

Gamma knife surgery for brain metastases from lung cancer

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Object. The authors conducted a study to evaluate the safety and efficacy of gamma knife surgery (GKS) for the treatment of brain metastases from lung cancer.

Methods. Between February 1993 and May 2003 191 patients underwent treatment for 424 brain metastases from non-small (171 cases) and small cell lung carcinoma (20 cases). Imaging and clinical status were monitored every 3 months following the treatment. Kaplan–Meier survival curves, Cox proportional hazards regression for risk factor analysis, and nonparametric methods for evaluating tumor response were used.

There was no difference in median survival following combined whole-brain radiation therapy (WBRT) and gamma knife surgery (14 months) and GKS alone (15 months). There was also no difference between the median survival rates for either tumor type. In the multivariate analysis, age less than 65 years, Karnofsky Performance Scale score greater than 70, normal neurological status, multiple GKS treatments, and pre-GKS craniotomy were related to longer survival.

Tumor control rates varied according to the volume of the metastases and were as follows: 84.4% (< 0.5 cm³), 94% (0.5–2 cm³), 89.1% (2–4 cm³), 93.4% (4–8 cm³), 85.7% (8–14 cm³), and 87.5% (> 14 cm³). Four lesions required post-GKS craniotomy due to swelling or rapid tumor progression. The rate of tumor shrinkage was higher when a volume was 2 cm³, lower in cystic lesions, lower in tumors with previous WBRT, and lower for margin doses less than 14 Gy.

Conclusions. The risk–benefit ratio of GKS in this series was satisfactory. There was no difference in response rates of the two tumor types, and WBRT did not improve the duration of survival.

KEY WORDS • gamma knife surgery • brain metastases • small cell lung cancer • non-small cell lung cancer

BEFORE the advent of GKS, fractionated radiotherapy and resection were the mainstays of treatment for brain metastases. Now, GKS offers effective tumor control and a relatively long survival period for patients compared with the natural history of the disease. Moreover, it does so while causing minimal morbidity and essentially no deaths. Radiosurgery can be used to treat multiple metastases during the same procedure and permits treatment of deep deposits considered surgically inaccessible.^{3,4,8–11,16–18,20,23,24} To date, however, the influence of factors such as WBRT, tumor histology, tumor volume, patient age, preoperative KPS score, control of the primary disease, and the presence of extracranial metastatic disease on the outcome of lung carcinoma brain metastases after GKS remain the subject of debate.^{9,12,15,19,22,25}

The aim of this study was to evaluate the safety and efficacy of GKS in the treatment of cerebral metastases from lung cancer.

Abbreviations used in this paper: GKS = gamma knife surgery; KPS = Karnofsky Performance Scale; MR = magnetic resonance; WBRT = whole-brain radiation therapy.

Clinical Material and Methods

Patient Population

Between February 1993 and May 2003, 424 brain metastases in 191 patients with lung cancer were treated with GKS. Eighty-eight patients harbored a single lesion, 39 two lesions, and 64 more than three lesions. One hundred forty-one patients underwent one session of GKS; 40 two sessions; six three sessions; and four patients underwent four sessions. The median age of the patient population was 59 years (range 32–87 years). The median tumor volume per patient was 9.3 cm³ (range 0.04–68.1 cm³). One hundred three patients were men and 88 were women.

Clinical presentation included seizure in 40 patients and a focal neurological deficit in 41; neurological deficit was absent in 110. The median KPS score was 70 (range 40–100). The histological diagnosis included non-small cell carcinoma (171 patients) and small cell carcinoma (20 patients). One hundred forty-two patients received the combined treatment of WBRT and GKS, whereas 49 patients underwent GKS alone. The median time interval between WBRT and GKS was 2 months (0–36 months). Table 1

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TABLE 1
Summary of clinical data

Characteristic	No. of Cases (%)
status	
deceased	168 (88)
alive	23 (12)
lung radiotherapy	
yes	103 (54)
no	88 (46)
chemotherapy	
yes	97 (51)
no	94 (49)
control of primary disease	
yes	97 (51)
no	94 (49)
other metastases	
yes	44 (23)
no	147 (67)
extensive lung op	
yes	74 (39)
no	117 (61)
no. of craniotomies	
1	43 (23)
2	4 (2)
0	144 (75)
post-GKS craniotomy	
yes	4 (2)
no	187 (98)

details additional information including control of the primary lung disease, presence/absence of extracranial metastases, history of radiotherapy of the lung, history of systemic chemotherapy, history of lung resection, pre-GKS craniotomy, and post-GKS craniotomy due to marked intracranial pressure.

Tumor Parameters

The brain metastases were widely distributed throughout the brain tissue as follows: 148 tumors in the frontal lobes; 43 in the temporal lobes; 86 in the parietal lobes; 65 in the occipital lobes; 17 in the brainstem; 20 in the thalamus; and 75 in the cerebellum. Tumors were divided into six groups according to their volume at the time of GKS: Group I, less than 0.5 cm³ (83 cases); Group II, 0.5 to 2 cm³ (132 cases); Group III, 2 to 4 cm³ (79 cases); Group IV, 4 to 8 cm³ (62 cases); Group V, 8 to 14 cm³ (43 cases); Group VI, greater than 14 cm³ (25 cases).

The mean tumor volume was 4.2 cm³ (range 0.01–56 cm³). The histologies were small cell carcinoma (39 lesions) and non-small cell carcinoma (385 lesions). Ten deposits were cystic and 414 were noncystic. Three hundred seventeen deposits were treated with both WBRT and GKS; 117 lesions were treated with GKS alone; and eight lesions were treated with repeated GKS when their volumes increased after the initial treatment.

Treatment Parameters

Gamma knife surgery was performed using the Leksell gamma unit (Model U; Elekta Instruments, Inc., Norcross, GA) before July 2001 and the Leksell gamma unit C after July 2001. All patients were treated by the senior author (L.S.).

Forty patients without a history of WBRT received pre-

TABLE 2
Tumor volume and response in 281 lesions*

Tumor Vol Group	Tumor Response Grade (%)					Total
	1	2	3	4	5	
I	25 (48.1)	13 (25)	1 (2)	5 (9.6)	8 (15.4)	52
II	24 (28.2)	29 (33.1)	24 (28.2)	3 (3.5)	5 (5.9)	85
III	4 (7.3)	23 (41.8)	14 (25.5)	8 (14.5)	6 (10.9)	55
IV	5 (11.1)	16 (35.5)	16 (35.5)	5 (11.1)	3 (6.6)	45
V	0 (0)	13 (46.4)	6 (21.4)	5 (17.8)	4 (14.3)	28
VI	0 (0)	4 (25)	7 (43.7)	3 (18.8)	2 (12.5)	16

* See text for definition of tumor volume group and response grade.

scription doses between 18 and 24 Gy; 142 patients with a history of WBRT received margin doses between 14 and 18 Gy. In three cases of repeated GKS for refractory brain metastases, the margin doses ranged from 3 to 6 Gy because of the previous WBRT and GKS. Overall, the mean maximum dose was 47 Gy (range 10–76.7 Gy), and the mean margin dose was 18 Gy (range 3–24 Gy). The mean treatment isodose was 40% (range 25–91%).

Follow-Up Imaging

Periodic follow-up neuroimaging was performed using MR imaging or with computerized tomography scanning when MR imaging was contraindicated; studies were obtained every 3 to 6 months following the treatment. The MR image slice thickness was 3 to 5 mm; imaging was performed with and without contrast medium. Tumor volumes were determined on MR images and compared with those obtained during GKS planning. We graded the tumor response according to the volume change as follows: Grade 1, tumor disappearance; Grade 2, more than 50% tumor volume decrease; Grade 3, volume change between –50 and –15%; Grade 4, volume change between –15 to +15%; and Grade 5, more than 15% volume increase.

Grades 1 to 4 were defined as tumor control, whereas Grade 5 was viewed as tumor progression. Postradiosurgical imaging studies were available for 281 of the 424 brain metastases.

Clinical Follow Up

The patients underwent regular neurological follow-up examination at 1- to 3-month intervals. Late-onset toxicities including delayed symptomatic edema, necrosis, and hemorrhage were assessed by physical examination and correlated with imaging findings. The causes of death were grouped as due to brain metastasis progression, any cause other than brain tumor progression, or unknown.

Statistical Analysis

The Kaplan–Meier survival analysis, Cox proportional hazards model for risk factor analysis, Mann–Whitney U-test for nonparametric independent two-group comparisons, and Kruskal–Wallis test for three or more independent samples comparisons were performed. The statistical analysis was performed with the aid of the software package SPSS 10.1.

Tumor Volumetry

Tumor volumes were measured using software devel-

TABLE 3
Summary of relative errors stratified by slice separation*

Variable	No. of Slices						
	1	2	3	4	5	6	7
>0.1 to <1 ml	1.4 (0.8)	13.0 (6.6)	30.5 (9.6)	75.6 (19.0)	78.4 (17.2)		
>1 to <5 ml	0.4 (0.3)	2.8 (1.5)	6.5 (2.8)	16.4 (8.2)	18.5 (5.9)	35.3 (10.9)	39.2 (6.9)
>5 to <10 ml	0.3 (0.5)	1.0 (0.7)	2.3 (1.4)	4.3 (2.0)	10.8 (5.5)	10.7 (4.5)	19.7 (5.1)
>10	0.2 (0.4)	0.6 (0.4)	1.7 (1.0)	3.5 (1.9)	5.1 (2.2)	7.6 (3.2)	11.6 (4.4)

* The values are presented in percentage of the mean relative error with standard deviations in parentheses.

oped at University of Virginia that allows calculation of volume without placing the patient in a head frame. The volumetry mean error and standard deviation as functions of slice separation are shown in Tables 3 and 4 (in Table 4, the slice separation is an implicit parameter that, together with the tumor size, influences the number of slices on which the tumor can be visualized). Given the margin of error in this volumetry methodology, at present we consider a change to be significant only if the magnitude of this change is at least 15% of the GKS treatment volume.

Results

Clinical Outcome

Duration of Survival. The overall median survival of all patients with brain metastasis in this study was 14 months (range 12–16 months). The median survival for those receiving both WBRT and GKS and those receiving GKS alone was 14 months (range 8–22 months) and 15 months (range 11–17 months), respectively. The 1-month difference in median survival was not statistically significant ($p = 0.574$). The median survival in patients with non-small cell and in small cell carcinoma was 14 months (range 12–16 months) and 16 months (range 9–23 months), respectively. Again, this difference in median survival was not statistically significant ($p = 0.831$).

The median survival of patients 65 years of age or older and those younger than 65 years of age was 8 months (range 5–11 months) and 16 months (range 13–19 months), respectively. The median survival was 12 months (range 8–16 months) for patients with KPS scores less than 70 and 16 months (range 13–19 months) for those with KPS scores greater than or equal to 70. The median survival for patients with or without preexisting neurological deficits was 12 months (range 8–16 months) and 15 months (12–18 months), respectively. The median survival according to the

numbers of treatments was 12 months (range 9–15 months) for one GKS and 19 months (range 15–23 months) for more than one GKS. The median survival for patients with and without a history of craniotomy was 19 months (range 15–23 months) and 12 months (range 9–15 months), respectively. Patients with well-controlled lung disease had a median survival of 18 months (range 15–21 months), whereas those with poor control of the primary carcinoma had a median survival of 10 months (range 8–12 months). In patients with or without extracranial metastases the median survival was 10 months (range 7–13 months) and 16 months (range 13–19 months), respectively. In multivariate analysis, only the combined factors of age (< 65 years) ($p = 0.028$), KPS score (≥ 70) ($p = 0.029$), absent preexisting neurological deficits ($p = 0.018$), more than one GKS treatment ($p = 0.002$), and a craniotomy before GKS ($p = 0.03$) correlated significantly with increased survival.

There were no direct complications related to GKS. Of 168 patients who died during the follow-up period, the cause of death was extracranial disease-related in 152 patients (90%) and related to intracranial disease progression in 16 patients (10%).

Imaging Outcome

The median MR imaging follow-up period was 6 months (range 3–63 months). Statistical analysis revealed that the following factors correlated with tumor shrinkage: a tumor volume less than 2 cm³ ($p = 0.005$); absence of a cystic portion associated with the brain metastasis ($p = 0.046$); a margin dose greater than 14 Gy ($p = 0.022$); and no history of WBRT ($p = 0.039$).

Tumor Response Related to Volume

Table 2 demonstrates the relationship between tumor shrinkage and tumor volume. Forty-nine (35.8%) of 137 tumors in which the volume was less than 2 cm³ disap-

TABLE 4
Summary of relative errors stratified by slice separation*

Variable	No. of Slices						
	7	6	5	4	3	2	1
>0.1 to <1 ml	3.5 (1.3)	5.1 (1.5)	6.4 (1.8)	11.4 (2.4)	21.2 (3.6)	43.1 (4.9)	93.1 (0.7)
>1 to <5 ml	1.8 (0.8)	3.6 (0.5)	4.3 (0.6)	9.6 (2.2)	19.0 (2.6)	40.9 (6.4)	86.7 (1.6)
>5 to <10 ml	3.5 (1.2)	4.1 (1.2)	7.2 (2.5)	13.1 (3.2)	22.9 (2.4)		
>10 ml	4.4 (1.6)	5.1 (1.6)	8.1 (2.0)	13.5 (2.2)	25.4 (1.0)		

* The values are presented in percentage of the mean relative error with standard deviations in parentheses.

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peared, 67 (48.9%) decreased in size, eight (5.8%) remained unchanged in size, and 13 (9.5%) increased in size. Nine (6.3%) of 144 lesions in which the volume was greater than or equal to 2 cm³ disappeared, whereas 109 (76%) decreased in size, 23 (16%) remained unchanged, and 15 (10%) increased. The shrinkage rate was significantly different between tumor volumes greater than or equal to 2 cm³ and those less than 2 cm³ ($p = 0.008$).

Tumor Control Related to Follow-Up Duration

The tumor control rates were 88.9, 80.5, 81, and 91% at 3, 6, 9, and 12 months, respectively; the numbers of lesions that could be analyzed were 281, 159, 100, and 59, respectively, at these time intervals. Thirty (10.7%) of 281 lesions initially exhibited a favorable response, but they later progressed at a median follow-up period of 9 months (range 3–54 months). Four of these lesions ultimately required a craniotomy due to brain edema and rapid tumor growth.

Disease control was achieved in 44 (84.6%) of 52 tumors in which the volume was less than 0.5 cm³, 80 (94.1%) of 85 with volumes between 0.5 and 2 cm³, 49 (89%) of 55 with volumes between 2 and 4 cm³, 42 (93%) of 45 with volumes between 4 and 8 cm³, 24 (85.7%) of 28 with volumes between 8 and 14 cm³, and 14 (87.5%) of 16 with volumes greater than 14 cm³. There was no statistically significant difference in the tumor control between the aforementioned tumor volume subgroups ($p = 0.314$).

Results in Lesions Treated With and Without WBRT

There were 201 lesions treated with both WBRT and GKS; 80 lesions were treated with GKS alone. In the latter, 21 (26%) of 80 lesions disappeared, 47 (58.5%) decreased in size, four (5%) remained unchanged, and eight (10%) increased in size. Following both WBRT and GKS, 38 (18.9%) of 201 lesions disappeared, 88 (58%) decreased in size, 25 (12.4%) remained unchanged, and 20 (10%) increased in size. Statistical analysis revealed a higher rate of tumor shrinkage (volume decrease > 15%) in lesions treated without WBRT compared with those receiving both treatments ($p = 0.039$). Seventy-two lesions (90%) following the GKS alone disappeared, shrank, or remained unchanged.

Tumor Response After Repeated GKS

In seven lesions, a second GKS was conducted because of tumor progression. In this retreated group, the mean tumor volume treated was 4 cm³ (range 1–12.6 cm³); the mean margin and maximum doses were 13.7 Gy and 30.5 Gy (range 10–53.3 Gy), respectively. One lesion (14%) disappeared, three (42.6%) decreased in size, and three (43%) increased further.

Margin Dose and Tumor Response

Of 20 lesions receiving a margin dose less than 14 Gy one (5%) disappeared, 12 (60%) decreased in size, four (20%) remained unchanged, and three (15%) increased in size. Margin doses between 14 and 18 Gy resulted in the disappearance of 41 (21%) of 197 lesions, a decrease in 118 (59.9%), no change in 20 (10.2%), and progression in 18 (9.1%). Margin doses greater than 18 Gy resulted in a dis-

appearance in 17 (26.6%) of 64 lesions, a decrease in 35 (46.8%), no change in five (7.8%), and an increase in seven (11%). The rate of tumor shrinkage was significantly better ($p = 0.022$) when peripheral doses were greater than or equal to 14 Gy compared with when the margin dose was less than 14 Gy. The tumor control rates by margin dose were as follows: less than 14 Gy, 85.9%; 14 to 18 Gy, 90.9%; and greater than 18 Gy, 89%.

Cystic Lesions Treated With GKS

Nine lesions had an additional cystic component in which the mean volume was 8.3 cm³ (1.2–23 cm³). Five (55%) of nine cystic tumors in which the mean volume was 4.6 cm³ (range 1.2–9.1 cm³) did shrink. Four (44%) lesions in which the mean volume was 13 cm³ (range 6.5–22 cm³) remained stable or increased.

Discussion

Role of WBRT for Brain Metastases

At present, the role of WBRT in the treatment of brain metastases is the subject of debate.^{3,4,10,16,20,24} It appears that GKS alone or used in combination with WBRT results in longer patient survival times than WBRT alone.^{4,8,10,12,16} The efficacy of adding WBRT to GKS in the treatment of brain metastases is being investigated in a multicenter study by the American College of Surgeons. Chen, et al.,³ have reported that the only added benefit of WBRT seems to be that it can reduce the incidence of new brain metastases and decrease the number of repeated GKS sessions, but its addition to radiosurgery does not favorably affect survival. Li, et al.,¹² found that the combined treatment compared with GKS alone does not significantly improve survival, local tumor control, or quality of life. In our study, the tumor control rate was the same (90%) for both the combined treatments and for GKS alone. The reduced tumor shrinkage rate observed in the combined subgroup was likely due to more advanced intracranial disease. The difference in the median survival of 15 months for GKS alone and 14 months for the combined of WBRT/GKS was statistically not significant.

Survival and Prognostic Factors

The median survival of patients with small cell lung carcinoma metastases in the brain is reportedly approximately 2 to 6 months after WBRT alone,² whereas it is longer following GKS.^{4,9,12,20,22} In our series, the median survival times were 14 months in patients with non-small cell brain metastases and 16 months in those with small cell carcinoma brain metastases.

It has been reported that the survival of patients with brain metastases from lung cancer after radiosurgery is related to age, neurological symptoms, KPS score, control of primary disease, resection of the lung lesion, number of new lesions, tumor volume, and histological type.^{9,15,19,22} In our multivariate analysis, we found that patients with age less than 65 years, a KPS score higher than or equal to 70, no preexisting neurological deficits, multiple GKS sessions, and a prior craniotomy survived longer. There was no sig-

nificant survival difference with respect to histological subtype or previous WBRT.

Volume and Tumor Response

The tumor shrinkage rate strongly correlated with size less than 2 cm³, absence of a cystic component, no prior WBRT, and a high peripheral dose (≥ 14 Gy). Usually, it is assumed that patients with lesions less than 3 cm (that is, volume < 14 cm³) are good candidates for GKS.^{1,7,14} In the present series, 36% of tumors in which volumes were less than 0.5 cm³, 28.6% between 0.5 to 2 cm³, and 7.3% between 2 and 4 cm³ disappeared after GKS. There was no evidence of complete tumor disappearance in those in which volume was larger than 8 cm³. Thirty-seven percent of tumors less than 2 cm³ and 6.3 % of those greater than or equal to 2 cm³ disappeared. Sixty-nine percent of tumors whose volumes were greater than 14 cm³ decreased in size, 18.8% remained unchanged, and 12.5% increased in size. The question concerning whether volume has any substantial impact on tumor outcome following GKS remains to be answered.

Tumor Control Rate

The tumor control rate in brain metastases reported in the literatures ranges from 62.3 to 98%.^{8-10,17,18,20,22,25} In our series, the tumor control rates were 88.9, 80.5, 81, and 91.5 at 3, 6, 9, and 12 months, respectively. Nevertheless, only 279 (100%), 159 (57%), 100 (36)%, and 59 (21%) lesions were assessed at 3, 6, 9, and 12 months, respectively, because of the progressive loss of follow-up data, which was due to extracranial causes of death for 90% of these lesions and due to intracranial causes of death for 10% of these lesions.

Radiation Dose in Retreated Lesions

The peripheral doses of GKS alone or combined with WBRT in brain metastases from lung carcinoma varies in the literature from 12 to 35 Gy.^{9,14,15,19,22,25} There is a scarcity of data concerning the optimal dose in retreating lesions or in lesions previously treated with WBRT.^{5,6,13} One group has reported on 54 patients previously treated with WBRT and who then underwent radiosurgery again at a median peripheral dose of 16.2 Gy. This group demonstrated a tumor control rate of 91.3% at 1 year.¹⁸ In our study, there were 201 lesions treated with WBRT and subsequent GKS with a median dose of 18 Gy. Margin doses of 14 Gy or greater resulted in a higher shrinkage rate than doses below 14 Gy.

Treatment of Tumors With a Cystic Component

Tumors with a large cystic component (> 10 cm³) do not appear to be effectively controlled by GKS alone. Microsurgical resection or a combination of stereotactic cyst aspiration and GKS for the solid component can result in 60% survival at 1 year.^{8,21} In our series, there were nine tumors with a cystic component. Five of nine lesions did shrink, but the other four cystic tumors progressed despite radiosurgery.

Conclusions

Gamma knife surgery yielded results that appear superior

to those obtained with other treatment options for single or multiple brain metastases from lung cancer. It provided relatively effective tumor control and prolonged survival with a low morbidity rate.

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