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ORIGINAL ARTICLE

Gamma knife radiosurgery in non small cell lung cancer patients with brain metastases: treatment results and prognostic factors

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Summary

Purpose: *To evaluate the efficacy of gamma knife radiosurgery (GKRS) for the treatment of brain metastases from non small cell lung cancer (NSCLC) and find out the prognostic factors for overall survival.*

Methods: *Between February 1997 and August 2003 100 patients underwent treatment for 184 brain metastases from NSCLC, either for recurrence (n=49) or with a new diagnosis (n=51). Median age was 55 years and 77 patients were male. Seventy-eight of the patients received whole brain radiotherapy (WBRT) prior to or after GKRS and 26 patients had surgical removal of the metastasis. Imaging and clinical status were monitored every 3 months following treatment. Kaplan-Meier survival curves, Cox proportional hazards regression for risk factor analysis were used.*

Results: *The median follow up after the procedure was 8 months and after the diagnosis 11 months. The median overall survival for all patients was 9 months from the date of GKRS and 14 months from the diagnosis of brain metastasis. Local tumor control was achieved in 95% of the lesions. In multivariate analysis, adenocarcinoma histology, Karnofsky performance status (KPS) score ≥80, 1-3 metastases and tumor diameter <2 cm were related to longer survival. Addition of WBRT did not have any effect on overall survival.*

Conclusion: *Gamma knife surgery appears to be effective in treating patients with brain metastases from NSCLC, either alone or with WBRT in selected groups of patients.*

Key words: lung cancer, metastases, prognostic factors, radiosurgery

Introduction

Brain metastasis is the most common intracranial tumor and NSCLC is the leading cause of brain metastasis. Treatment options for brain metastases include symptomatic treatment with corticosteroids and WBRT which lead to median survival of 3-6 months [1-3]. The addition of surgical resection of solitary brain metastases or stereotactic radiosurgery (SRS) has been suggested to improve the overall survival in selected patients [4-6]. In a randomized trial (RTOG 95-08) where 64% of the patients had NSCLC, patients with single brain metastasis who received WBRT+SRS had longer survival compared to WBRT alone [7].

Metastatic tumors of the brain are round-shaped enhanced lesions that can be easily identified on computerized tomography (CT) or magnetic resonance imaging (MRI). This character makes them amenable to SRS with high precision, providing good local control. In this study, we aimed to assess the efficacy of GKRS for the treatment of patients with brain metastases from NSCLC in various settings and identify the prognostic factors related to improved patient survival.

Methods

Patient population

We retrospectively reviewed the records of 100 consecutive NSCLC patients with brain metastases who received GKRS at our hospital between February 1997 and August 2003. All patients signed informed consent prior to the procedure. Patients with KPS score ≥70, 1-4

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metastases and the largest tumor <4 cm were eligible for GKRS. If new metastatic lesions were seen on contrast-enhanced planning MRI they were also covered by extra shots due to its technical feasibility.

There were 77 male and 23 female and the median age was 55 years (range 32-82). The percentage of patients aged ≤ 60 years was 70%. The median KPS score was 90 (range 70-100). Pathologic subtypes were adenocarcinoma (n=35), squamous cell carcinoma (n=16), large cell carcinoma (n=1) and unclassified NSCLC (n=48). Fifty-one patients presented with newly diagnosed brain metastases, whereas 49 patients presented with recurrent or progressive brain disease. Primary lung disease was controlled in 53% of the patients. Extracranial distant metastasis was present in 15% of the patients. Overall 51(51%) patients had active extracranial disease during GKRS. Primary treatment for lung cancer before GKRS consisted of thoracic surgery in 34 patients, thoracic irradiation in 28 patients and systemic chemotherapy in 55 patients, either alone or in combination.

Indications for GKRS were: 1) after WBRT for recurrence (n=31); 2) combined with WBRT as a boost (n=19); 3) GKRS alone for new diagnosis (n=24); 4) combined with brain surgery for residual metastases (n=3); 5) after brain surgery for recurrence (n=3); 6) after brain surgery and WBRT for recurrence (n=15); and 7) combined with brain surgery and WBRT for new diagnosis (n=5). Conclusively, GKRS was performed for recurrence in 49 patients (groups 1, 5 and 6), and for newly diagnosed brain metastases in 51 patients (groups 2, 3, 4 and 7).

Brain metastases were detected by gadolinium-enhanced MRI scans in all patients. A brain metastasis diagnosed within 2 months of primary NSCLC was classified as synchronous while a metastasis identified >2 months from primary diagnosis was considered metachronous. Median times from diagnosis of primary lung carcinoma to brain metastasis and to GKRS procedure were 4 months (range 0-45) and 8 months (range 0-72), respectively.

One hundred patients harbored 184 metastatic tumors in the brain (median=1, mean=1.84). Sixty patients had single metastasis, 14 had 2 metastases, 14 had 3 metastases, 8 had 4 metastases, 2 had 5 metastases and 2 patients had 6 metastases. Tumors were located supratentorially in 70 patients, infratentorially in 14 and at both locations in 16 patients. Tumor localizations within the brain were as follows: 61 in the frontal lobe; 37 in the parietal lobe; 18 in the temporal lobe; 26 in the occipital lobe; 31 in the cerebellum; 6 in the thalamus; and 5 in the brainstem. The largest tumor localization comprised the frontal lobe (n=29), parietal lobe (n=28), temporal lobe (n=11), occipital lobe (n=9), cerebellum (n=17), thalamus (n=3), and brainstem (n=3).

Radiosurgery technique

Leksell model G stereotactic head frame (Elekta Instruments, Atlanta, GA) was applied to the patient's head under local anesthesia along with mild sedation when necessary. Three-millimeter thick gadolinium-enhanced axial MR slices were obtained with a 1.5 tesla magnet. Imaging data was transferred to the workstation by ethernet. Leksell Gamma Plan software (version 5.30) was used for treatment planning. All radiosurgery procedures were performed by model B Leksell Gamma Knife unit (Elekta Instruments, Atlanta, GA). Peripheral isodose line was conformed to the contrast-enhancing lesion. One to 19 isocenters (median 1 isocenter) were used for each lesion. Largest tumor diameter ranged between 4 and 40 mm (median 19). The median peripheral dose was 16 Gy (range 10-25), and the median maximal dose was 32 Gy (range 16-50). Dose selection was based on tumor volume, location, prior radiotherapy and predicted dose-response relationship for brain necrosis, as reported previously [8]. Eighty-nine patients underwent one radiosurgery procedure and 11 underwent 2 procedures (8 patients after new brain metastases and 3 after local progression).

Follow-up

Patients were followed with physical and neurological examination and contrast-enhanced MRI at 2 months after GKRS and 3 monthly thereafter. The median follow-up after radiosurgery was 8 months (range 1-64), and the median follow-up after diagnosis of brain metastasis was 11 months (range 2-64). Radiologic response of brain metastases after GKRS was evaluated using the McDonald criteria. Complete response was defined as complete disappearance of the lesion which was defined as the product of 2 diameters of the lesion in the axial T1 weighted image; partial response as ≥50% reduction in tumor size; stable disease as < 50% reduction or ≤ 25% increase; and progressive disease as >25% increase in tumor size.

Survival time in months was calculated from the date of first GKRS procedure and from the date of first diagnosis of brain metastases. Local brain control was defined as any response (complete or partial) or stable size of the metastatic lesion after GKRS. Local and brain progression-free survival rates were calculated from the date of GKRS to progression of the metastatic lesion after GKRS or any progression in the brain, respectively.

Statistical methods

Survival curves were plotted using the Kaplan-Meier method. Factors affecting survival (histologic subtype, gender, age, KPS, largest tumor diameter, recursive partitioning analysis [RPA] score, the status of the primary tumor, presence of extracranial systemic disease, number of metastases, WBRT) were assessed with the log-rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis. Statistical significance was put at $p < 0.05$.

Results

At the time of analysis 24 of 100 (24%) patients were still alive and 76 had died. The median overall survival for all patients was 9 months (95% CI 7-11) from the date of GKRS and 14 months (95% CI 11-17) from the diagnosis of brain metastasis (Figure 1). The 6-, 12- and 18-month actuarial overall survival rates were calculated as 61.8±4.9%, 34.5±5.2% and 17.2±4.4%, respectively.

The median overall survival from the date of GKRS for 49 patients treated for recurrent brain disease was 8 months vs. 10 months for 51 patients with new diagnosis (p=0.292). However, the median overall survival from the diagnosis of brain metastasis was better for recurrent patients compared to patients with new diagnosis (16 vs. 11 months, p=0.0232).

Patients with metachronous brain metastases had a longer survival compared to the ones with synchronous metastases from the onset of brain metastasis (median survival 25 vs. 9 months, $p<0.0001$). However, median survival for both groups was 9 months when the survival was calculated from the date of GKRS.

Local tumor control

Radiologic response was evaluated in 94 patients. MRI could not be performed in 6 patients because of systemic progression before brain evaluation. Local tumor control was achieved in 161 (95%) of 170 lesions and 87 (93%) of 94 evaluable patients. Response of individual tumors were complete in 26 (15.3%) and partial in 97 (57.1%). Stable disease was observed in 38 (22.3%) tumors and progressive disease in only 9 (5.3%) tumors. Local progression-free survival at 1 year was 78% (Figure 2). Median brain progression-free survival was 12 months (95% CI 6-18).

Prognostic factors for survival

Patient- and treatment-related prognostic factors for overall survival are shown on Table 1.

Patients with supratentorially and infratentorially located tumors had similar survival rates (median 10 months), however patients with tumors in both locations had inferior survival rates (median 4 months). Although this difference was statistically significant (p=0.005), localization of metastases in both sides of the tentorium correlated with the number of metastases. For this reason tentorial localization was not included in the multivariate analysis as a prognostic factor.

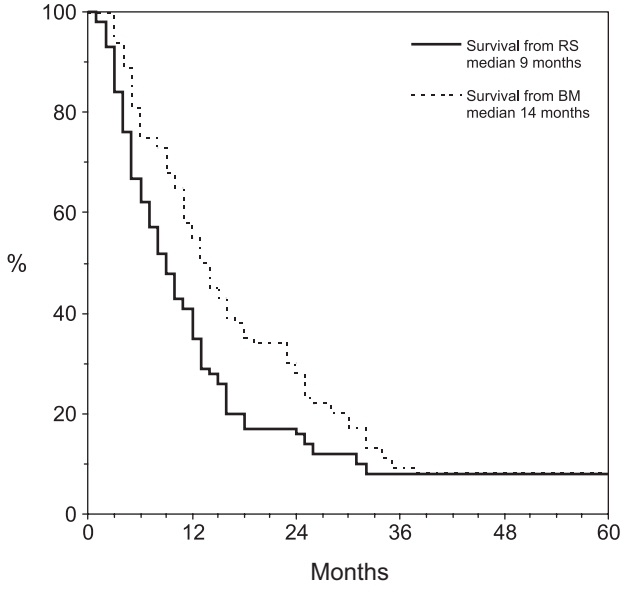

Figure 1. Overall survival rate of all patients from radiosurgery (RS) and diagnosis of brain metastasis (BM).

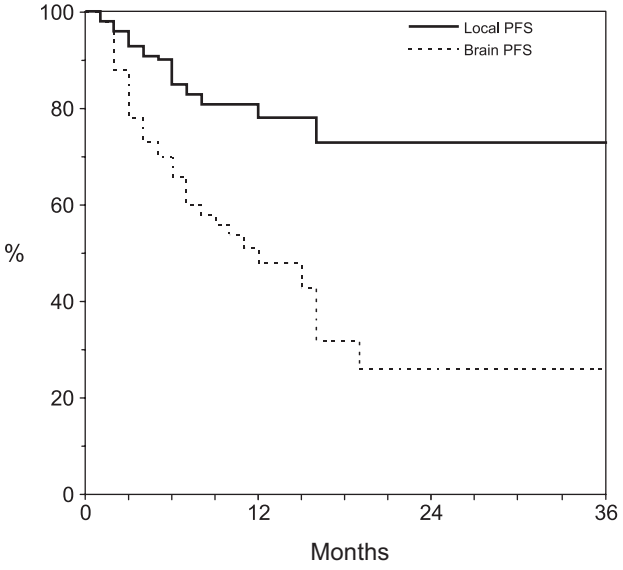

Figure 2. Local and brain progression-free survival (PFS) rates in 94 patients evaluated for response.

Table 1. Patient and treatment characteristics assessed for prognostic significance on overall survival

Characteristics	*Patients, n*	*Median OS (months)*	*p-value (univariate)*	*p-value (multivariate)*
Histologic subtype				0.005
Adenocarcinoma	35	13	Adeno vs. others = 0.0378	
Squamous cell carcinoma	16	10	Squamous vs. others = 0.5142	
Unclassified NSCLC	49	7	NSCLC vs. others = 0.109	
Sex				0.665
Male	77	9	0.6263	
Female	23	8		
Age (years)				0.511
≤60	70	8	0.7676	
>60	30	9		
KPS				0.008
≤80	35	5	0.0081	
>80	65	11		
RPA				0.451
1	44	12	0.0178	
2	56	7		
Primary tumor				0.756
Controlled	53	12	0.0049	
Uncontrolled	47	6		
Other systemic metastasis				0.321
Absent	85	10	0.0485	
Present	15	6		
Primary or systemic disease				0.289
Controlled	49	12	0.0009	
Uncontrolled	51	6		
Number of metastases				0.01
1	60	12	1 vs. 2-3 = 0.0094	
2-3	28	7	1 vs. 4-6 = 0.0042	
4-6	12	5	2-3 vs. 4-6 = 0.4046	
Largest tumor diameter (cm)				0.045
<2	54	10	0.05	
≥2	46	7		
Any WBRT*				0.874
No	22	8	0.757	
Yes	78	9		

OS: overall survival, NSCLC: non-small cell lung cancer, KPS: Karnofsky performance status, RPA: recursive partitioning analysis, WBRT: whole brain radiotherapy.
*Including patients who received WBRT after gamma knife radiosurgery for brain recurrence

Multivariate analysis revealed adenocarcinoma histology (p=0.005, RR=0.46), less number of brain metastases (1 vs. 2-3, p=0.0094; 1 vs. 4-6, p=0.0042; 2-3 vs. 4-6, p=0.4046; RR=1.32), diameter of largest metastasis < 2 cm (p=0.045, RR=0.60) and KPS score >80 (p=0.008, RR=0.47) as the best prognostic factors for overall survival (Figures 3-5). RPA class and absence of extracranial systemic disease were found to be significant for prolonged survival in univariate analysis only (Figure 6).

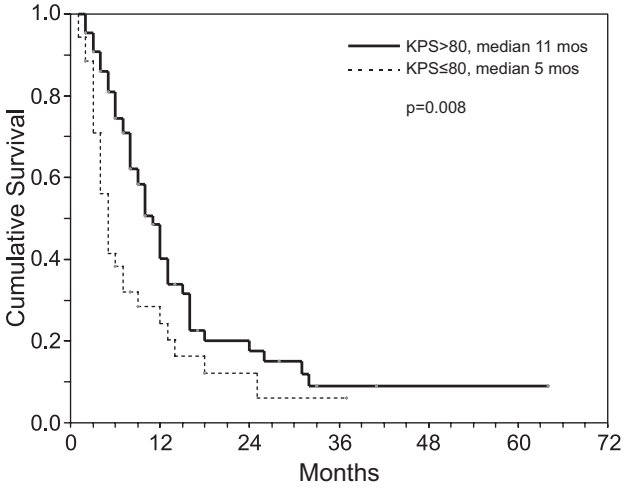

Figure 3. Overall survival rates for all patients according to their Karnofsky performance status (KPS) scale.

Discussion

Brain metastasis from NSCLC lung cancer is the most frequent form of intracranial metastatic disease

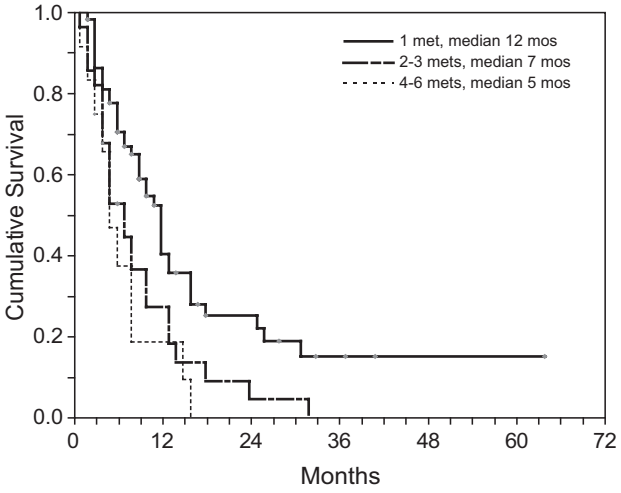

Figure 4. Overall survival rates for all patients according to the number of brain metastases. 1 vs. 2-3 p=0.0094; 1 vs. 4-6, p=0.0042; 2-3 vs. 4-6, p=0.4046.

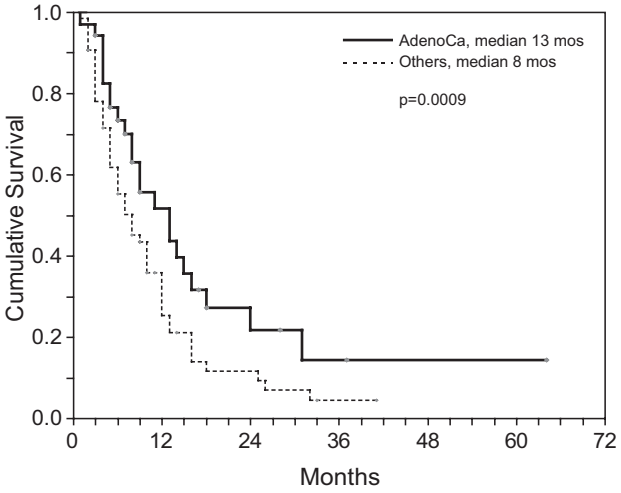

Figure 5. Overall survival rates of adenocarcinoma patients compared to other histologies.

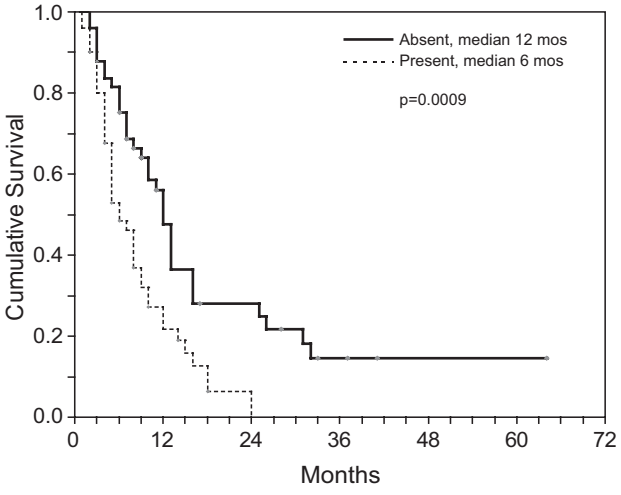

Figure 6. Overall survival rates for all patients according to presence or absence of extracranial systemic disease.

[9]. The incidence of brain metastasis from lung cancer at the time of diagnosis ranges between 10-18%, and 2 years post-diagnosis this rate increases to 50% [10].

Historically, the results of conventional treatments consisting of WBRT and corticosteroids have usually been disappointing, with a median survival of 2-7 months according to different series in the literature [9,11-14]. The addition of surgery to WBRT in a selected group of patients with favorable prognostic features increased the overall survival to 9-19 months [15-17].

SRS is an acceptable, non-invasive technique alternative to surgery for achieving local control of brain metastases in selected patients [18]. This treatment can be delivered via different treatment machines including gamma knife and Linac-based systems. Nonetheless, when used alone or in combination with WBRT it appears to prolong survival [19,20].

NSCLC metastases are usually small, well-enhanced lesions and radiosurgery can provide local tumor and symptom control in these patients with low morbidity. This can be achieved in different groups of patients such as those with < 4 metastases, patients who have undergone WBRT and have persistent or new lesion on MRI scan, with progression after resection or new lesions afterwards.

In previous studies, a median survival time between 6-11 months was reported in patients treated with gamma knife surgery for brain metastases for all histological subtypes [21-23]. In retrospective series of radiosurgery for lung primaries (including small cell histology in some of them) median survival times ranged between 7-14 months [24-28]. In our series the median survival was 9 months from the date of GKRS and 14 months from the brain metastases diagnosis. Although it is difficult to compare these results with previous ones given the retrospective nature of all studies and different inclusion criteria of the patients, our results were consistent with the literature.

The prognostic factors affecting the survival of patients with brain metastases after conventional radiotherapy and radiosurgery have been explored thoroughly previously and these factors were found to be histological subtype, number of metastases, presence of active systemic disease, age, presence of neurological symptoms, KPS score and status of the primary disease in different series [24-27,29-36]. In our study population, patients with adenocarcinoma lived longer compared to other subtypes (median overall survival 13 vs. 8 months; p=0.005); in accordance with the results of Sheehan et al. [24]. In their series of 273 patients median survival of patients with adenocarcinoma was 10 months, whereas in patients with all other histological subtypes the survival was 7 months and adenocar-

cinoma histology was an independent prognostic factor for better survival. Adenocarcinoma histology was also found to be a major prognostic factor in a study by Gerosa et al. [27].

The number of brain metastases was another prognostic factor for overall survival in the multivariate analysis in our study population. The median overall survival of patients with 1 metastasis, 2-3 metastases and 4-6 metastases were 12, 7 and 5 months, respectively. This finding is consistent with the study by Gerosa et al. [27] where a solitary lesion was stated as a major prognostic factor for overall survival when compared with multiple lesions. Among other studies exploring the number of metastases as a prognostic factor, none could prove this [21,24,30,37]. This might be due to the retrospective nature of the studies and different inclusion criteria of the gamma knife procedure.

Small metastases (< 2 cm) are often round-shaped, well-circumscribed lesions that enhance diffusely on MRI scan. This makes these lesions a good candidate for radiosurgery with a high accuracy for tumor control. In our series the overall survival of patients having metastases < 2 cm had a median overall survival of 10 months which was found as independent prognostic factor. In a study by Kim et al. [21], intracranial tumors < 2 cm were included as "favorable group" in their patient population.

In our study group the median overall survival from the diagnosis of brain metastasis was better for recurrent patients when compared to patients with new diagnosis (16 vs. 11 months; $p < 0.0001$. It is difficult to draw a precise conclusion from this result because this is probably due to selection of patients with better prognosis who have lived long enough to relapse in the brain.

Most patients in the current series (78%) also received WBRT which remains widely as standard treatment for brain metastases, either prior to or following radiosurgery. When WBRT was analyzed, we were not able to show it as a prognostic factor. There are conflicting results in the literature regarding the influence of WBRT when added to radiosurgery. Jawahar et al. [25], Sheehan et al. [24] and Gerosa et al. [27] found no effect of previous WBRT on survival, whereas in the study by Kong et al. [37] it remained significant. Yet, these results should be evaluated with caution as none of these studies were prospectively randomized to assess the importance of WBRT and may potentially contain selection bias for the radiosurgery-alone group. One phase III randomized trial from Japan evaluating the effect of WBRT when added to SRS for brain metastases showed no improvement in overall survival, with a median survival of 7.5 vs. 8 months, although the 12-month brain tumor recurrence rate was lower [38]. Another phase III randomized trial from EORTC trying to find the value of adding WBRT to either surgery or radiosurgery in oligometastases has just finished patient accrual and researchers are finalizing the results.

In conclusion, gamma knife surgery appears to be effective in treating patients with brain metastases from NSCLC. The primary aim should be intracranial tumor control as we know that brain metastases are the most important clinical factor in these groups of patients in historical studies for prolonging overall survival. Moreover, it can be delivered with low morbidity and almost no mortality when compared with craniotomy. Therefore, we recommend radiosurgery for brain metastases from NSCLC, either alone or with WBRT in carefully selected groups of patients.

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