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Radiosurgery for patients with recurrent small cell lung carcinoma metastatic to the brain: outcomes and prognostic factors

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Object. Lung carcinoma is the leading cause of death from cancer. More than 50% of those with small cell lung cancer develop a brain metastasis. Corticosteroid agents, radiotherapy, and resection have been the mainstays of treatment. Nonetheless, median survival for patients with small cell lung carcinoma metastasis is approximately 4 to 5 months after cranial irradiation. In this study the authors examine the efficacy of gamma knife surgery for treating recurrent small cell lung carcinoma metastases to the brain following tumor growth in patients who have previously undergone radiation therapy, and they evaluate factors affecting survival.

Methods. A retrospective review of 27 patients (47 recurrent small cell lung cancer brain metastases) undergoing radiosurgery was performed. Clinical and radiographic data obtained during a 14-year treatment period were collected. Multivariate analysis was utilized to determine significant prognostic factors influencing survival.

The overall median survival was 18 months after the diagnosis of brain metastases. In multivariate analysis, factors significantly affecting survival included: 1) tumor volume ($p = 0.0042$); 2) preoperative Karnofsky Performance Scale score ($p = 0.0035$); and 3) time between initial lung cancer diagnosis and development of brain metastasis ($p = 0.0127$). Postradiosurgical imaging of the brain metastases revealed that 62% decreased, 19% remained stable, and 19% eventually increased in size. One patient later underwent a craniotomy and tumor resection for a tumor refractory to radiosurgery and radiation therapy. In three patients new brain metastases were demonstrating on follow-up imaging.

Conclusions. Stereotactic radiosurgery for recurrent small cell lung carcinoma metastases provided effective local tumor control in the majority of patients. Early detection of brain metastases, aggressive treatment of systemic disease, and a therapeutic strategy including radiosurgery can extend survival.

KEY WORDS • gamma knife surgery • metastasis • small cell lung carcinoma

BRAIN metastasis is the most common type of intracranial tumor.[47] Each year, the number of brain tumor metastases diagnosed outnumbers the total number of other intracranial tumors.[47] Lung carcinoma is the leading cause of death from cancer and the most common source of brain metastasis.[36] Small cell carcinoma is the subtype most strongly associated with tobacco exposure and accounts for 20 to 25% of all lung cancer cases (approximately 45,000 new cases each year in the US).[11] Although 10% of patients have at least one brain metastasis at the time of small cell carcinoma diagnosis, the overall incidence of this type of brain metastasis is more than 50% in over 2 years, and this figure appears consistent with the rate found in autopsy series.[1,5,6,16,25,32] The clinical picture is further complicated by the fact that between 54 and 64% of patients with lung carcinoma metastases to the brain either have or develop multiple lesions.[15,23,47] Nearly one half of those who develop brain metastases die of central nervous system progression.[50] Moreover, with improvements in the control of extracranial disease achieved through better chemotherapeutic agents and thoracic radiotherapy, the duration of survival for patients with small cell lung cancer and, in turn, the cumulative risk of brain metastases are increasing.[5,11,32]

Untreated, the median survival for patients with small cell lung cancer is only 6 to 12 weeks.[11] Patients currently undergo chemotherapy combined with thoracic radiotherapy to treat extracranial disease. After the diagnosis of small cell lung carcinoma brain metastasis, the median survival is 4.5 months despite treatment with high-dose cranial irradiation.[4,5,33] The relatively short median survival after WBRT is surprising given that small cell lung cancer is typically radiosensitive.[5,33,50] It has been suggested that improved survival and functional status can be achieved with resection and WBRT compared with WBRT alone.[40,57] Nevertheless, a third and larger randomized trial demonstrated no significant survival benefit associated with the addition of resection to WBRT.[37] All three randomized trials included patients with different types of brain metastases rather than small cell lung cancer metastases specifically.

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

TABLE 1

Summary of demographic and treatment data obtained in 27 patients

Variable	Median (range)	Total
age in yrs	65 (38–82)	
no. of tumors	1 (1–4)	47
KPS score	90 (70–100)	
time to diagnosis in mos	7 (0–24)	
no. of brain resections	0 (0–1)	1
no. of brain biopsies	0 (0–1)	4
WBRT dose in Gy	30 (24–56)	
margin dose in Gy	16 (13–20)	
max dose in Gy	32 (26–40)	
isodose treatment in %	50 (40–60)	
tumor vol in ml	5.4 (0.065–24.6)	
no. of isocenters	4 (1–14)	
survival after GKS (mos)	4.5 (1–31)	
survival after diagnosis in mos	18 (2–40)	
tumor size decreased		13
tumor size stable		4
tumor size increased		4

In patients with metastatic small cell lung carcinoma, systemic disease and distant metastases are not uncommon. Consequently, aggressive intervention and a low morbidity rate are desirable. Since brain metastases are frequently easily identifiable and demarcated lesions on either CT or MR imaging, they are usually amenable to stereotactic radiosurgery.[2,9,12,13,18,21,29,34,35,51] Since little is written on the role of radiosurgery for patients with small cell lung cancer, we reviewed the efficacy of radiosurgery following WBRT for treatment of these brain metastases and identified factors that correlated with improved survival.

Clinical Material and Methods

We reviewed data, collected prospectively, from all 27 patients with brain metastases due to small cell lung carcinoma managed with GKS at the University of Pittsburgh between 1987 and 2001. These patients represented approximately 3% of our radiosurgical series of all patients with brain metastases. All procedures were performed using models U, B, or C Gamma Knife units (Elekta Instruments, Atlanta, GA). Currently, MR images on a 1.5-tesla magnet are obtained for each patient. The sequences used are 1-,

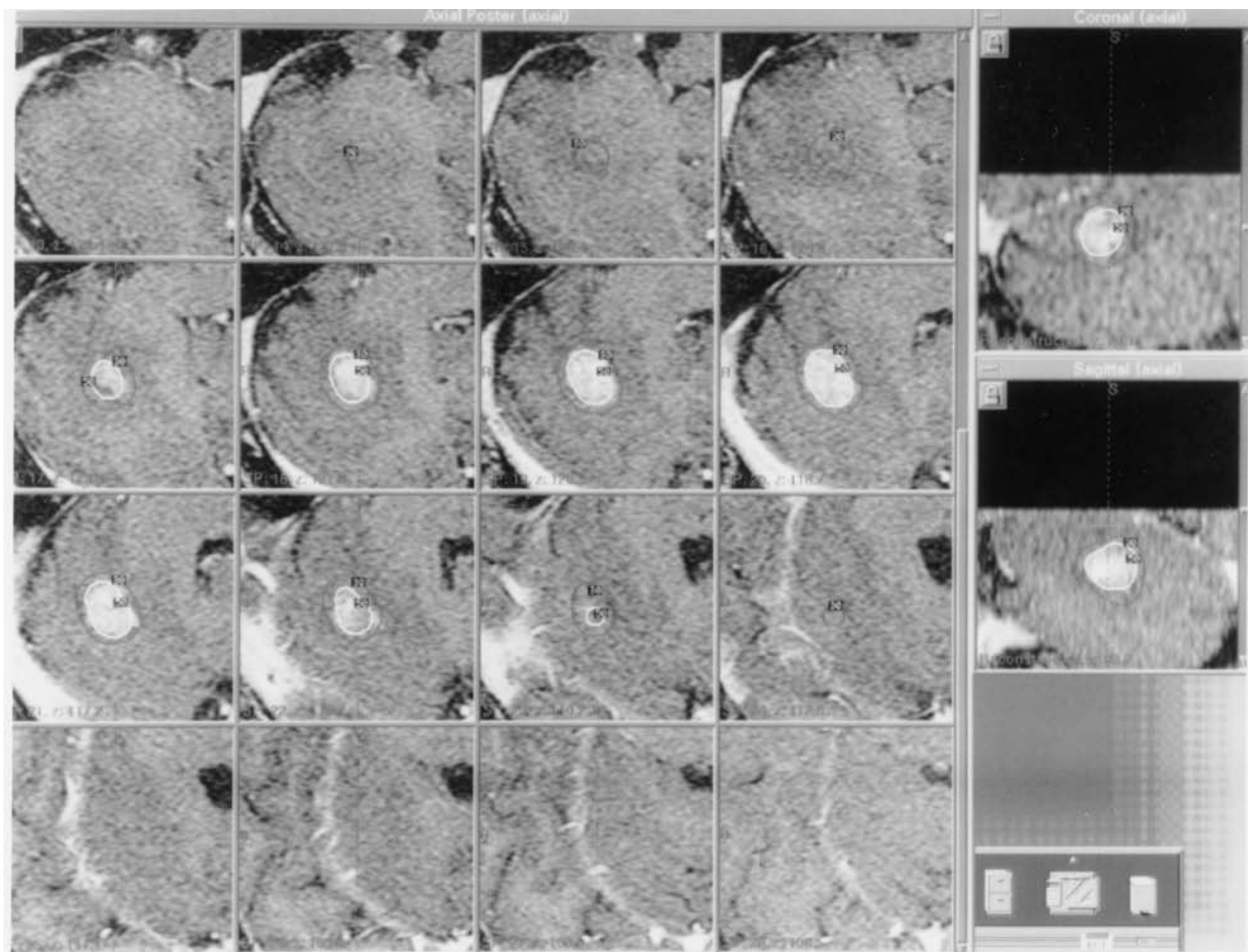

Fig. 1. Radiosurgical dose plan for the treatment of a small cell lung carcinoma metastasis in the right cerebellum. Axial, coronal, and sagittal MR images are shown. The respective isodose curves are denoted by the numbers on the dose plan.

TABLE 2
*Multivariate analysis of prognostic variables for survival in 27 patients**

Variable	p Value	Tested for Favorable Status
age	0.3243	≤55 yrs old
margin dose	0.2576	continuous variable
maximal dose	0.2389	continuous variable
sex	0.6043	male
no. of isocenters	0.3008	increased no. of isocenters
treatment isodose curve	0.2859	isodose >50
preop KPS score	0.0035	≥90
no. of metastases	0.9633	≤2 metastases
prior resection	0.7439	yes
prior radiation therapy	0.3377	yes
tumor vol	0.0042	decreasing tumor vol
time from diagnosis of SCLC to brain metastasis diagnosis	0.0127	increasing interval time as a continuous variable
active extracranial disease	0.7204	yes

* SCLC = small cell lung carcinoma.

2-, or 3-mm axial slice thickness volume acquisitions with intravenous Gd contrast. If patients were unable to undergo MR imaging, a contrast-enhanced CT scan was obtained using 1-, 2-, or 3-mm contiguous axial slices through the patient's entire brain. Patients were initially treated with fractionated radiation therapy. Patients were then eligible for radiosurgery if the tumor recurred or there was evidence of new tumors after radiation therapy, and if they harbored between one to six metastases. In addition, no single metastasis in a patient was greater than 3 cm in mean diameter. Both clinical and radiographic data were collected from medical records, national death records, and direct follow-up examination and entered into a database.

Patients varied in age from 38 to 82 years (median 65 years; Table 1). The male/female ratio was 15:12. A single GKS treatment was given in 27 patients, and two GKS treatments were given in two patients. Repeated radiosurgery or external-beam fractionated radiotherapy was performed for new brain metastases. The median time between diagnosis of primary lung carcinoma and brain metastasis was 7 months. Preoperative symptoms included seizures (three patients), motor or sensory deficits (seven patients), ataxia (four patients), visual dysfunction (two patients), and headaches (five patients). Seven patients (26%) were neurologically asymptomatic. The median KPS score was 90 (range 70–100). Twelve patients (44%) had active extracranial disease.

Brain metastases were identified on CT scan or MR imaging. Typically, tumors were contrast enhancing lesions in the brain parenchyma with surrounding edema. The tumor histology was based on diagnosis at the time of resection or biopsy sampling of the lung primary. Four patients (15%) had stereotactic brain–biopsy confirmed pathology, and one patient (3.7%) had confirmation of the histological subtype during craniotomy and subtotal tumor resection. Patients had undergone prior radiotherapy and demonstrated failure of tumor control on posttreatment neuroradiological imaging. The median WBRT dose was 30 Gy (range 24–56 Gy).

Gamma knife surgery was performed on a total of 47 tumors described in Table 1. The median number of tumors per patient was one (range one–four). The tumor location in the brain was as follows: frontal lobe (13 patients); parietal lobe (10 patients); temporal lobe (four patients); basal ganglia or thalamus (three patients); occipital lobe (seven patients); and posterior fossa (10 patients). The radiation volume was determined and shaped to the typically irregular tumor morphology in all 47 tumors. A median number of four isocenters (range one–14) was used per radiosurgical procedure. The median radiosurgery tumor volume was 5.4 cm^3 (range 0.065–24.6 cm^3). In eight patients tumor volume was less than 2 cm^3, and in 19 patients it was greater than or equal to 2 cm^3. The median dose to the tumor margin was 16 Gy (range 13–20 Gy). Dose selection was based on various factors including tumor volume and location, prior radiation therapy, and a predicted dose–response relationship for brain parenchymal necrosis.[22] A representative dose plan is illustrated by Fig. 1.

Either MR imaging when possible or CT scanning was performed at 2 months after GKS and then every 3 months for the 1st year, and at 4 to 6 monthly intervals thereafter. Imaging was performed to assess changes in tumor size and identify the development of any new tumors. Contrast enhancement defined the tumor margin. A significant change in tumor size was defined as either an increase or decrease of 2 mm in the outer dimensions (that is, anterior–posterior, right–left, and superior–inferior) of the tumor compared with the tumor size at the time of radiosurgery.

Survival time was computed both from the time of radiosurgery and from the time of initial diagnosis of small cell lung carcinoma brain metastasis. Survival curves and median survival were calculated using the Kaplan–Meier method.[28] Factors affecting survival from the time of brain metastasis diagnosis were determined using the Cox proportional hazards model.[14]

Results

Prognostic Factors for Survival

The overall median survival was 18 months (range 2–40 months) from diagnosis of brain metastasis and 4.5 months (range 1–31 months) from radiosurgery. Overall survival times from the diagnosis of small cell lung carcinoma brain metastasis and the point of GKS are depicted in Fig. 2 by using the Kaplan–Meier method.

Multivariate testing using the Cox proportional hazards model revealed only three factors that favorably influenced survival (Table 2). These favorable prognostic factors in-

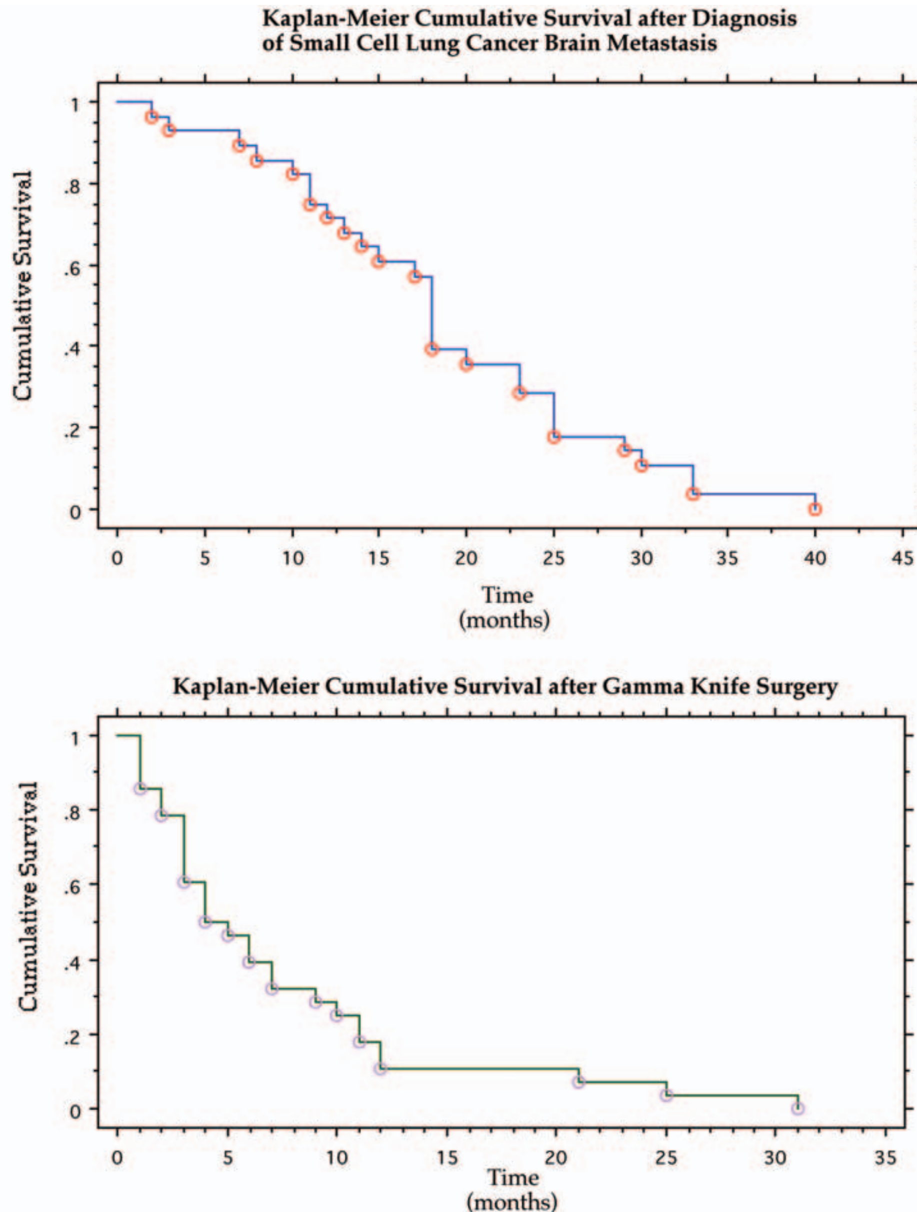

FIG. 2. Kaplan–Meier curves showing overall survival rate of all patients from the time of diagnosis of small cell lung carcinoma brain metastasis *(upper)* and from the time of GKS *(lower)*.

cluded the following: tumor volume at the time of radiosurgery; preoperative KPS score; and time from lung cancer diagnosis until the development of brain metastasis. Median survivals for those with one brain metastasis and those with multiple metastases did not differ in a statistically significant fashion.

In those with lung cancer who were diagnosed with brain metastasis 15 or more months after their initial diagnosis of lung cancer (five patients), the median survival was 25 months after time of brain metastasis diagnosis; however, in those with a shorter interval between diagnoses of lung cancer and brain metastasis (< 15 months [22 patients]), median survival was 18 months after brain metastasis diagnosis. The median survival after brain metastasis diagnosis was 20.5 months for those with tumor volumes less than or equal to 1.8 cm^3 (seven patients), and 18 months for those with volumes greater than 1.8 cm^3 (20 patients).

Nineteen patients died within 24 months of brain metastasis diagnosis. Eight patients were alive 24 or more months after brain metastasis diagnosis. One patient lived more than 3 years after brain metastasis diagnosis. Eleven patients (41%) died of primary disease progression. One patient (4%) died of known central nervous system progression of his brain metastasis, and 15 patients (56%) died of unknown causes.

Local Tumor Control

Radiosurgery was used to treat 47 tumors in 27 patients. Postradiosurgery imaging (MR or CT imaging) was used to

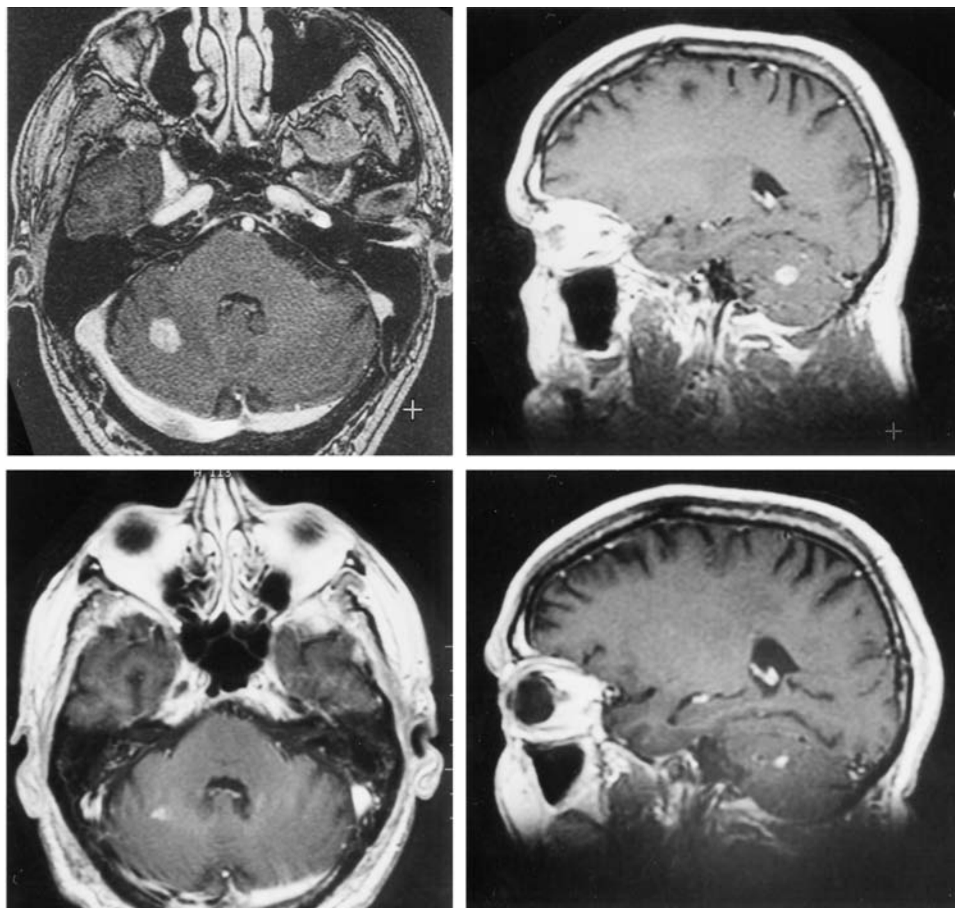

FIG. 3. Magnetic resonance images of a small cell lung carcinoma brain metastasis before and after GKS. These axial *(upper left)* and sagittal *(upper right)* contrast-enhanced images depict a small cell lung carcinoma brain metastasis prior to GKS. Similar axial *(lower left)* and sagittal *(lower right)* contrast-enhanced views of this region obtained 22 months following radiosurgery are illustrated. A marked decrease in tumor size is observed.

evaluate 21 of these tumors in 14 patients. Tumor size was measured in anterior–posterior, right–left, and superior–inferior dimensions and compared with images obtained at the time of stereotactic planning. The remaining tumors were not imaged due to either early patient death of imaging systemic disease or failure of the patient to comply with follow-up imaging. Local tumor control was achieved in 17 (81%) of 21 tumors and in 12 (86%) of 14 patients with follow-up imaging. A representative radiological response from radiosurgery is illustrated by Fig. 3.

Radiosurgical Failures and Incidence of New Brain Metastases

Two patients (7.4%) demonstrated radiological evidence of progression of tumors previously treated with radiosurgery and fractionated radiation therapy. One of these two patients underwent a craniotomy and resection for the larger and more symptomatic of his two brain metastases and died 18 months after brain metastasis diagnosis. The other patient underwent retreatment of her brain metastases with GKS. She ultimately died of extracranial disease progression 25 months after brain metastasis diagnosis and did so before imaging studies were obtained following her second radiosurgery. Three patients (11%) developed new brain metastases on follow-up imaging. One of these patients underwent repeated radiosurgery, and another underwent additional WBRT.

Discussion

Brain metastases represent the most common type of intracranial tumors based on both neuroimaging and autopsy studies.[10,43,58] In patients with small cell lung cancer, brain metastasis occur frequently.[5,6,8,16,17,32,49,50]As many as 30 to 80% of patients with small cell lung cancer develop brain metastasis during the course of the disease, and 10 to 15% have brain metastasis as part of the initial presentation or as the sole manifestation of recurrence.[11,20,44] If untreated, the median time for survival of patients with brain metastases is a dismal 6 to 12 weeks.[11]

In patients with small cell carcinoma of the lung WBRT has been the subject of much investigation.[4–6,20,24,33,41,42,44,45,49] With the high incidence of brain metastasis and the severe morbidity and mortality associated with brain metastases, most centers now advocate the use of prophylactic cranial irradiation for patients with small cell lung cancer.[4,5,24] Fractionated radiation therapy has increased the median survival to 4 to 5 months.[4,5,33] Most centers use 30 to 40 Gy

delivered over 10 to 20 fractions.[5,21,49] In the present series, all patients were treated with prior fractionated radiation therapy.

Adjuvant chemotherapy, primarily with etoposide and cisplatin, has also become well accepted for the treatment of extracranial disease in small cell lung cancer;[11] however, systemic chemotherapy has and continues to play a limited role in the treatment of metastatic brain tumors.[26,27,42] Most chemotherapeutic agents have been ineffective in the treatment of small cell lung cancer brain metastasis because of their failure to cross the largely intact blood–brain barrier.[26,27,42]

Resection is an important part of the neurosurgical armamentarium for treatment of brain metastases; however, surgery is less frequently used in patients with brain metastases due to small cell lung cancer than other types of cancers (for example, non–small cell lung cancer). Recent series coupling resection with fractionated radiation therapy report median survival times of 10 to 14 months, although there is limited data published on such cases.[3,7,19,40,55] Median survival in surgically treated patients with multiple tumors is typically worse.[7] An operative mortality rate of 1.3% was noted in one large series.[59] These large surgical series generally focus on patients with non–small cell lung carcinoma metastases. An occasional case of a surgically treated patient with small cell lung cancer metastatic to the brain is reported in the literature.[1] Resection is generally reserved for selected small cell lung cancer patients who have well-controlled extracranial disease and a solitary brain metastasis.[1] In larger series of patients with brain metastases of various origins, surgical outcomes were best in patients with solitary, surgically accessible tumors and in patients without active systemic disease.[39,40,57] In the present radiosurgical series, no treatment-related mortality occurred. Neither the overall number nor the location of metastases correlated with survival. Radiosurgery can be used to treat multiple, widely separated brain metastases in a single session.

Rationale for Radiosurgery

Small cell lung cancer metastases are well suited for radiosurgery because they are typically small lesions (< 3 cm in greatest dimension), semispherical in shape, and enhance well on MR or CT imaging. Radiosurgery for these lesions is intended to provide local tumor control, stabilize or improve clinical symptomatology, and enhance survival. All of these radiosurgical goals are generally achieved with low morbidity, low cost, and essentially no mortality.[38,46,51,52]

Traditionally, in North America, a patient with small cell lung carcinoma is referred for WBRT first. Patients with a large solitary symptomatic brain metastasis in a surgically amenable location and with inactive systemic disease undergo resection. At the University of Pittsburgh, radiosurgery is utilized for the following conditions: 1) patients with one to six new brain metastases after treatment with WBRT and in locations not amenable to resection; 2) patients who have undergone fractionated radiation therapy but demonstrate growth of at least one tumor afterward; and 3) patients who have undergone prior resection and WBRT and demonstrate residual tumor or recurrence on follow-up imaging.

After radiosurgery, each patient should be followed clinically and by neuroimaging. Neuroimaging follow up entails serial contrast-enhanced imaging studies if possible or, alternately, contrast-enhanced CT scans if MR imaging is contraindicated in a particular patient. In either case, thin-section axial and coronal scans should be obtained to detect changes in tumor dimensions and evaluate for the presence of new metastases.

Previous reports demonstrate overall median survivals of 6 to 11 months in patients treated with radiosurgery for brain metastases of all origins.[18,21,29–31,53] Median survival in the present series of patients with small cell lung carcinoma was 18 months after brain metastasis diagnosis and 4.5 months from radiosurgery. In other series, survival depended on numerous factors including specific tumor primary, number of metastases, KPS status, and the presence of active systemic disease.[9,30,51,56] One large study comprising patients with non–small cell and small cell lung cancer brain metastases demonstrated improved KPS scores and freedom from new brain metastases as well as a decreased mortality from intracranial disease progression in those treated with stereotactic radiosurgery and WBRT as opposed to either modality alone.[34] The present study demonstrated that KPS score, tumor volume, and the interval time between primary diagnosis and brain metastasis development were related to overall survival. Local tumor control was achieved in 81% of small cell lung carcinoma tumors treated with stereotactic radiosurgery. In a recent study of 34 patients with small cell lung cancer brain metastases treated with stereotactic radiosurgery, the authors reported a tumor control rate at 1 year postradiosurgery of 94.5%.[48] Both this study by Serizawa, et al.,[48] and the present one suggest that stereotactic radiosurgery affords a high degree of local tumor control for small cell lung cancer brain metastases.

Given the high incidence of brain metastases in patients with small cell lung cancer and the ease with which a neuroimage of the brain can be obtained, screening imaging of the brain may prove useful in detecting metastases when they are small and asymptomatic. It remains to be seen if early detection and treatment of brain metastases with radiosurgery or other methods will lead to increased survival.

Historically, many patients with small cell lung carcinoma brain metastases frequently died of intracranial disease progression;[11,16,50] however, at least 41% of the patients in the present series died of extracranial disease progression or of known active systemic disease. In this series, 4% of patients died of intracranial disease progression and 56% died of unknown causes, presumably a mixture of both intra- and extracranial disease. As such, the overall management of these patients requires a multimodality approach emphasizing more than their intracranial disease. Longer-term survival with intracranial disease may prompt more aggressive treatment of both the primary site and other extracranial sites of metastatic disease.

Conclusions

Stereotactic radiosurgery appears to be effective in treating recurrent small cell lung carcinoma brain metastases. Treatment of small cell lung carcinoma brain metastases with radiosurgery can enhance survival and facilitate local brain tumor control. Moreover, it does so with low morbidity and essential no mortality. Radiosurgery also can lead to local tumor control in patients in whom resection or radia-

tion therapy has failed. As part of staging a patient with small cell lung cancer, imaging of the brain may reveal small (< 3 cm in diameter) and even asymptomatic lesions well suited for radiosurgery. Whole-brain radiation therapy coupled with radiosurgery and aggressive therapies to address extracranial disease will hopefully lead to longer survival and a better quality of life.

Disclosure

Drs. Lunsford and Kondziolka are consultants for Elekta; however, no funds from Elekta were used to perform this study.

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