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Clinical Study

Gamma knife radiosurgery for multiple brain metastases from lung cancer

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ABSTRACT

The aim of this study was to compare the effectiveness of gamma knife radiosurgery (GKS) for the treatment of multiple brain metastases from lung cancer with that of whole brain radiation therapy (WBRT). Patients with multiple (2-20) brain metastases were divided into two groups for initial brain tumor management: a GKS group (14 patients) and a WBRT group (19 patients). The patients were stratified by gender, age, initial Karnofsky performance status score, control of the primary site, known extracranial metastases, number of brain metastases, diameter of the maximal lesion, chemotherapy, and recursive partitioning analysis (RPA) Class. The 6-month and 1-year overall survival rates were 64.3% and 47.7%, respectively, in the GKS group, and 42.1% and 10.5%, respectively, in the WBRT group. The median survival time was 32 weeks in the GKS group and 24 weeks in the WBRT group. The overall survival time in the GKS group was significantly longer than in the WBRT group ($p = 0.04$). The univariate analysis suggests that survival was increased in both patients with a controlled primary tumor site and in the GKS group ($p = 0.03$, 0.04). The use of GKS in patients with multiple brain metastases significantly improved patient survival compared to the employment of WBRT. When we assessed the subgroups, systemic disease control and GKS were significant variables by univariate analysis.

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1. Introduction

Brain metastases develop in 20% to 40% of patients with cancer.[1] The most common primary cause of brain metastases is lung cancer, which is the leading cause of cancer-related deaths in the United States of America. Whole brain radiation therapy (WBRT) has long been recognized as the standard treatment for patients with brain metastases. However, the prognosis remains poor with this treatment approach. After WBRT, patients have an average expected survival time of less than 6 months.[2] In the last decade, use of gamma knife radiosurgery (GKS) has become more common in clinical practice worldwide. Because this technology has the ability to deliver higher biological doses of radiation to brain lesions, GKS may provide more effective control of brain metastases than WBRT, and therefore potentially improve survival in these patients.[3] In patients with solitary brain metastasis, GKS has shown excellent local control and survival benefits.[4,5] However, the use of GKS as part of the initial management of patients with multiple brain metastases is controversial.

In this study, GKS was compared to WBRT in the treatment of patients with multiple brain metastases. The aim of the study was to determine the efficacy of GKS as a treatment of multiple brain metastases when compared to WBRT, and to examine patient survival rates and prognostic factors.

2. Materials and methods

2.1. Patient population

Between January 2005 and December 2006, 80 patients with multiple metastatic brain tumors from lung cancer were treated at our center using either GKS or WBRT. Depending on the preference of both consulting physician and the patient, participants were allocated to either the GKS or WBRT treatment group. Thirty-three patients (41.3%) with 211 lesions were available for the survival analysis. Patients were included in this study if they had: (i) from 2 to 20 brain metastases; (ii) a life expectancy of more than 2 months; (iii) no history of previous treatment with either GKS or WBRT; and (iv) lesions with a maximal diameter of no more than 3 cm. Patients' ages ranged from 42 years to 76 years, with a median of 60 years. Nine patients (27.3%) were female and 24 (72.7%) were male. The patients were divided into two groups according to the treatment modality: a GKS group (14 patients) and a WBRT group (19 patients). The following radiological studies were performed to determine the active disease status: a chest X-ray, a bone scan (when indicated), and a CT scan of the chest, abdomen and pelvis (as indicated).

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2.2. WBRT and GKS techniques

Based on the Radiation Therapy Oncology Group (RTOG) trials, the standard treatment recommendation for the last two decades for most patients with brain metastases has been WBRT, with 30 Gy administered in 15 fractions over 3 weeks or 10 fractions over 2 weeks.

GKS was performed using a Gamma Knife Model C (Elekta, Stockholm, Sweden). The stereotactic frame was fixed to the head of the patient under local anesthetic and the frame position was centred over the metastatic tumors. Gadolinium double-enhanced T1-weighted MRI, with a slice thickness of 2 mm and no gap, was used to determine the target coordinates and treatment planning. The GammaPlan planning system (Elekta) was used for GKS planning.

2.3. Follow-up examination

We performed neurological evaluations 1 and 3 months after treatment, and then every 3 months thereafter. A diminished quality of life (QoL) was defined as an impaired neurological status, as reflected by a Karnofsky performance status (KPS) score of less than 70. Follow-up MRI was performed every 3 months after the GKS or WBRT treatment. Unless there was evidence of recurrence, the total resection of the primary tumor was considered control of the primary site, as was the completed treatment of the primary tumor at least 1 month before the diagnosis of brain metastases, without evidence of progression.

2.4. Statistical analysis

Overall survival was recorded from the date of diagnosis of the brain metastases until death. The actuarial survival was calculated using the Kaplan-Meier method, with 95% Greenwood confidence intervals (95% CI). Qualitative survival, intervals from the date of diagnosis to the date of impaired QoL, was also calculated using the Kaplan-Meier method. Comparison of prognostic groups was performed using the log rank analysis. To test and then adjust for the influence of the prognostic factors on survival, univariate analysis was performed for various patient subgroups, and for all patients.[6] Parameters tested for their influence on survival included gender, age (<65 vs. ⩾65 years) and treatment modality (WBRT vs. GKS). In addition, the initial KPS score (<70 vs. ⩾70), control of the primary site (yes vs. no), known extracranial metastases (yes vs. no), number of brain metastases (<10 vs. ⩾10), maximal diameter of the lesion (<15 mm vs. ⩾15 mm), chemotherapy (yes vs. no), and RTOG recursive partitioning analysis (RPA) (Class 1 [age < 65 years; KPS ⩾ 70; no extracranial disease] vs. Class 2 [KPS ⩾ 70; age ⩾ 65 years; and/or extracranial disease present] vs. Class 3 [KPS < 70]) were evaluated.[7] The distribution of the covariates between the two groups was compared using the Fisher's exact test. All analyses were performed using the Statistical Package for the Social Sciences version 14.0 for Windows (SPSS, Chicago, IL, USA). A p value of < 0.05 was accepted as the threshold for statistical significance.

3. Results

3.1. Patient summary

The distribution of the patient characteristics is summarized in Table 1. The mean number of lesions treated by GKS was 5.9. The mean maximal diameter of the tumors was 22.1 mm. The mean prescription dose applied to the tumor margin was 19.2 Gy (range: 18–21 Gy). The mean prescription isodose at the tumor margin was 50% (range: 40–60%). The mean follow-up time was 55 weeks (range: 10–124 weeks) in the GKS group and 31 weeks (range: 8–104 weeks) in the WBRT group.

Table 1
Summary of patient characteristics in the GKS and WBRT groups

Characteristic	GKS group	WBRT group	p value*
Number of patients	14	19	
Sex			
Male	9	15	0.35
Female	5	4	
Age			
<65 years	10	9	0.17
⩾65 years	4	10	
Initial KPS score			
<70	0	2	0.21
⩾70	14	17	
Control of primary site			
Yes	8	7	0.25
No	6	12	
Known extracranial metastases			
Yes	6	10	0.58
No	8	9	
RPA class			
1	6	3	0.14
2	8	14	
3	0	2	
Number of brain metastases			
<10	12	15	0.62
⩾10	2	4	
Diameter of the maximal lesion			
<20 mm	4	8	0.42
⩾20 mm	10	11	
Chemotherapy			
Yes	10	14	0.89
No	4	5	

GKS = gamma knife radiosurgery, KPS = Karnofsky performance score, RPA = recursive partitioning analysis classes defined by Gaspar et al.[8], WBRT = whole brain radiotherapy.
* Probability value is based on Fisher's exact test.

3.2. Overall survival and qualitative survival

Fig. 1 shows the survival curves comparing the overall survival rate between the GKS and WBRT treatment groups using the Kaplan-Meier method. The median survival time was 32 weeks in the GKS group and 24 weeks in the WBRT group. The 6-month

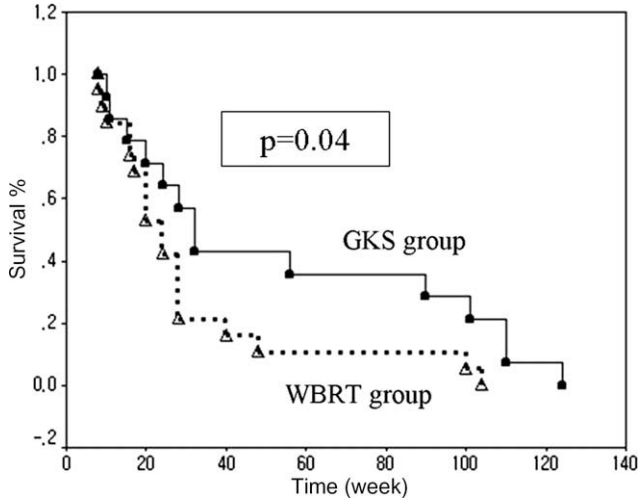

Fig. 1. Kaplan-Meier survival curves showing the overall survival in the gamma knife radiosurgery (GKS) and whole brain radiation therapy (WBRT) groups.

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