Gamma Knife radiosurgery for brain metastases from pulmonary large cell neuroendocrine carcinoma: a Japanese multi-institutional cooperative study (JLGK1401)

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OBJECTIVE In 1999, the World Health Organization categorized large cell neuroendocrine carcinoma (LCNEC) of the lung as a variant of large cell carcinoma, and LCNEC now accounts for 3% of all lung cancers. Although LCNEC is categorized among the non–small cell lung cancers, its biological behavior has recently been suggested to be very similar to that of a small cell pulmonary malignancy. The clinical outcome for patients with LCNEC is generally poor, and the optimal treatment for this malignancy has not yet been established. Little information is available regarding management of LCNEC patients with brain metastases (METs). This study aimed to evaluate the efficacy of Gamma Knife radiosurgery (GKRS) for patients with brain METs from LCNEC.

METHODS The Japanese Leksell Gamma Knife Society planned this retrospective study in which 21 Gamma Knife centers in Japan participated. Data from 101 patients were reviewed for this study. Most of the patients with LCNEC were men (80%), and the mean age was 67 years (range 39–84 years). Primary lung tumors were reported as well controlled in one-third of the patients. More than half of the patients had extracranial METs. Brain metastasis and lung cancer had been detected simultaneously in 25% of the patients. Before GKRS, brain METs had manifested with neurological

ABBREVIATIONS GKRS = Gamma Knife radiosurgery; KPS = Karnofsky Performance Scale; LCNEC = large cell neuroendocrine carcinoma; MET = metastasis; MST = median survival time; NSCLC = non–small cell lung carcinoma; PCI = prophylactic cranial irradiation; RPA = recursive partitioning analysis; RTOG = Radiation Therapy Oncology Group; SCLC = small cell lung carcinoma; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

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symptoms in 37 patients. Additionally, prior to GKRS, resection was performed in 17 patients and radiation therapy in 10. A small cell lung carcinoma–based chemotherapy regimen was chosen for 48 patients. The median lesion number was 3 (range 1–33). The median cumulative tumor volume was 3.5 cm³, and the median radiation dose was 20.0 Gy. For statistical analysis, the standard Kaplan-Meier method was used to determine post-GKRS survival. Competing risk analysis was applied to estimate GKRS cumulative incidences of maintenance of neurological function and death, local recurrence, appearance of new lesions, and complications.

RESULTS The overall median survival time (MST) was 9.6 months. MSTs for patients classified according to the modified recursive partitioning analysis (RPA) system were 25.7, 11.0, and 5.9 months for Class 1+2a (20 patients), Class 2b (28), and Class 3 (46), respectively. At 12 months after GKRS, neurological death–free and deterioration–free survival rates were 93% and 87%, respectively. Follow-up imaging studies were available in 78 patients. The tumor control rate was 86% at 12 months after GKRS.

CONCLUSIONS The present study suggests that GKRS is an effective treatment for LCNEC patients with brain METs, particularly in terms of maintaining neurological status.

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KEY WORDS brain metastases; stereotactic radiosurgery; Gamma Knife; lung cancer; oncology; LCNEC; large cell neuroendocrine carcinoma

IN 1999, pulmonary large cell neuroendocrine carcinoma (LCNEC) was categorized as a new histological type of lung cancer and recognized as a variant of large cell carcinoma by the World Health Organization.³ LCNEC is an uncommon lung cancer subset, accounting for only 3% of all lung cancers.^{8,22,28} Since Travis et al. first reported LCNEC in 1991, many authors have reported that LCNECs are aggressive tumors, and patients with these tumors have very poor prognoses.^{8,12,17,19,22,23,28,29} Although LCNEC is categorized among the non–small cell lung carcinoma (NSCLC), the biological behavior of these tumors is very similar to that of small cell lung carcinoma (SCLC). Given the complex clinicopathological and biological features of LCNEC, there is controversy as to whether LCNEC should be treated according to NSCLC or SCLC protocols. Brain metastases (METs) are a common, life-threatening neurological problem for patients with advanced LCNEC, but little information is currently available regarding management of LCNEC patients with brain METs. Prophylactic cranial irradiation (PCI) might be recommended for patients with SCLC, as it prolongs both disease-free and overall survival.^{2,26} Conversely, PCI is not administered in patients with NSCLC.¹¹ In recent years, stereotactic radiosurgery (SRS) combined with whole-brain radiation therapy (WBRT) has generally been recommended as the first treatment for brain METs.¹ However, debate persists as to whether WBRT is necessary for all patients with brain METs. The primary argument against WBRT (especially PCI) stems from the risk of deterioration of neurocognitive function.^{4,5} Based on a large cohort originating from a multicenter study conducted by the Japanese Leksell Gamma Knife Society (JLGK1401 study), we aimed to evaluate the efficacy of Gamma Knife radiosurgery (GKRS) for treatment of patients with brain METs from LCNEC.

Methods

Patients

The Japanese Leksell Gamma Knife Society planned this retrospective study. Twenty-one Gamma Knife centers in Japan that treat LCNEC patients with brain METs participated. All centers obtained institutional review

board approvals from their own facilities to participate in this study, and their outcome data were then retrospectively combined. Written informed consent was obtained from all patients. This allowed us to examine the data from 101 patients and 387 lesions for this study.

Table 1 summarizes the clinical characteristics of the patients and tumors. The study included 20 women and 81 men. The mean age at the time of radiosurgery was 67 years (range 39–84 years). The mean and median tumor numbers per patient were 4 and 3 (range 1–33). Of the 387 lesions, 304 were located in the supratentorial region and 83 in the infratentorial region. Specifically, 123 lesions were located in the frontal lobe, 77 in the cerebellum, 67 in the parietal lobe, 48 in the temporal lobe, 46 in the occipital lobe, and 26 at other sites. Cumulative tumor volumes ranged from 0.08 to 67.8 cm³ (median 3.5 cm³), and the volumes of the largest tumors ranged from 0.04 to 51.5 cm³ (median 2.7 cm³).

The primary lung cancer was reported by the referring primary physician to be well controlled in only 33 patients, while 56 also had extracranial METs, i.e., 26 patients had METs in lymph nodes, 15 in bone, 13 pulmonary, 11 hepatic, and so on. Among the 101 patients, tumor presentation was synchronous in 26 and metachronous in the other 75. Thirty-three patients had various neurological symptoms caused by brain METs. The median Karnofsky Performance Scale (KPS) score¹⁴ at the time of radiosurgery was 90% (range 40%–100%). The KPS score was 80% or better in 85 patients and 70% or worse in 16. According to the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification system,⁹ 8 patients were in RPA Class 1, 84 in RPA Class 2, and 8 in RPA Class 3. Using the modified RPA system,^{30,31} there were 20 patients in Class 1+2a, 28 in Class 2b, and 46 in Class 2c+3. Prior treatments performed at other facilities included surgical removal in 17 patients and WBRT (30 or 40 Gy) in 8 (no patients with PCI). An SCLC-based chemotherapy regimen had been chosen for 48 patients (70%). The median irradiation dose at the tumor periphery was 20.0 Gy (range 9.0–28.0 Gy), and the median dose at the tumor center (maximum dose) was 36.0 Gy (range 18.0–50.0 Gy).

TABLE 1. Summary of clinical characteristics in 101 patients with brain METs from pulmonary LCNEC

Characteristic	No. (range)
Sex	
Women	20
Men	81
Mean age in yrs	67 (39–84)
Mean/median no. of tumors	4/3 (1–33)
Total lesions	387
Tumor location	
Supratentorial	304
Infratentorial	83
Tumor vol (cm ³)	
Median cumulative vol	3.5 (0.08–67.8)
Median vol of largest lesion	2.7 (0.04–51.5)
Primary cancer	
Controlled	33
Not controlled	59
Extracerebral METs	
No	37
Yes	56
Diagnosis	
Synchronous	26
Metachronous	75
Median % KPS score	90 (40–100)
≥80%	85
<70%	16
Modified RPA class	
1+2a	20
2b	28
2c+3	46
Symptom	
No	64
Yes	37
Prior surgery	
No	84
Yes	17
Prior WBRT	
No	93
Yes	8
Chemotherapy	
SCLC based	48
NSCLC based	21
Median radiation dose in Gy	20.0 (9.0–28.0)

Statistical Analysis

Neurological and neuroimaging evaluations were performed every 2–3 months after the initial GKRS. Overall survival time was defined as the interval between the first SRS for brain METs and death from any cause or the day of the last follow-up. Neurological death was defined as death caused by all intracranial diseases, i.e., tumor recur-

rence, carcinomatous meningitis, cerebral dissemination, and progression of other untreated intracranial tumors. Neurological death-free survival time was defined as the interval between the first SRS for brain METs and death from any brain disease or the day of last follow-up.

Control of the GKRS-treated lesion was defined as no remarkable increase, namely regression or unchanged, in tumor diameter. Generally, the criteria for local recurrence were an increased size (over 10% increase in the maximum diameter) of an enhanced area on postgadolinium T1-weighted MR images and an enlarged tumor core on T2-weighted MR images.¹³ Neurological deterioration-free survival time was defined as the interval between the first SRS and the day in which any brain disease-caused neurological worsening manifested (that is, local recurrence, progression of new lesions, and SRS-induced complications). In patients with KPS scores of 20% or less, decreases in scores due to neurological worsening were regarded as events and any others were regarded as censored. Complication-free survival time was defined as the interval until the first SRS-induced complication occurred.

All data were analyzed according to the intention-to-treat principle. For the baseline variables, summary statistics were constructed employing frequencies and proportions for categorical data, and means and standard deviations (SD) for continuous variables. We compared patient characteristics using Fisher's exact test for categorical outcomes and t-tests for continuous variables, as appropriate. For time-to-event outcomes, the time elapsed until a first event was compared using the log-rank test, while the Kaplan-Meier method was used to estimate the absolute risk of each event for each group. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated employing the Cox proportional hazards model. In addition, the cumulative incidences of neurological death, impaired neurological status, and local control failure were estimated employing a competing risk analysis, because death is a competing risk for loss to follow-up.^{10,25}

All comparisons were planned, and the tests were 2-sided. A p value of less than 0.05 was considered to be a statistically significant difference. All statistical analyses were performed by one of the authors (Y.S.), who was not involved in either GKRS treatment or patient follow-up, using SAS software version 9.4 (SAS Institute) and the R statistical program, version 3.10.

Results

Overall Survival

The median post-GKRS follow-up time was 7.2 months (range 2.4–64.0 months) for 26 censored observations, and 75 patients had died as of the end of March 2014. The overall median survival time (MST) after GKRS was 9.6 months (95% CI 7.8–13.1 months). The Kaplan-Meier plots of all 101 patients are shown in Fig. 1A. Actuarial survival rates were 66.8%, 46.0%, and 17.4% at 6, 12, and 24 months after GKRS, respectively. For patients classified within the modified RPA system, MSTs were 25.7 months (95% CI 12.4–NA) for patients in class 1+2a, 11.0 months (95% CI 7.3–14.8) for those in class 2b, and 5.9

FIG. 1. Overall survival in all 101 patients included in the study (**A**) and in the patients categorized according to modified RPA classes (**B**), estimated using the standard Kaplan-Meier method. NA = not available.

months (95% CI 3.8–8.6) for class 2c+3 (stratified $p < 0.001$; Fig. 1B). For chemotherapy selection, i.e., SCLC-based versus NSCLC-based regimen, there was no significant post-GKRS difference in MST between the 2 groups (8.4 months [95% CI 6.3–11.9] vs 23.4 months [95% CI 20.3–32.4]; $p = 0.905$). Among the 13 pre-GKRS clinical factors reported (age, sex, histopathological diagnosis, KPS score, number of tumors, cumulative tumor volume, largest tumor volume, peripheral dose, primary tumor status, nonbrain METs, symptoms, prior resection, prior WBRT), multivariate analyses showed 3 clinical factors to be significantly favorable for longer survival: 1) single MET (HR 1.122, 95% CI 1.051–1.192; $p = 0.001$), 2) well-controlled primary tumors (HR 2.284, 95% CI 1.137–4.718; $p = 0.020$), and 3) no extracranial METs (HR 2.904, 95% CI 1.417–6.212; $p = 0.003$).

Neurological Death-Free Survival

Among the 75 deceased patients, the cause of death could not be determined in 2, but was confirmed in the remaining 73: nonbrain disease in 62 (85%), progression of brain METs in 10 (14%), and cerebral infarction (no rela-

tion to GKRS treatment) in 1 (1%). In the 62 patients who died due to the primary cancer or nonbrain METs, good brain condition was maintained until 1 to several days before death. Actuarial neurological death rates were 7.4% and 13.8% at 12 and 24 months after GKRS, respectively. Among the aforementioned 13 factors, multivariate analyses showed 3 clinical factors to significantly favor longer neurological death-free survival: 1) synchronous MET (HR 52.71, 95% CI 1.877–6052; $p = 0.018$), 2) single MET (HR 1.337, 95% CI 1.096–1.868; $p = 0.003$), and 3) large peripheral dose (HR 1.672, 95% CI 1.124–3.062; $p = 0.010$).

Neurological Deterioration-Free Survival

After treatment, decreased performance status caused by neurological deterioration occurred in 14 patients (Table 2). Cumulative incidences of neurological deterioration were 13.2% and 17.5% at 12 and 24 months after GKRS, respectively (Table 3). Among the aforementioned 13 factors, multivariate analyses showed 3 clinical factors to significantly favor longer neurological deterioration-free survival: 1) better KPS score (HR 1.122, 95% CI 1.001–1.267; $p = 0.049$), 2) single MET (HR 1.208, 95% CI 1.047–1.443; $p = 0.010$), and 3) extracerebral METs (HR 7.346, 95% CI 1.101–63.292; $p = 0.039$).

Follow-Up MRI for Local Tumor Control and New Distant Lesions

In this series, follow-up MR images were available for 78 patients and 281 lesions. Local recurrence of the treated lesions occurred in 10 patients and 18 lesions, as shown in Table 2. Cumulative incidences of local recurrence were 13.8% and 13.8% at 12 and 24 months after GKRS, respectively (Table 3). Six of the 10 patients with recurrence underwent additional treatment (a second GKRS procedure in 2, stereotactic radiotherapy in 2, surgical removal in 1, and a combination of surgical removal and stereotactic radiotherapy in 1), while the other 4 patients received conservative therapies because of their poor systemic conditions. In 3 patients for whom posttreatment follow-up MR images were available, these images demonstrated 5 of the treated tumors to be well controlled, while 2 other tumors were not well controlled. None of the 6 clinical factors (tumor volume, peripheral dose, central dose, tumor location [supra- or infratentorial], prior resection, prior WBRT) was found to be statistically significantly associated with a higher recurrence rate on multivariable analyses.

New distant lesions were detected during the post-GKRS observation period in 34 patients (Table 2). As shown in Table 3, cumulative incidences of new distant lesion appearance were 45.7% and 51.9% at 12 and 24 months after GKRS, respectively. As an additional treatment for new distant lesions, 26 patients underwent a second GKRS procedure, 4 underwent WBRT, and 4 did not have additional treatment. Among the aforementioned 13 factors, multivariable analyses showed 3 clinical factors to be significantly favorable for longer new distant lesion-free survival: 1) male sex (HR 4.660, 95% CI 1.609–13.075; $p = 0.005$), 2) synchronous MET (HR 5.357, 95% CI 1.558–20.918; $p = 0.007$), and 3) single MET (HR 1.136, 95% CI 1.032–1.266; $p = 0.011$).

TABLE 2. Treatment results after GKRS: crude incidences

Treatment Result	No. of Patients (%)
Neurological death*	11 (15.1)
Neurological deterioration	14 (13.9)
Local recurrence†	10 (12.8)
New distant lesions†	34 (43.6)
Repeat GKRS procedure	28 (27.7)
SRT	3 (3.0)
WBRT	4 (4.0)
Surgery	3 (3.0)
GKRS-related complications	6 (5.9)

* Based on 73 deceased patients whose cause of death was determined (2 were excluded because cause of death was not available).

† Based on 78 patients (23 were excluded because neuroimaging results were not available).

GKRS-Related Complications

GKRS-related complications occurred in 6 patients (Table 2). One was RTOG Class 1, 3 were RTOG Class 2 (mild transient motor weakness), and 2 were RTOG Class 3. Of the 2 patients with RTOG Class 3, one experienced motor weakness 4 months after GKRS and the other experienced intratumoral hemorrhage, eventually necessitating resection 2 days after GKRS. As shown in Table 3, cumulative incidences of GKRS-related complications were 5.5% and 5.5% at 12 and 24 months after GKRS, respectively. None of the aforementioned 13 factors was found to be statistically significantly associated with a higher complication rate on multivariable analyses.

Discussion

Overall Survival and Maintenance of Good Neurological Condition

Patients with advanced LCNEC generally have poor survival, as seen with all lung cancers. In patients with Stage IV LCNEC, the MST of the entire cohort was reported to be 10.2 months from the time of initial diagnosis.^{6,16,20,24,27,33} Brain METs are a common, life-threatening neurological problem for patients with advanced LCNEC. SRS, which allows radical treatment of brain METs, may have contributed greatly not only to prolonged overall survival but also to maintenance of neurological condition and, ultimately, to reducing the neurological death rate. As Yamamoto et al. reported recently, based on 1194 patients with brain METs treated with GKRS alone, approximately 90% of patients with brain METs died because of progression of extracranial diseases.³² Also, they reported the MST of their lung cancer subset to be 12.5 months (95% CI 11.2–13.4); 13.1 months (95% CI 12.0–14.0) in patients with NSCLC and 8.7 months (95% CI 7.3–11.5) in patients with SCLC. The post-GKRS MST of the present study, 9.6 months, was slightly worse than that of NSCLC while being slightly better than that of SCLC.

We consider our herein-reported data set, with a relatively large sample size, to show that GKRS has the potential to achieve prolonged maintenance of neurological function and to minimize neurological death for LCNEC

TABLE 3. Treatment results after GKRS*

Treatment Result	Cumulative Incidences After GKRS (%)				
	12 Mos	24 Mos	36 Mos	48 Mos	60 Mos
Neurological death†	7.4	13.8	15.8	15.8	15.8
Neurological deterioration	13.2	17.5	17.5	17.5	17.5
Local recurrence‡	13.8	13.8	16.6	16.6	16.6
New distant lesions‡	45.7	51.9	51.9	51.9	51.9
GKRS-related complications	5.5	5.5	5.5	8.4	8.4

* Cumulative incidences calculated using a competing risk analysis.

† Based on 73 deceased patients whose cause of death was determined (2 were excluded because cause of death was not available).

‡ Based on 78 patients (23 were excluded because neuroimaging results were not available).

patients with brain METs, as shown in Table 3. Also, both crude (5.9%) and cumulative (5.5% at 12 months post-GKRS) incidences of GKRS complications were acceptably low as compared with those (11.0% and 5.7%–8.3%, respectively) of the JLGK0901 study.³²

Chemotherapy

The response to chemotherapy is poorer in patients with LCNEC than in those with extensive-stage SCLC. Several studies focusing on LCNEC divided patients into groups receiving NSCLC-based versus SCLC-based chemotherapy regimens.^{24,27} In these series, response rates were better in those administered SCLC-based chemotherapy. However, there is some overlap between NSCLC-based and SCLC-based regimens, which might limit the value of such analyses. Furthermore, our results showed no statistically significant difference between these 2 chemotherapy treatments. In the near future, the role of molecularly targeted agents in treating patients with LCNEC should be assessed.

Is PCI Necessary?

Naidoo et al. reported on a large group of patients with brain METs: 35% of patients with Stage IV LCNEC had intracranial lesions at the time of initial diagnosis ($n = 17/49$), and 12% had brain METs develop later in the disease course ($n = 6/49$).¹⁹ The clinical course of patients with SCLC was found to be similar to that of those with LCNEC, i.e., brain METs were detected in up to 18% of patients at the time of initial diagnosis, and the probability of developing such lesions ranged from 50% to 80% in patients who survived for 2 years.¹⁵ Naidoo et al. suggested that patients with advanced LCNEC may benefit from routine brain-directed surveillance during their disease course and prophylactic therapy similar to that administered for patients with SCLC.¹⁹ However, nowadays, PCI for the treatment of SCLC is no longer an option, as reported by Nosaki et al. based on a Japanese Phase III study.²¹ In a considerable number of the herein-reported patients, brain METs were detected soon after the initial diagnosis, similar to patients with SCLC. However, salvage treatment with GKRS for new lesions was available and was regarded as being sufficient in most cases. We achieved good neurological death-free and neurological deteriora-

tion-free survivals without PCI. Therefore, we do not consider it to be necessary to treat LCNEC patients with PCI.

Study Limitations

The relatively small number of patients and the heterogeneity of the population are limitations of the present study. There might have been a patient selection bias, which would include possible misclassification of LCNEC versus SCLC or other types of NSCLC.^{7,18} Because this study was based on a retrospective chart review at each participating facility, pathological diagnoses were made by a pathologist at each facility, i.e., a systematic pathological review was not performed.

Another possible weakness of this study is that neuroimaging follow-up was lacking in approximately 25% of patients. However, in most patients in this subset, MRI could not be performed because of early post-SRS death or remarkable deterioration of the patient's general condition, not because the patients were lost to follow-up. As to the low complication rate, the primary physicians who managed our GKRS patients might not have reported relatively minor problems to us. Therefore, an additional weakness of this study is that we may not have surveyed all patients with minor complications.

Conclusions

To our knowledge, this is the first retrospective multicenter study of patients with brain METs from LCNEC treated with GKRS. Our present study suggests GKRS is an effective treatment for brain METs from LCNEC, particularly in terms of maintenance of neurological status.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kawabe, Yamamoto. Acquisition of data: all authors. Analysis and interpretation of data: Kawabe, Yamamoto, Y Sato. Drafting the article: Kawabe, Yamamoto, Y Sato. Critically revising the article: Kawabe, Yamamoto, Y Sato. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kawabe. Statistical analysis: Kawabe, Yamamoto, Y Sato. Administrative/technical/material support: Kawabe, Yamamoto. Study supervision: Yamamoto, Y Sato.

Supplemental Information

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