

Gamma knife radiosurgery for metastatic brain tumors from lung cancer: a comparison between small cell and non–small cell carcinoma

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Object. The purpose of this retrospective study was to evaluate the effectiveness of gamma knife radiosurgery (GKS) for the treatment of metastatic brain tumors from lung cancer, with particular reference to small cell lung carcinoma (SCLC) compared with non-SCLC (NSCLC).

Methods. Two hundred forty-five consecutive patients meeting the following five criteria were evaluated in this study: 1) no prior brain tumor treatment; 2) 25 or fewer lesions; 3) a maximum of three tumors with a diameter of 20 mm or larger; 4) no surgically inaccessible tumor 30 mm or greater in diameter; and 5) more than 3 months of life expectancy. According to the same treatment protocol, large tumors (≥ 30 mm) were surgically removed and the other small lesions (< 30 mm) were treated with GKS. New lesions were treated with repeated GKS. Chemotherapy was administered, according to the primary physician's protocol, as aggressively as possible. Progression-free, overall, neurological, qualitative, and new lesion-free survival were calculated with the Kaplan–Meier method and were compared in the SCLC and NSCLC groups by using the log-rank test. The poor prognostic factors for each type of survival were also analyzed with the Cox proportional hazard model.

Conclusions. Tumor control rate at 1 year was 94.5% in the SCLC group and 98% in the NSCLC group. The median survival time was 9.1 months in the SCLC group and 8.6 months in the NSCLC group. The 1-year survival rates in the SCLC group were 86.5% for neurological survival and 68.9% for qualitative survival; those in the NSCLC group were 87.9% for neurological and 78.9% for qualitative survival. The estimated median interval to emergence of a new lesion was 6.9 months in the SCLC group and 9.8 months in the NSCLC group. There was no significant difference between the two groups for any type of survival; this finding was verified by multivariate analysis. The results of this study suggest that GKS appears to be as effective in treating brain metastases from SCLC as for those from NSCLC.

KEY WORDS • gamma knife • radiosurgery • metastasis • lung cancer • small cell lung carcinoma

CHEMOTHERAPY and/or WBRT have been the gold standards for metastatic brain tumors from SCLC because SCLCs characteristically spread rapidly and result in numerous microscopic brain metastases.^{1,9,10,12} Few reports on radiosurgery for metastatic SCLC-induced brain tumors are available. In this retrospective study, we reviewed the results of GKS alone for the treatment of brain metastases from SCLC compared with the results from NSCLC according to the same treatment protocol at a single institute.

Abbreviations used in this paper: CT = computerized tomography; GKS = gamma knife radiosurgery; KPS = Karnofsky Performance Scale; MR = magnetic resonance; MST = median survival time; NSCLC = non–small cell lung carcinoma; PFS = progression-free survival; QOL = quality of life; SID = skull internal dose; WBRT = whole-brain radiotherapy.

Clinical Material and Methods

Patient Population

Three hundred twenty-four patients with metastatic brain tumors from lung cancer were treated at the Chiba Cardiovascular Center between January 1998 and December 2001. Data obtained in patients meeting the following five criteria were evaluated retrospectively: 1) no prior brain tumor treatment; 2) 25 or fewer lesions; 3) a maximum of three tumors with a diameter of 20 mm or more; 4) no surgically inaccessible tumor 30 mm or more in diameter; and 5) more than 3 months of life expectancy. All diagnoses were confirmed histologically. Two hundred forty-five consecutive patients (167 men and 78 women) with a mean age of 63.9 years met these requirements. The cases were divided into two groups depending on the lung cancer entity: a SCLC group (34 patients) and an NSCLC group (211 patients).

TABLE 1
Summary of patient characteristics

Characteristic	SCLC Group	NSCLC Group	p Value*
no. of patients	34	211	
follow up (mos)			
mean ± SD	8.4 ± 7.4	10.1 ± 8.3	
range	4-42	1.1-48.6	
median	6.9	7.7	
age (yrs)			
mean ± SD	64.3 ± 8.2	63.8 ± 10.7	
range	48-81	34-89	
median	65.5	64	
no. of cases <65 yrs	17	98	0.7152
no. of cases ≥65 yrs	17	113	
male/female	28:6	139:72	0.0732
initial KPS score (no. of cases)			
<70	3	33	0.4343
≥70	31	178	
systemic disease			
controlled	7	36	0.6288
uncontrolled	27	175	
no. of brain lesions			
≤10	29	196	0.6188
>10	5	15	
size of maximum lesion (no. of cases)			
<25 mm	23	155	0.5384
≥25 mm	11	56	
carcinomatous meningitis			
yes	2	12	0.6980
no	32	199	
chemotherapy			
yes	24	113	0.0580
no	9	98	
craniotomy			
yes	5	41	0.6409
no	28	170	

* Probability value is based on chi-square test.

All metastatic lesions were diagnosed on gadolinium-enhanced MR imaging (1.5-tesla, Magnetom VISION, SIEMENS) with a 5-mm slice thickness and no gap acquisition. At diagnosis of brain metastases, the primary physician evaluated the status of systemic disease by using chest radiography, CT scanning of the chest and abdomen, and radionuclide scanning. In this series, tumors more than 30 mm in diameter were removed surgically. All other smaller brain metastases were treated with GKS. New distant lesions detected by gadolinium-enhanced MR imaging were treated with repeated GKS. The calculated total SID for each radiosurgical procedure was less than 10,000 mJ, thus preventing acute brain swelling, as we have previously reported.¹⁴ If the SID was calculated to be over 10,000 mJ on the dose planning system (Leksell GammaPlan, Elekta), the radiosurgical procedure was divided into two sessions. Chemotherapy was administered according to the referring physician's protocol.

Follow-Up Evaluation

Neurological and neuroradiological evaluations were

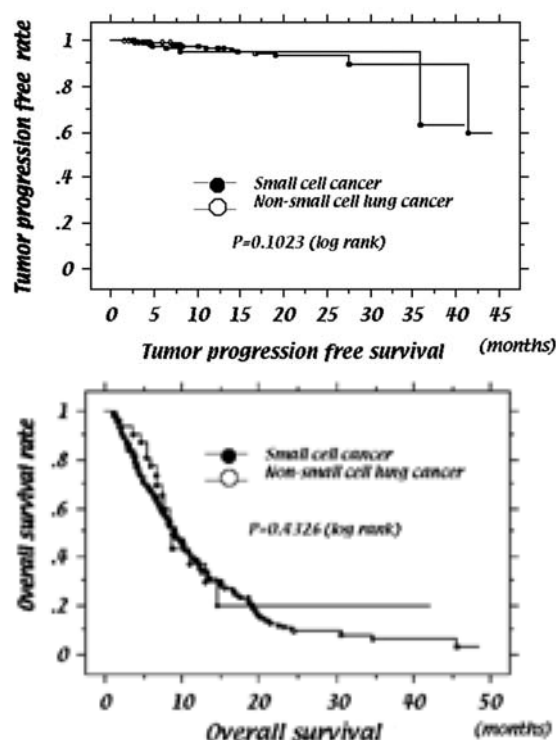


FIG. 1. Upper: Graph showing tumor PFS. Lower: Graph showing overall survival.

performed every 1 to 3 months after the initial GKS. Maximum tumor diameter on the follow-up MR images was measured in the axial and coronal planes. Control of the lesion treated with GKS was defined as a lack of any significant increase in tumor diameter (< 10%). Neurological death was defined as death from any expression of the intracranial metastases, such as tumor recurrence, carcinomatous meningitis, and cerebral dissemination, in keeping with the study by Patchell, et al.¹³ The differential diagnosis between tumor recurrence and radiation injury has been previously described.¹⁴ Diminished QOL was defined as an impaired neurological status as reflected by a KPS score of less than 70. A distant new lesion was defined as the appearance of a new brain metastasis at a site that was not involved on the day of initial treatment.

Statistical Analysis

The intervals between initial diagnosis of brain metastases and death (overall survival); to the date of neurological death (neurological survival); to the date of impaired QOL (qualitative survival); and to the date of the appearance of new distant lesions (new lesion-free survival) were all calculated using the Kaplan-Meier method. The PFS for all lesions treated with GKS was also analyzed. Kaplan-Meier comparison curves between SCLC and NSCLC groups were calculated using log-rank statistics. Prognostic values of the individual covariates for overall survival, neurological survival, qualitative survival, and new lesion-free survival were determined using the Cox proportional hazards model.⁷ The following nine dichotomized covariates were entered: pathological type of lung cancer (SCLC vs NSCLC); age (≥ 65 vs < 65 years); sex; initial KPS score (≥ 70 vs < 70); status of systemic dis-

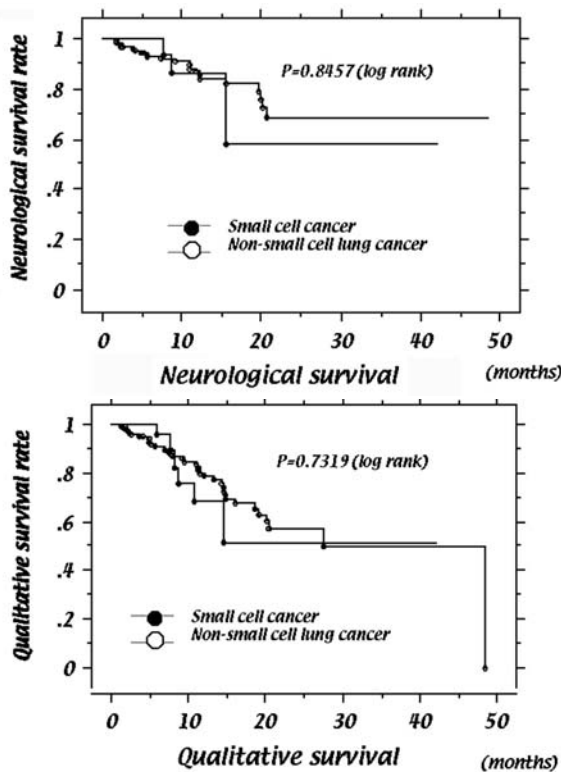


FIG. 2. Upper: Graph showing neurological survival. Lower: Graph showing qualitative survival.

ease control (controlled vs uncontrolled); number of brain lesions (≤ 10 vs > 10); diameter of the maximum lesion (≥ 25 vs < 25 mm); presence versus absence of carcinomatous meningitis; chemotherapy (yes vs no); and craniotomy (yes vs no). Covariates that appeared important ($p < 0.2$) after univariate analyses were included in the multivariate prognostic model verified by stepwise methods in the final model. The distribution of the covariates between the two groups was compared using the chi-square test. All computations were performed using StatView 5.0 (SAS Institute Inc., Cary, NC). A probability value of less than 0.05 was defined as statistically significant.

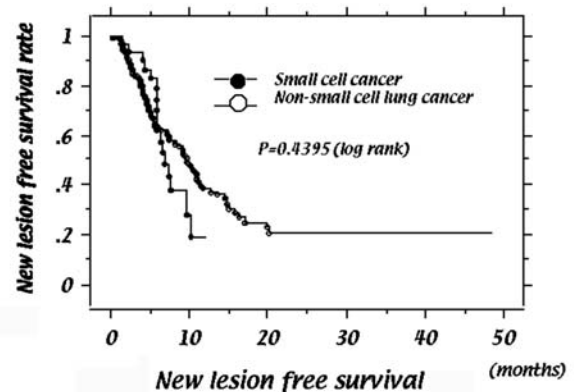


FIG. 3. Graph showing new lesion-free survival.

Results

Patient Characteristics

The distribution of characteristics is summarized in Table 1. The two groups did not differ in terms of the nine dichotomized covariates. The mean number of lesions treated at initial GKS was 4.6 in the SCLC group and 4.2 in the NSCLC group. The mean number of GKS procedures in the SCLC group was 1.9 (range one–10) whereas in the NSCLC group it was also 1.9 (range one–seven). The mean calculated tumor volume was 0.93 ± 2.45 cm³ in the SCLC group and 0.71 ± 2.22 cm³ in the NSCLC group. The mean prescription dose applied to the tumor margin was 21.3 Gy (21.0 Gy in the SCLC group and 21.4 Gy in the NSCLC group), and the mean prescription isodose was 72.4% (71.2% in the SCLC group and 72.6% in the NSCLC group). There was no significant difference in radiosurgical treatment factors between the two groups. No patients suffered acute brain swelling.

Tumor Progression-Free Survival

Figure 1 shows the cumulative tumor PFS curves determined in both groups. The 1-year tumor control rate was 94.5% in the SCLC group and 98% in the NSCLC group. There was no significant intergroup difference ($p = 0.1023$, log-rank test).

Overall Survival

Figure 2 depicts the survival curves in both groups. The

TABLE 2
Prognostic variables of overall survival in all cases of lung carcinoma*

Variable	High-Risk Group	p Value†	HR	p Value‡	HR
age (yrs)	≥ 65	0.6812	1.064		
sex	male	0.0005	1.758	0.0003	1.806
pathological type	SCC	0.4341	1.222		
initial KPS score	< 70	< 0.0001	1.600	< 0.0001	2.882
systemic control	uncontrolled	< 0.0001	3.273	0.0002	2.179
no. of lesions	> 10	0.7283	1.110		
max size of lesion	≥ 25 mm	0.8585	1.030		
presence of CM	yes	0.2829	1.420		
chemotherapy	no	0.7842	1.045		
microsurgery	no	0.1099	1.364	0.0772	1.431

* CM = carcinomatous meningitis; HR = hazard ratio; SCC = small cell carcinoma.

† Univariate analysis (Cox proportional hazards model).

‡ Multivariate analysis (Cox proportional hazards model).

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mean survival was 9.1 months in the SCLC group and 8.6 months in the NSCLC group, with no significant difference ($p = 0.4326$, log-rank test). The values of the prognostic factors for overall survival in all cases calculated with the Cox proportional hazard model are shown in Table 2. In multivariate analysis in the final model, significant poor prognostic factors were systemic control ($p = 0.0002$), low initial KPS score ($p < 0.0001$), and male sex ($p = 0.0003$).

Neurological Survival and Qualitative Survival

Neurological survival curves for both groups are shown in Fig. 3 and qualitative survival for both groups in Fig. 4. Neurological survival at 1 year following GKS was 86.5% in the SCLC group and 87.9% in the NSCLC group. The intergroup difference in neurological survival was similarly nonsignificant ($p = 0.8457$, log-rank test). In the all-lung cancer cases, the mean neurological survival time was 9 months, whereas the mean nonneurological survival time was 9.9 months. Among the 28 neurological deaths in the all-lung cancer cases (four in the SCLC group), the cause was diagnosed as carcinomatous meningitis in 12 (1), cerebral dissemination in eight (two), local control failure in GKS-treated lesions in four (zero), and growth of untreated lesions in four (one). The values of the prognostic factors for neurological survival in all patients are indicated in Table 3. The prognosis of neurological survival in patients with carcinomatous meningitis ($p > 0.0001$) was poor (multivariate analysis).

The 1-year qualitative survival was 68.9% in the SCLC group and 78.9% in the NSCLC group, with no significant difference ($p = 0.7319$, log-rank test). Multivariate analysis revealed that the significant poor-prognosis factors for qualitative survival in all patients were carcinomatous meningitis ($p < 0.0001$), low initial KPS score ($p = 0.0015$), and male sex ($p = 0.0380$).

New Distant Lesions

Figure 5 shows the new lesion-free survival curves of the SCLC and NSCLC groups. The mean new lesion-free survival times were 6.9 months in the SCLC group and 9.8 months in the NSCLC group. Four patients received WBRT for numerous (< 25) cerebral disseminations (two in the SCLC group and two in the NSCLC group). New lesions tended to emerge more often in the SCLC group, but no significant difference was noted ($p = 0.4395$, log-rank test). The only significant high risk factor in the final Cox proportional hazard model for new lesions was uncontrolled status of extracranial disease ($p = 0.0072$).

Discussion

Whole-brain radiotherapy and chemotherapy have been considered to be the standard treatment modalities for metastatic brain tumors from SCLC, because the tumors spread and grow rapidly, even when only a single tumor is present.^{1,9,10,12} Excellent radiosurgical results for a small number in cases involving a small lung cancer-induced metastatic brain tumors have been reported.^{14,15} In most of these reports, however, the authors analyzed only NSCLC patients. In this study, we undertook a retrospec-

tive review of the results of GKS for metastatic brain tumors from lung cancer, with emphasis on the comparison between SCLC and NSCLC. The results suggest that there is no significant intergroup difference.

Indication of GKS for Metastatic Brain Tumors From Lung Cancer

It has now been clearly established that radiosurgery is indicated for some small brain metastases.^{2,5,6,8} We have previously reported our own specialized criteria by which the SID should be within 10,000 mJ in a single radiosurgical procedure.¹⁴ This dose is roughly equivalent to the energy of 4 to 5 Gy of whole-brain radiation in one session. Within this limit, we believe that 25 small (< 10 -mm) or three medium (> 20 -mm) lesions can be safely irradiated in a single GKS session, as reported by Yang, et al.¹⁶ If the SID exceeds 10,000 mJ, as suggested by pre-GKS MR imaging evaluation, WBRT should be considered.

Tumor Progression-Free Survival

Small cell lung carcinoma is widely known to be a radioresponsive tumor, but in our study we found no difference in tumor PFS between the SCLC and NSCLC cases. This suggests that GKS in which the peripheral dose is 21 to 22 Gy may be considered sufficient not only in the radioresponsive SCLC but also in NSCLC. The tumor control rate in this study was higher than that reported previously,^{2,8} which may be due to the preponderance of smaller tumors in this study.

Overall Survival

The mean survival time for patients with metastatic brain tumors from SCLC has been reported to be very short—only 2 to 4 months.^{1,3,9,10,12} In this study, the mean survival time of the SCLC patients proved to be longer. In patients with relatively favorable prognoses, shorter treatment periods and less invasive procedures may contribute to a greater tolerance for more aggressive chemotherapy. Moreover, GKS might be helpful in maintaining better general status in poor-prognosis patients. Small cell lung carcinoma was not shown to be a negative prognostic factor with respect to overall survival, which might be attributed to the fact that overall survival depends primarily on the status of extracranial disease and initial KPS score, as previously reported.^{4,11}

Neurological Survival and Qualitative Survival

A high local control rate with GKS contributes to the prevention of neurological death and the maintenance of a good QOL. Proper salvage treatment for new lesions is important. The two main causes of neurological death were carcinomatous meningitis and cerebral dissemination, but there was no evidence of a higher incidence in the SCLC group. Multivariate analysis suggested that the most important negative prognostic factor for both neurological and quality survival was carcinomatous meningitis, which suggests that it represents a contraindication for GKS.

New Distant Lesions

It has been commonly believed that patients with met-

astatic lesions from SCLC characteristically harbor numerous microscopic metastases.^{1,3,9,10,12} The difference in new lesion-free survival between the SCLC and NSCLC groups, however, was not statistically significant. Modern high-quality MR imaging can detect tumors of even a few millimeters in diameter during initial evaluations. The survival period may be too short for invisible metastases or true new lesions to be identified on follow-up MR imaging. On the other hand, chemotherapy may play an important role in controlling or killing the micrometastases. It is suggested that local disease control is the most important goal when treating metastatic brain tumors from lung cancer. If new lesions are detected, a new GKS treatment may be considered.

Conclusions

Gamma knife radiosurgery appears to be as effective for metastatic brain tumors from SCLC as for lesions from NSCLC.

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