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ORIGINAL ARTICLE

Gamma Knife Radiosurgery in the Management of Non-solitary Brain Metastases: A Retrospective Analysis of Survival

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OBJECTIVE

This study aims to evaluate the effectiveness of Gamma Knife Radiosurgery (GKRS) in patients with two or more brain metastases.

METHODS

A retrospective analysis of 40 patients treated between 2002 and 2013 in one of the largest medical centers of India was performed. Patients were categorized into three categories according to RPA classification. The demographic and clinical characteristics of the patients, including age and gender, were extracted from case records.

RESULTS

The most common location was the frontal lobe. Breast cancer was the commonest source of metastases. The median survival of patients treated with GKRS for non-solitary brain metastases was four months. The median survival of RPA III category patients was three months, whereas it was four months in both the RPA category II and RPA category I patients.

CONCLUSION

The findings suggest that GKRS is a safe and effective option of palliative treatment in patients with non-solitary brain metastases. The neurocognitive morbidity associated with whole brain radiotherapy is negligible with Gamma Knife radiosurgery (GKRS).

Keywords: Brain metastases; Gamma Knife radiosurgery; stereotactic radiosurgery; survival.

Introduction

Brain metastases are one of the most common intracranial malignancies that remain a substantial source of morbidity and mortality in cancer patients.[1] The incidence of brain metastases has been increasing over the last few years.[2,3]

The recent novel advances in the management of carcinomas have increased the demand for a safe and effective control of cerebral metastases.[4] Whole Brain Radiotherapy (WBRT) has remained one of the most widely used treatment option in patients with non-solitary brain metastases, although recent clinical experiences permitted local control of non-solitary brain metastases using Stereotactic Radio Surgery (SRS).[5] As a focal, highly precise treatment option, SRS provides many benefits, including a short treatment timeline, a low probability of normal tissue complication, and a high probability of treated lesion control.[6] The use of SRS and imaging accessibility has led to a dramatic re-

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duction in mortality related to intracranial tumor progression.[7,8] Recent studies have indicated GKRS as an effective treatment modality for non-solitary brain metastases with good local control and lesser neurological and neuropsychological side-effects.[9,10] However, the current literature is relatively devoid of information concerning extensive metastatic disease, it is necessary to determine the effectiveness of SRS treatment for patients with non-solitary brain metastases. In this regard, few studies have evaluated the effectiveness of GKRS in the management of non-solitary brain metastases in Indian setting.[11-13]

The management of choice of single metastasis is still surgical, with or without adjuvant WBRT/SRS. Hence, the prognosis and overall survival defers significantly when compared to two or more metastatic lesions.[14] For the patients with two or more metastatic lesions the overall survival did not show any significant difference concerning the number of lesions in the brain. The management of these patients is usually non-surgical with WBRT/WBRT+GKRS/GKRS alone.[15]

Recently, Yamamoto reported a prospective, non-randomised multicenter study of 1194 patients with tumor number up to 10 and treated with GKRS alone. Only 17 percent patients had more than four lesions in the brain. The median overall survival after GKRS was significantly longer in patients with single tumor than those with two or more tumors. Further, the median overall survival for the two groups of patients with more than one tumor (2-4 tumors vs. 5-10 tumors) was the same.[15]

Based upon this study, which suggested a significant management change between patients with single lesion and those with two or more lesions, it was decided to analyze the chances of overall median survival in patients with two or more lesions. This kind of study has not been reported in the literature. Therefore, the present study aimed to assess the effectiveness of GKRS in patients with non-solitary brain metastases.

Materials and Methods

Study Design

A retrospective study was conducted to review case records of the patients diagnosed with non-solitary brain metastases. The data of the patients who were treated with GKRS in Gamma Knife centre, All India Institute of Medical Sciences, New Delhi, India, were included in this study. Seventy nine patients received GKRS for brain metastasis from the period of 2002 to 2013.

Inclusion criteria were as follows:

1. Two or more metastatic lesions detected by MRI and confirmed by neuro oncologist
2. Age >18 years
3. Known histological proven primary cancer

Exclusion criteria were:

1. Unfeasible GKS treatment or an overriding indication for surgery because of high ICP or the need to obtain a histological diagnosis;
2. Prior treatment of brain metastases with GKRS
3. Previous treatment for single brain metastatic lesion
4. Contradicted MRI findings

Study Procedure

The demographic and clinical information was extracted from the clinical records, which included gender, age, location of lesions, tumor histology, number of metastases, Kanofsky Performance Status (KPS) score, information regarding previous WBRT, status of the primary tumor, status of extra-cranial metastasis, peripheral dose, tumor volume, Recursive Partition Analysis (RPA). The RPA helps to guide clinical decision making for brain metastases. It divides patients with brain metastases into three broad categories based on patient age, KPS, presence of extracranial metastases, and the status of the primary tumor control.[16] RPA was used because it has been shown to be of prognostic value in patients with brain metastases, and has been invariably used in various studies that have evaluated the effectiveness of GKRS.[17]

GKRS was performed using Leksell B and Leksell Perfexion model. Treatment was planned by using Electa's Gamma Plan Software. In this regard, RTOG 95-08 [18] guidelines, as well as parameters, such as total number of metastases, tumor volume, and prior WBRT were considered for the dose selection.

Overall Survival was defined as the time duration between GKRS treatment and death. The survival time data were obtained by asking the caregivers using telephonic or postal communication.

Statistical Analysis

The Kaplan–Meier analysis was performed to estimate the overall survival time and the survival duration for the patients' subgroups. All statistical analyses were performed using SPSS for Windows, Version 19 (SPSS Inc., Chicago, IL, USA).

Results

Seventy nine patients received GKRS for brain metastasis between 2002 and September 2013. Thirty two patients (40.5%) had single metastatic lesion, and 47 patients (59.4%) had non-solitary lesions (range: 2 to 13). Of the 47 patients, only 40 patients whose date of death or clinical status could be established by postal or telephonic communication were included in the study.

The clinical and demographical details of patients are presented in Table 1. The median age of patients at the date of GKRS was 54 years (range 35 to 76 years). In this analysis, 131 lesions were treated in 40 patients. Fifty eight lesions (44.28%) were present in the frontal lobes.

In majority of the patients, metastasis initiated from breast carcinoma (42.5%). At the time of GKRS, 11 patients (27.5%) had KPS less than 70, while eight patients (20%) had KPS score of 90 or more. Extracranial tumor was present in eight cases. Of the 40 cases, eight patients had received prior WBRT while the remaining 32 had not received any treatment before GKRS. In 22 cases (55%), the primary tumor was controlled (Table1).

Table 2 reveals the radiological parameters of the present study. Most of the patients had two or three lesions (82.5%), while only three patients (7.5%) had more than five lesions. The planned tumor volume (PTV) ranged between 0.018 cm^3 and 39.1 cm^3. The median dose prescribed was 20 Gy (range; 8–25 Gy).

The distribution of the RPA score for patients is also shown in Figure 1. There were 15 patients (37.5%) in RPA Class I, 14 patients (35%) in RPA Class II and 11 patients (27.5%) in RPA Class III (Fig. 1).

The results obtained from survival analysis indicated that the median survival time for different RPA scores was significantly different. The median survival was three months in class III and four months in classes II and I (Table 3).

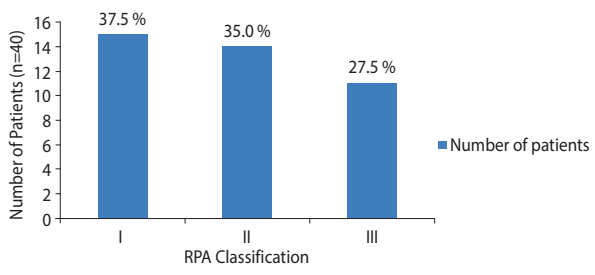

Fig. 1. Number of the patients in different categories of RPA.

Table 1. Clinical and demographic characteristics of the patients (N=40)

Characteristics		No. of patients (%)
Gender	Male	13 (32.5)
	Female	27 (67.5)
Age (years)	Median	54
	Range	34-76
	≤ 65	32 (80 %)
	> 65	8 (20%)
Location of metastatic lesion	Frontal	58 (44)
	Temporal	15 (11)
	Parietal	26 (20)
	Occipital	4 (3)
	Cerebellar	19 (15)
	Others	9 (7)
Primary Source of Metastasis	Breast	17 (42.5)
	Lung	6 (15.0)
	Renal cell Carcinoma	7 (17.5)
	Esophagus	2 (5)
	Ovary	2 (5)
	Thyroid	1 (2.5)
	Larynx	1 (2.5)
	Unknown	4 (10)
KPS Score	≥90	8 (20)
	80	10 (25)
	70	11 (27.5)
	<70	11 (27.5)
WBRT	Received	8 (20)
	Not received	32(80)
Status of primary tumor	Controlled	22 (55)
	Uncontrolled	14 (35)
	Unknown	4 (10)
Status of extracranial tumor	Present	8 (20)
	Absent	32 (80)

Table 3. RPA classification of the patients and median survival

RPA Class	Median Survival (months)	p-Value	Hazard ratio
I	4	-	1.0
II	4	0.418	1.212
III	3	0.004	1.908

The median overall survival was four months (range 1 to 12 months). The overall survival curve is shown in Figure 2. Twenty two patients (55%) succumbed to their extracranial disease, 17 patients (42.5%) died because of progressive intracranial disease and one pa-

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Table 2. Radiosurgical parameters

Characteristics	Number (%)	
Number of lesions	Median	3
	Range	2-13
	2	17 (42.5)
	3	16 (40)
	4	2 (5)
	5	2 (5)
	>5	3 (7.5)
Planned tumor volume (PTV)	Median	1.00 cm^3
	Range	0.018 cm^3-39.1cm^3
Mean PTV	≤2	11 (27.5)
	>2-≤5	15 (37.5)
	>5-≤9	7 (17.5)
	>9	7 (17.5)
Peripheral dose (GY)	Median	20 Gy
	Range	8–25 Gy
	25	16 (40)
	20	14 (35)
	15-19	7 (17.5)
	<15	3 (7.5)

tient (2.5%) survived till twelve months. The survival curves are shown in Figure 3.

Discussion

Non-solitary brain metastases (BMs) have a poor prognosis. Hence, estimation of overall survival is significant when deciding on treatment protocol.[19] Therefore, this study aimed to evaluate the effectiveness of

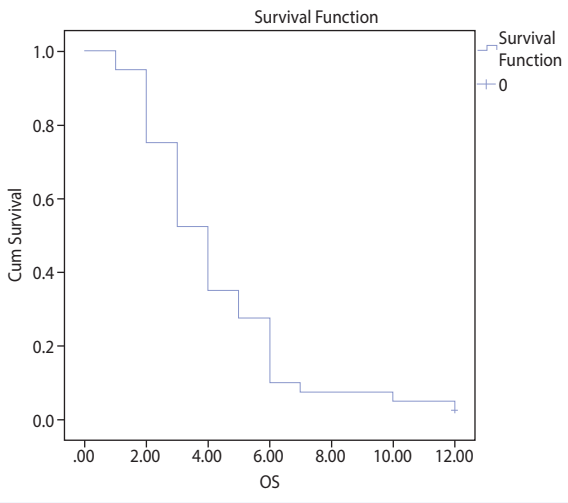

Fig. 2. Kaplan-Meier curve showing the overall survival rate.

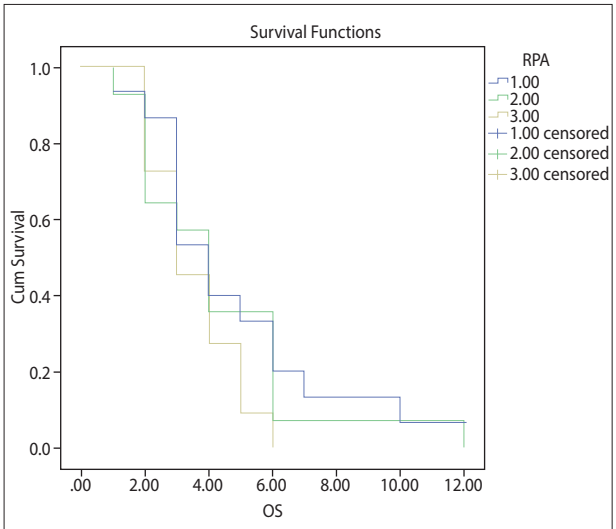

Fig. 3. Kaplan-Meier curve showing cumulative survival rate stratified by RPA class.

Gamma Knife Radio Surgery (GKRS) in patients with non-solitary brain metastases and role of RPA classification in overall survival in these patients.

The descriptive findings of present study showed that breast cancer was most likely to present with non-solitary brain metastases, followed by lung cancer. Most of the previous evidences show that most of brain metastases initiate from lung cancer.[20,21] One explanation for such observation may be due to that there were fewer men than women in the present study.[22] In addition, there is evidence that the cases with breast cancer with distant involvement is increasing.[23,24] In the present study, the most common location of lesion was found to be in the frontal lobe which is also in line with previous studies.[25]

The present study showed an increased overall survival in patients with brain metastases after GKRS which is in line with findings of previous study.[26-33] In a retrospective analysis of 5216 case records, Azimi et al.[22] have reported that GKRS helped in adequately controlling brain metastasis and thus prolonging overall survival. Other studies have also documented an excellent effectiveness of GKRS in treatment of non-solitary brain metastases.[29-33]

The median overall survival of the patients was four months. Higuchi et al.[34] and Hasegwa et al.[35] have reported seven to eight months of survival in patients after GKRS treatment of brain metastases. Yamamoto et al.[36] in two patients with two tumors has reported survival of 3.5 and 5.3 months. It should be noted that most of the patients who were treated in this centre

were referred case. Hence, the late presentation for the treatment may be a parsimonious reason for low survival rate in patients in present study.

Concerning RPA classification and patients' survival, this study also correlates with the earlier findings which suggested a significant difference in the overall survival among patients who differed in RPA classification. Salvetti et al. analyzed 96 patients with five or more metastatic lesions and showed a significant association between RPA class and overall survival.[26] Grandhi et al.[27] and Sanghavi et al.[28] have found significant difference in survival of different RPA category patients. The RPA classification is based on patient age, KPS, presence of extracranial metastases, and the status of primary tumor control.[16] These factors are critical in predicting overall survival in patients with non-solitary brain metastases. Therefore, RPA has been shown to be of prognostic value in patients with brain metastases.[17]

In our study also, only seven patients (17 %) had more than four lesions. On statistical analysis, it was further confirmed that the number of lesions did not alter the median survival significantly, which could be attributed to the progression of the primary carcinoma.

Whole brain radiotherapy (WBRT) has a long list of toxic effects which include scalp erythema, reversible hair loss, fatigue, hyper pigmentation, irritable behavior and anorexia. These may develop over a period of 5 to 10 weeks after WBRT.[37] Long duration side effects of WBRT are usually not seen in the patients of Brain metastasis due to their short overall survival. However, DeAngelis et al. reported 12 patients who developed dementia, urinary incontinence and ataxia within five months to 36 months of treatment with WBRT.[38,39] On the other hand, GKRS uses collimated high energy Gamma rays directed to the area of interest with minimal exposure of the normal brain and is usually administered as a single dose. As such, the chances of complications are minimal with GKRS and acute side effects are negligible if any.

Delayed toxicity in the form of neurocognitive decline, seizures, sensory-motor deficits, dysarthria, cerebellar ataxia and others were studied prospectively and reported by Yamamoto et al. but were not found to be significant in patients with multiple metastases.[40] In the present study, the clinical records of the patients have been evaluated retrospectively and almost all the patients died at the time of this study. None of the patients visited the hospital in the follow up period. This behavior could be ascribed to the detailed pre-GKRS counseling about the prognosis and natural course of the disease. Hence, no toxicity data could be collected from the records. These patients had a very short overall survival and neurotoxin features are a late development in the clinical course of patients receiving GKRS. Therefore, it was not possible to evaluate these delayed changes in this study.

It is clear from the literature that deferring WBRT and using SRS as a frontline treatment for patients with non-solitary brain metastases has gained widespread popularity. GKRS is better than conventional radiotherapy owing its efficacy concerning improved cognitive functioning [41,42] non-invasive nature, faster recovery, shorter hospital stay and cost-effectiveness. [5] In the Indian context, the major discordance exists between practice patterns and the lack of facilities of SRS in Indian medical hospitals.[43]

Limitations

In this study, GKRS was found to be a safe and effective upfront and salvage treatment for patients with ≥2 brain metastases; however, there were principle weaknesses in this study. The first weakness is its retrospective nature and the inherent limitations of this methodology. Second, the sample size is small and a larger study is suggested for more authoritative recommendations.

Conclusion

Our series shows that GKRS is a valuable, effective, and well-tolerated treatment modality for patients with non-solitary intracranial metastases. The findings also showed that a high proportion of patients succumbed to death with other regions rather than the metastases. Thus, the implementation of an effective plan of GKRS can help in improving the overall survival of the patients with brain metastases.

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