radiosurgery has been successfully used in selected cases to avoid repeat whole-brain irradiation (WBI) in patients with multiple brain metastases of most solid tumor histological findings. Few data are available for the use of radiosurgery for small-cell lung cancer (SCLC).

Methods and Materials—Between November 1999 and June 2009, 51 patients with SCLC and previous WBI and new brain metastases were treated with GammaKnife stereotactic radiosurgery (GKSRS). A median dose of 18 Gy (range, 10–24 Gy) was prescribed to the margin of each metastasis. Patients were followed with serial imaging. Patient electronic records were reviewed to determine disease-related factors and clinical outcomes after GKSRS. Local and distant brain failure rates, overall survival, and likelihood of neurologic death were determined based on imaging results. The Kaplan-Meier method was used to determine survival and local and distant brain control. Cox proportional hazard regression was performed to determine strength of association between disease-related factors and survival.

Results—Median survival time for the entire cohort was 5.9 months. Local control rates at 1 and 2 years were 57% and 34%, respectively. Distant brain failure rates at 1 and 2 years were 58% and 75%, respectively. Fifty-three percent of patients ultimately died of neurologic death. On multivariate analysis, patients with stable (hazard ratio [HR] = 2.89) or progressive (HR = 6.98) extracranial disease (ECD) had worse overall survival than patients without evidence of ECD (p = 0.00002). Concurrent chemotherapy improved local control (HR = 89; p = 0.006).

Conclusions—GKSRS represents a feasible salvage option in patients with SCLC and brain metastases for whom previous WBI has failed. The status of patients' ECD is a dominant factor predictive of overall survival. Local control may be inferior to that seen with other cancer histological results, although the use of concurrent chemotherapy may help to improve this.

Keywords

Small cell lung cancer; Brain metastases; Stereotactic radiosurgery

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Introduction

Whole-brain irradiation (WBI) is the standard therapy for treatment of the brain in small-cell lung cancer (SCLC), either in the prophylactic setting or with known brain metastases. The rationale for WBI is primarily due to the high incidence of brain metastases in SCLC and the increased likelihood of a diffuse failure pattern of brain metastases (1–3). Evidence suggests a modest survival benefit in the setting of both limited stage and extensive stage disease with the addition of prophylactic cranial irradiation (PCI) after complete or substantive partial response to treatment of the primary site (4, 5).

Despite the relative radio-responsive nature of SCLC, disease failure in the brain after previous WBI is not uncommon (4). Historically, salvage options in this setting are limited. Repeated WBI has been reported to be minimally effective in a limited number of patients with recurrent brain metastases of all histological results, and median survival time after reirradiation is short (6). Moreover, there is scant evidence regarding reirradiation of the whole brain for SCLC and few neurocognitive toxicity data for whole-brain reirradiation in general.

GammaKnife stereotactic radiosurgery (GKSRS) has been used successfully in the salvage setting for brain metastases in patients for whom WBI has failed (7). However, given the propensity of SCLC for multiple metastases, the benefit of focal reirradiation and the factors predictive of successful outcome are unknown. The potential to spare patients from high cumulative integral radiation doses of whole-brain reirradiation makes radiosurgical salvage a potentially attractive option to avoid the increased risk of neurocognitive decline. The possibility remains, however, for multiple brain failures outside the SRS-treated lesions, and the timing and pattern of such out of field failure are poorly defined.

At our institution, we have practiced a strategy of radiosurgical salvage of brain metastases in patients with SCLC for whom WBI has previously failed. Those with four or fewer brain metastases are offered radiosurgery for salvage; however, occasionally, patients with greater numbers of metastases have been treated. We report our single-institution series documenting the failure patterns of such an approach, as well as an analysis of the disease-related factors that may affect survival, to help determine which patients may warrant salvage radiosurgery with delay or avoidance of repeat WBI.

Methods and Materials

Data acquisition

This study was approved by the Wake Forest University Institutional Review Board. The Wake Forest University Medical Center GammaKnife Program Tumor Registry was searched for all patients who received GKSRS and had a diagnosis of SCLC. Two patients who did not previously receive WBI were excluded. Between November 1999 and June 2009, 51 GKSRS procedures were performed at Wake Forest University Baptist Medical Center in Winston-Salem, NC, on patients with SCLC with recurrent brain metastases for whom previous prophylactic or therapeutic WBI had failed. Clinical outcome measures were determined using the patients' electronic medical records and paper charts. Dosimetric data for radiosurgical treatment were obtained using archived plans from the Leksell GammaPlan treatment planning system (Elekta, Norcross, GA).

Patient characteristics

Patient characteristics are summarized in Table 1. FIfty-one patients with SCLC with brain metastases for whom previous WBI had failed were treated with salvage GKSRS. Seventeen

patients had been previously treated with PCI, while 34 patients had been treated with therapeutic WBI after having known brain metastases. Median time between previous WBI and salvage GKSRS was 8 months (range, 2–70 months). Patient factors, including age, histology, recursive partitioning analysis (RPA) class, status of primary and extracranial metastatic disease, and intervals between diagnosis and development of metastases, were all determined from electronic medical records. The RPA class was defined as per the Radiation Therapy Oncology Group (RTOG) analysis reported by Gaspar et al. (8). The status of extracranial disease (ECD) was categorized as “none,” "stable," or “progressive,” based on review of systemic imaging at the time of salvage radiosurgery. The extent of ECD was characterized as none, oligometastatic with or without visceral metastases, or widespread. Oligometastatic disease with visceral metastases was defined as ≤5 metastases, including involvement of the liver, lungs, kidneys, or adrenal glands. Oligometastatic disease without visceral metastases was defined as ≤5 nonbrain metastases in areas such as bone, chest, or pelvis without diffuse involvement of any one organ. Widespread metastatic disease included patients with >5 metastases or diffuse distant organ involvement. Significant time intervals that were recorded included time to development of first brain metastases after diagnosis of SCLC, time interval between WBI/PCI and brain failure, time interval between salvage radiosurgery and date of death, and time interval between salvage radiosurgery and either local or distant brain failure. The number of brain metastases was recorded and grouped as single, 2 to 4, and greater than 4.Chemotherapy data, including pre-GKSRS, concurrent, and post-GKSRS chemotherapy, were recorded. Patients who were heavily pretreated with chemotherapy prior to GKSRS were determined to be those who received greater than six cycles of a platinum-based doublet prior to GKSRS. Concurrent chemotherapy was defined as chemotherapy that occurred within 3 weeks of GKSRS.

Radiosurgical technique

After patients were evaluated by a radiation oncologist and neurosurgeon, they gave informed consent for GKSRS. Patients were treated with a Leksell model C unit (Elekta, Norcross, GA) prior to May 2009 and with a Leksell GammaKnife Perfexion unit (Elekta) thereafter. Prior to undergoing radiosurgery, the patient underwent high-resolution contrast-enhanced stereotactic magnetic resonance imaging (MRI) study of the brain. Treatment planning was performed using the Leksell GammaPlan treatment planning system (Elekta). A median dose of 18 Gy (range 10–24 Gy) was prescribed to the margin of each metastasis. Dose prescription was determined based upon size and volume of the metastasis, generally following the guidelines published by Shaw et al. (9) for single-fraction radiosurgical treatment of previously irradiated primary brain tumors and brain metastases.

Patient follow-up and further salvage

Patients were followed with repeat MRI of the brain 4 to 8 weeks after the initial GKSRS procedure and then approximately every 3 months thereafter. Distant brain failures were generally treated with repeat GKSRS, with repeat WBI reserved for patients with numerous distant brain failures or declining performance status. Local failure was defined as either a pathologically proven recurrence of SCLC within the GK treatment field or a combination of imaging and clinical characteristics of local treatment failure. Patients with suspected treatment failure were generally followed with serial imaging and treated conservatively with either steroid therapy or a combination of vitamin E and pentoxifylline prior to determination of a treatment failure. Imaging characteristics of treatment failure included serial increases in size of enhancement and/or increased perfusion on perfusion-weighted imaging. Events were considered treatment failures if they contributed to a neurologic cause of death.

Local failures were treated with surgical resection or repeat WBI or were observed until symptomatic. Steroid use and doses were recorded, and any reoperations for recurrent tumor and/or radiation necrosis were also recorded. A patient's date of death was determined either from the social security index or hospital electronic database.

Statistics

Kaplan-Meier analysis was performed to determine actuarial local control, distant brain control, and overall survival of our patient population. Local control was determined per treated lesion and also per patient (freedom from local failure). These two measures of local control were performed because patients commonly had more than one lesion, and the consequences of a single local failure in a patient with multiple lesions were often quite significant. Multivariate analysis was performed using stepwise Cox proportional hazard regression to determine relative value of factors that independently predicted for endpoints of survival, local control, and distant brain failure. Stepwise logistic regression was used to determine factors that predicted for lifetime likelihood of neurologic death. Multivariable models were built by *a priori* consideration of the factors for which data were gathered. Only variables with a p significance of ≤0.2 were entered into the multivariable model, and if factors did not reach a significance of 0.2 on stepwise regression, they were subsequently removed from the model.

Results

Survival

Median survival time of the entire cohort was 5.9 months. One-and 2-year overall survival rates were 24% and 15%, respectively. Kaplan-Meier plot for overall survival is shown in Figure 1. Multivariate analysis assessing factors that predicted for survival is depicted in Table 2. Multivariate analysis revealed that the status of ECD (stable or progressive vs. absent) at time of salvage GKSRS predicted for overall survival (stable, hazard ratio [HR] = 2.89; progressive, HR = 6.98, $p = 0.00002$). Patients with absent ECD at the time of initial salvage GKSRS had a median overall survival of 6.8 months. Finally, patients who received post-GKSRS chemotherapy also had better overall survival (HR = 3.00, $p = 0.01$).

Patterns of failure

Local control rates were determined per patient and per lesion by using the Kaplan-Meier method. One- and 2-year rates of actuarial freedom from local failure were 57% and 34%, respectively. One-and 2-year actuarial local control rates for each individual lesion were 54% and 40%, respectively. Figure 2 depicts Kaplan-Meier curves for freedom from local failure. Median time to local failure was 8.7 months. The proportion of patients who achieved local control until time of death was 79%. Figure 3 depicts imaging from a patient with local failure. Multivariate analysis showed that the use of concurrent chemotherapy (HR = 89, $p = 0.006$) predicted for improved local control. Greater than one brain metastasis also predicted for increased likelihood of local failure (HR = 118, $p = 0.02$). There was also a trend toward decreased local control with lower marginal doses (HR = 0.91 per Gy, $p = 0.08$).

The 1- and 2-year rates of actuarial freedom from distant brain failure were 42% and 25%, respectively. Median time to distant brain failure was 3 months. All 3 patients who were free of distant failure at 18 months had only a single metastasis at the time of GKSRS. Multivariate analysis revealed an increased risk of distant brain failure in patients who had a greater number of lesions at time of GKSRS (HR = 4.04 for 2–4 lesions, HR = 6.13 for >4 lesions, $p = 0.03$). There was, additionally, a nonstatistically significant trend toward increased distant brain failure for patients receiving PCI ($p = 0.12$).

The most common cause of death was neurologic (53%). Twenty-two percent of deaths were from distant extracranial metastatic disease, 20% from progression of the primary lung tumor, and 6% from intercurrent disease. While no factors statistically predicted for neurologic death on multivariate analysis, there was a trend in patients who received PCI (versus therapeutic WBI) for increased likelihood of neurologic death (HR = 4.28, $p = 0.06$). Eight of 12 patients who had previously received PCI died from neurologic death. Ten of 30 patients who received WBI for management of known brain metastases died from neurologic death. Seven of the patients receiving therapeutic WBI died of distant metastatic disease, while 6 of those patients died from their primary lung cancers. Moreover, lower minimal dose delivered to a lesion also trended toward statistical significance regarding the prediction of neurologic death (HR = 0.80, $p = 0.06$).

Toxicity

Three of 47 patients (6%) experienced significant toxicity after GKSRS. Two patients experienced symptomatic radiation necrosis. One patient required surgery for radionecrosis that appeared on imaging to be treatment failure, one patient was hospitalized for short-term intravenous steroid therapy, and one patient required long-term outpatient oral steroid therapy.

Discussion

The role of radiosurgery in patients with SCLC for whom prophylactic or therapeutic WBI has failed is controversial. Thus far, a single additional series has been published evaluating the efficacy of GKSRS in SCLC after WBI failure. In that series, the authors reported a median overall survival time of 18 months, with an overall local control rate of 81% (3). In our series, freedom from local failure was 57% at 1 year, which is substantially worse than that generally seen for brain metastases from other histological results, suggesting that recurrent SCLC may be inherently radioresistant despite an initial response to GKSRS. Previous series evaluating chest radiotherapy for SCLC have shown a propensity for local failure despite initial radioresponsiveness (10). The possibility of an insufficient marginal dose in several patients who experienced local treatment failure cannot be discounted. The median marginal dose used in the current series was 18 Gy. There was also a trend toward lower marginal doses that predicted both local failure ($p = 0.08$) and neurologic death ($p = 0.06$) on multivariate analysis, which suggests that larger tumors tend to cause failure more often, thus leading to neurologic death. A series from the Cleveland Clinic of patients with brain metastases of various histological results for whom previous WBI had failed demonstrated better local control with doses of at least 22 Gy (7). A prior bias at our institution may have been to deliver lower doses to brain metastases from SCLC, given its initial radioresponsiveness.

While repeated WBI is an option for treatment failures after WBI, the late toxicities of a single application of WBI have been well documented in the scientific literature (11, 12). Neurocognitive decline can be detected at 4 months after a single course of WBI (13), and the toxicities of WBI do not reach a plateau in either incidence or severity with time (14). These toxicities are likely to be worse in cases of repeated WBI, given the higher cumulative doses to the brain, but the tolerance to repeated WBI in the late setting is generally unknown, given the short median survival time of 4 months in these patients (6). Both cumulative dose and heavy pretreatment with chemotherapy have been implicated in worsening the toxicities of WBI (15). Moreover, patients with SCLC have been found to have baseline neurocognitive abnormalities even prior to WBI (16). While the median overall survival in the current series was 5.9 months, 24% of the population did survive for at least 12 months. It is for the patients with the possibility of extended survival that the potential benefit of radiosurgery in avoiding repeat WBI is the greatest.

The identification of factors that predict for improved survival in patients with SCLC with recurrent brain metastases will be critically important to the ability to assign patients to the proper salvage modality. The European Organization for Research and Treatment of Cancer (17) conducted a phase II trial of WBI for patients with SCLC and brain-only metastases and reported that this population commonly died from brain metastases or leptomeningeal carcinomatosis, suggesting that adequate control of central nervous system disease is an important factor relating to outcomes in this population. Moreover, identification of factors that predict death from brain disease may ultimately help to properly determine proper doses or modalities of treatment to be used. In this current series, the extent of ECD predicted overall survival, although all patients experienced a high likelihood of neurologic death. In the series published by Sheehan et al. (3), the interval between diagnosis of SCLC and development of brain metastases was the major factor that predicted for longer survival after salvage radiosurgery. There was a trend in patients in the current series that suggested that those patients who had previously received PCI were more likely to die from neurologic death than those who had previously received therapeutic WBI. This is likely because patients who previously received PCI were more likely to have had a lower burden of systemic disease, as PCI had until only recently been given to patients with limited stage disease who had achieved a response to chemotherapy (5). Patients receiving therapeutic WBI are likely to have a greater extracranial disease burden and have a greater competing risk of dying from systemic disease.

As the likelihood of neurologic death was high for this patient population in general, especially in patients with minimal systemic disease, improved treatment options are necessary. In our cohort, GKSRS alone appears to have conferred a higher rate of local failure with SCLC than with other metastatic tumor types. Approaches such as increased marginal radiosurgical dose, use of concurrent chemotherapy, or a combination of WBI with GKSRS boost may potentially be beneficial to optimize the therapeutic index. In the University of Pittsburgh's experience with SCLC patients with brain metastases, patients who received WBI with GKSRS boost had the most favorable outcomes compared to cohorts who received WBI or GKSRS alone (18). For repeated WBI, doses and doses per fraction would need to be decreased from that which is generally delivered when WBI is used as monotherapy for brain metastases. The finding from the current multivariate analysis that the use of concurrent chemotherapy improved GKSRS local control suggests that this approach could be used to improve the therapeutic ratio of radiosurgery for SCLC brain metastases. Prior studies of SCLC treated with concurrent chemotherapy and chest irradiation also showed improved outcomes because of a synergy between chemotherapy and radiation (19).

There were several limitations of this study. First, as a retrospective analysis, it was subject to biases and systematic error, and its conclusions should thus be limited to hypothesis generation. In addition, the relatively small number of patients and relative heterogeneity regarding patients who received prior PCI versus therapeutic WBI limit the statistical power of our analysis. The questions that will need to be addressed in future prospective trials will be the proper risk stratification of patients with metastatic brain disease from SCLC and the proper dose fractionations to be used for metastatic brain disease. The ongoing RTOG protocol 0813 trial assessing the relative benefit of hypofractionated radiotherapy in patients with early extensive stage SCLC may help to determine if either fractionating or dose-escalating radiotherapy to systemic metastases may improve local control rates. Prospective trials are obviously necessary for brain metastases as well, given the high rate of local failure and neurologic death.

Conclusions

GKSRS is a modestly effective salvage treatment option for patients with SCLC for whom previous prophylactic or therapeutic WBI has failed. Patients with absent or stable extracranial oligometastatic disease have improved survival times. Local control may be inferior to that seen with other cancer histological results.

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Summary

This is a retrospective review of patients with small-cell lung cancer who received radiosurgery for brain metastases. We have found that local failure rates are high, with the most common mode of death being neurologic. Multivariate analysis identified absent systemic disease as a predictor of survival, while patients receiving concurrent chemotherapy have improved local control. Results following radiosurgery are modest for small cell, although chemotherapy may improve outcomes in terms of local control and survival.

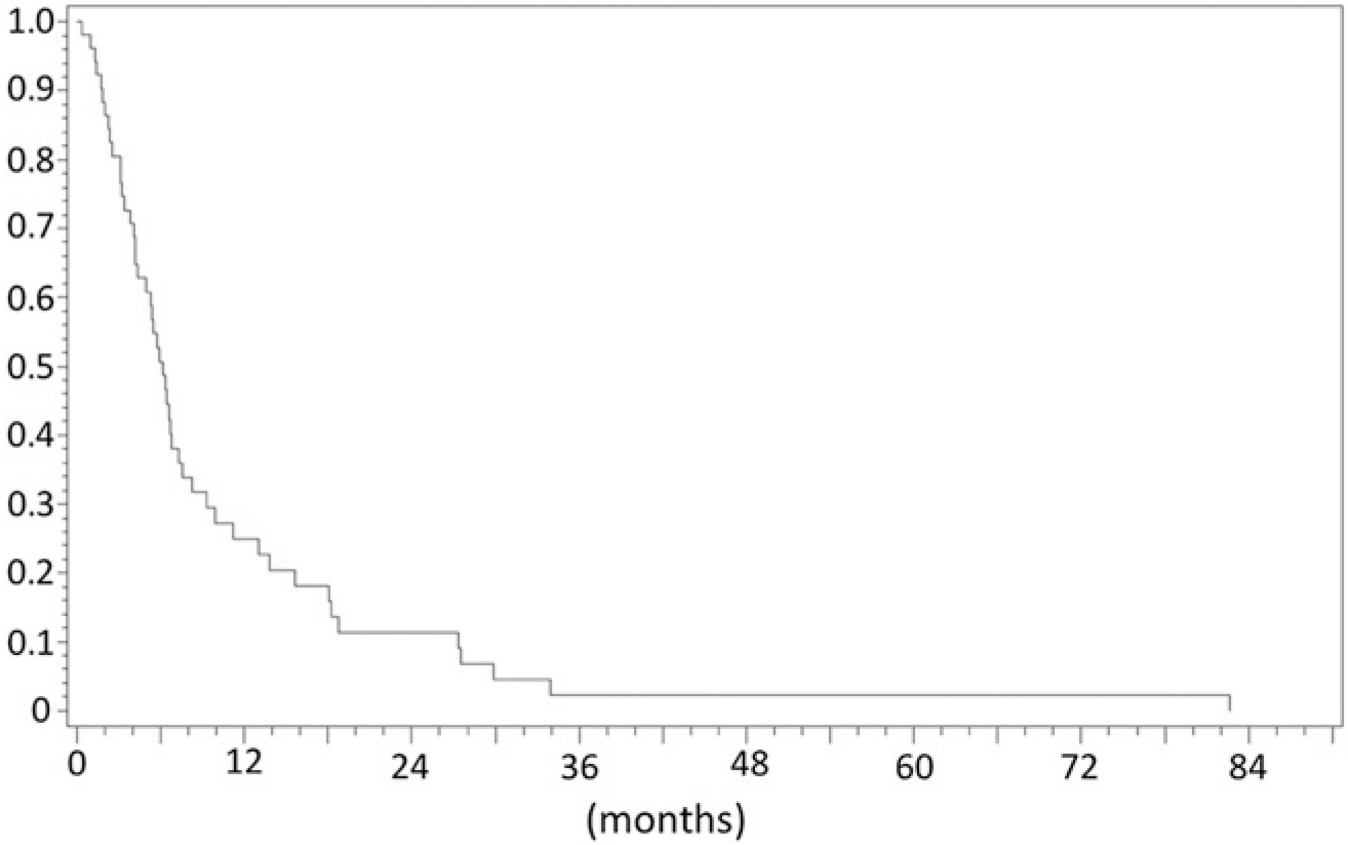

Fig. 1.
Kaplan-Meier plot of overall survival.

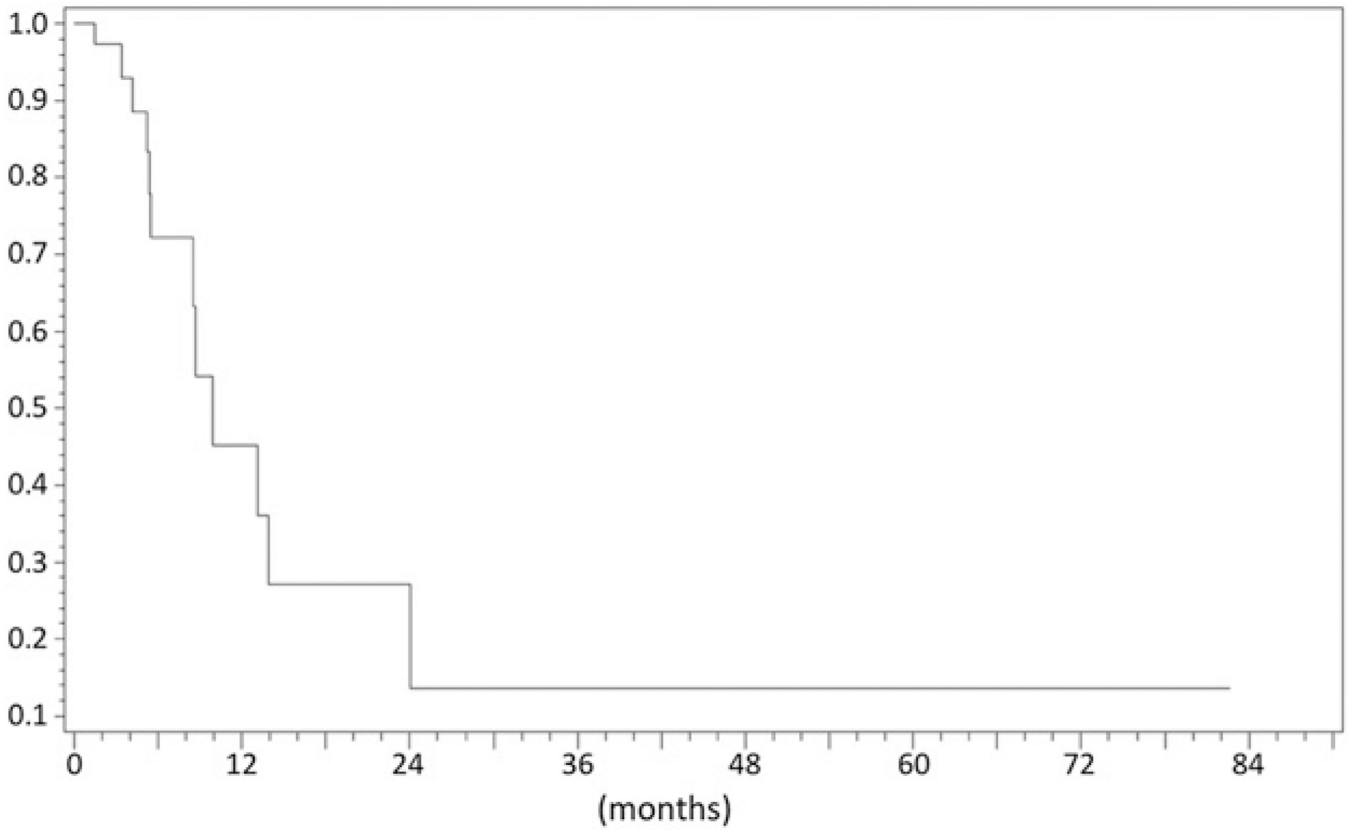

Fig. 2.
Kaplan-Meier plot of freedom from local failure.

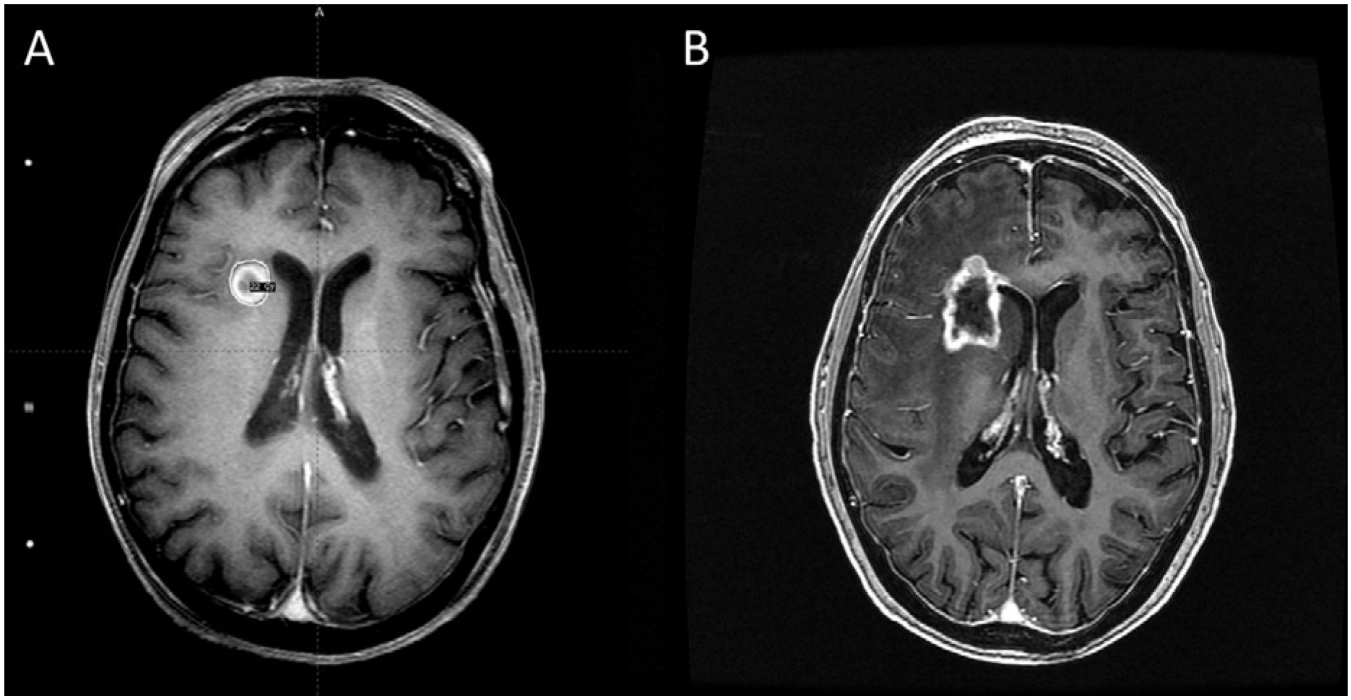

Fig. 3.
(A) Axial contrast-enhanced SPGR MRI sequence showing 50% isodose line from a GKSRS plan delivering 22 Gy to the margin of the metastasis. (B) Axial contrast-enhanced SPGR MRI sequence 6 months after GKSRS showing tumor recurrence within the high-dose region.

Table 1

Patient characteristics

Characteristic	No. of patients (range)	
	PCI	Therapeutic WBI
Total no. of patients	16	35
Median age (years)	64 (50–73)	60 (38–73)
Sex		
Female	11	23
Male	5	11
Status of extracranial disease		
Progressive	4	11
Stable	5	13
None	8	10
Unknown	1	0
Extent of extracranial disease		
None	7	10
Oligometastatic without visceral	6	15
Oligometastatic with visceral	2	6
Widespread	0	3
Unknown	1	0
Median time to GKSRS (months)	13.5 (7–42)	7 (range, 2–70)
Number of brain metastases		
1	7	15
2–4	6	12
>4	3	8
Mode of failure of previous brain irradiation		
Local failure of known brain metastases	0	20
Development of new brain metastases	16	9
Simultaneous local and distant failure	0	6
Salvage after further brain failure		
Craniotomy	2	2
Repeat GKSRS	5	5
Repeat WBI	11	
No further therapy	2	5
Chemotherapy		
>6 cycles of pre-GKSRS chemotherapy	4	10
Concurrent (yes)	0	9
Post-GKRS (yes)	2	12
Cause of death		
Neurologic	8	10
Primary disease	1	7

Characteristic	No. of patients (range)	
	PCI	Therapeutic WBI
Distant metastases	2	7
Intercurrent disease	1	1
Unknown	2	5
Alive	2	6

Abbreviations: GKSRS = GammaKnife stereotactic radiosurgery; PCI = prophylactic cranial irradiation; WBI = whole-brain irradiation.

Table 2

Multivariate analysis of factors affecting local control, distant control, overall survival and neurologic death

Multivariate factor	Hazard ratio (95% CI)	*p* value
Age	0.78 (0.65–0.93)	0.007
Sex		
Female	1.00*	0.10
Male	0.15 (0.02–1.40)	
Prior WBI		
Therapeutic	1.00*	0.15
PCI	3.97 (0.62–25.3)	
Concurrent GKSRS + chemotherapy		
Yes	1.00*	0.006
No	89.0 (2.12–3737)	
No. of brain metastases		
1	1.00*	0.02
2–4	118.1 (3.35–4156)	
5 or more	14.3 (1.24–165)	
Distant control		
Prior WBI		
Therapeutic	1.00*	0.12
PCI	2.29 (0.80–6.60)	
No. of brain metastases		
1	1.00*	0.03
2–4	4.04 (1.11–14.7)	
5 or more	6.13 (1.49–25.2)	
Overall survival		
Disease status		
None	1.00*	0.00002
Stable	2.89 (1.12–7.41)	
Progressive	6.98 (2.72–17.9)	
Post-GKSRS chemotherapy		
Yes	1.00*	0.01
No	3.00 (1.29–6.94)	
No. of brain metastases		
1	1.00*	0.07
2–4	1.86 (0.91–3.80)	
5 or more	2.94 (1.11–7.82)	
Minimal dose (per 1 Gy)	0.91 (0.82–1.01)	0.08
Neurologic death		
Prior WBI		

Multivariate factor	Hazard ratio (95% CI)	*p* value
Therapeutic	1.00 *	0.06
PCI	4.28 (0.94–19.6)	
Minimal dose (per 1 Gy)	0.80 (0.64–1.01)	0.06

Abbreviations: CI = confidence interval; GKSRS = GammaKnife stereotactic radiosurgery; PCI = prophylactic cranial irradiation; WBI = whole-brain irradiation.

* Reference values.