The Role of Gamma Knife Radiosurgery in Brain Metastatic Tumors

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ABSTRACT:

BACKGROUND:

Brain metastasis represents a significant source of morbidity and mortality in patients with systemic cancer, In adults, cerebral metastasis are by far the most common intracranial tumors, and their incidence is rising because of increased cancer survival.

GKRS has arguably been the most important advancement in the management of metastatic brain tumors since the 1980s.

PATIENTS AND METHODS:

This is a prospective study of 50 patients of brain metastasis treated with (GKRS) between January 2017 and January 2019. A group of 14 males and 36 females with mean age was 59.1 years, 34 patient were <65 years old and 16 patients were >65 years old.

Patients status assessed according Karnofsky Performance Score (KPS), 4 % were >70 KPS and 96% were <70 KPS. The lung cancer was the primary lesion in 56% of patients, breast was 32%, and Skin Melanoma 8% and unknown origin 4%.

80% of the patients had previous treatment: surgery and chemotherapy (22%), chemotherapy (20%), surgery (16%), surgery, chemotherapy and DXT (10%), surgery, chemotherapy and WBRT (8%) WBRT (2%) and DXT (2%), while absent in 20%.

Brain MRI with contrast follow up was done in 6 months, and after 12 months

RESULTS:

After 12 months of follow up the mean of tumor volume after (GKRS) decrease from $6.2cm^3$ to $3.4cm^3$, The mean KPS improve from (61) to (75) , Local tumor recurrence was (16%) and edma was seen in (20%) ,The Age of patients > 65, KPS < 70, patients with previous treatment surgery, chemotherapy and WBRT had poor prognosis ,The mortality was seen in (20%) half of them related to neurological death and the other to primary tumor.

CONCLUSION:

The Gamma knife radiosurgery is effective and safe treatment modality of secondary brain metastasis and is effective in increasing survival rate and Karnofsky performance scale in addition to reduction of the tumor size of patients with brain metastasis.

KEYWORDS: Brain Metastasis , Gamma Knife , Radiotherapy , Karnofsky Performance Score .

INTRODUCTION:

Brain Metastasis:

Brain metastasis represents a significant source of morbidity and mortality in patients with systemic cancer, In adults, cerebral metastasis are by far the most common intracranial tumors, and their incidence is rising because of increased cancer survival. Treatment of brain metastasis consists of surgical resection, radiation therapy, or

advances in surgery and stereotactic radiosurgery (SRS), therapeutic options have increased, and long-term survival has become a reasonable goal.(1) The most common source of brain metastasis in this patient group are cancers of the lung and breast, and melanoma, in descending order. In children, the most common cause of brain metastasis is leukemia, followed by lymphoma.(2) Osteogenic sarcoma and rhabdomyosarcoma are the most frequent causes of solid brain metastasis among children younger than 15 years old whereas

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germ cell tumors most frequently produce them in patients 15 to 21 years old.[(3)]

Patients status assessed according Karnofsky Performance Score (KPS)

Score, %	State of Health
100	Healthy, no symptoms or signs of disease
90	Capable of normal activity, few symptoms or signs of disease
80	Normal activity with some difficulty, some symptoms or signs
70	Caring for self, not capable of normal activity or work
60	Requiring some help, can take care of most personal requirements
50	Requires help often, requires frequent medical care
40	Disabled, requires special care and help
30	Severely disabled, hospital admission indicated but no risk of death
20	Very ill, urgently requiring admission, requires supportive measures or treatment

AIM OF THE STUDY:

The aim of this study is to evaluate the effectiveness of gamma knife radiosurgery as a treatment of metastatic brain tumors, with assessing multiple factors that may interfere with the success rate of this procedure.

PATIENT AND METHOD:

This is prospective study performed in Saad Al Witry for neuroscience hospital, to assess the effect of Gamma Knife in brain secondary metastasis and cases was collected between January 2017 to January 2019.

Fifty patients were assessed according to Karnofsky Performance Score (KPS) and obtained 3 tesla brain MRI study with contrast prior to gamma knife. Then performing gamma knife by a procedure mentioned later , after that cases were followed up clinically with neurologic examination after three weeks, then after eight weeks (3 months after GRKS), then with three months interval , brain MRI with gadolinium contrast enhancement was done after 6 and 12 months for the survived patients after gamma knife.

Tumor response was evaluated on contrast-enhanced T1-weighted images, and the peritumoral edema assessed on T2-weighted image or FLAIR MRI sequences. Edema volume was defined as the peritumoral increased signal detected on T2-weighted images.

Tumor volume calculated by maximum length, maximum width, and number of slices multiply by thickness divided by 2.

Procedure

Radiosurgery was performed using the Leksell Gamma Knife® Perfexion™, 192 beams of Cobalt 60 radiation are delivered through the skull to the metastatic brain tumors.

Following are the steps in radiosurgery with the Gamma Knife Perfexion: [4]

1. Stereotactic frame placement after Patients were injected with local anesthesia, xylocaine with adrenaline 0.4% (3M) injected in the scalp in screws area.
2. Frame adaptor and frame cap measurement check
3. Stereotactic brain imaging with magnetic resonance imaging (MRI), computed tomography (CT) with indicators.
4. Coregistration of neurological images with computed tomography (CT) and importation to radiosurgical software
5. Treatment planning
6. Dose prescription between (15-25) Gy.
7. Dose limitations to critical structures: shielding and plugging technique
8. Conformal radiosurgical dose planning by the radiosurgery team
9. Stereotactic delivery of radiation to the target volume by positioning of the patient's head inside a collimator system

RESULTS:

This study included 50 patients with brain secondary metastasis with mean age of 59.1±9.9 years; 68% of them were in age group ≤65 years and 32% of them were in age group of more than 65 years. Male gender was represented by 28% of patients with brain secondary metastasis, while 72% of them were females with female to male ratio as 2.5:1. (***Table*** 1)

Table 1: Demographic characteristics of patients with brain secondary metastasis.

Variable	No.	%
Age mean±SD (59.1±9.9 years)		
≤65 years	34	68.0
>65 years	16	32.0
Total	50	100.0
Gender		
Male	14	28.0
Female	36	72.0
Total	50	100.0

The tumor lesion type was single lesion for 48% of patients with brain secondary metastasis, multiple for 48% of them and solitary for 4% of them as a solitary brain metastasis can defined as the only known metastasis of a tumor which appears to localize in the brain without known primary tumor.
The tumor location of brain secondary metastasis was distributed as followings; frontal (32%), parietal (18%), occipital (14%), cerebellum (12%), temporal (10%), thalamus (6%).
Mean number of tumor lesions was (1.8); 52% of patients with brain secondary metastasis had one lesion, 20% of them had two lesions, 26% of them had three lesions and 2% of them had four lesions and there were no more than four lesions . (Table 2)

Table 2: Tumor characteristics of patients with brain secondary metastasis.

Variable	No.	%
Type of lesion		
Single	24	48.0
Multiple	24	48.0
Solitary	2	4.0
Total	50	100.0
Tumor locations		
Frontal	16	32.0
Parietal	9	18.0
Occipital	7	14.0
Cerebellum	6	12.0
Thalamus	3	6.0
Temporal	5	10.0
Frontal & Temporal	1	2.0
Cerebellum & thalamus	1	2.0
Parietal, Occipital & Cerebellum	1	2.0
Frontal & Parietal	1	2.0
Total	50	100.0
Number of tumors mean±SD (1.8±0.9)		
1	26	52.0
2	10	20.0
3	13	26.0
4	1	2.0
Total	50	100.0

The primary origin for brain secondary metastasis was commonly lung carcinoma (56%), followed by; breast carcinoma (32%), skin melanoma (8%) and unknown origin (4%). (***Table*** 3)

Table 3: Primary tumor origin of patients with brain secondary metastasis.

Variable	No.	%
Primary origin		
Lung Ca	28	56.0
Breast Ca	16	32.0
Skin melanoma	4	8.0
Unknown	2	4.0
Total	50	100.0

20% of patients do not have Previous treatment modalities for patients with brain secondary metastasis, while 80% of them do; surgery and chemotherapy (22%), chemotherapy (20%), surgery including (biopsy or debulking) (16%), surgery, chemotherapy and DXT (10%), surgery, chemotherapy and WBRT (8%) WBRT (2%) and DXT (2%). (Table 4 and Figure 1)

Table 4: Previous treatment of patients with brain secondary metastasis.

Variable			No.	%
Previous treatment				
No			10	20.0
Surgery	Debulking (5)	Biopsy (3)	8	16.0
Chemotherapy			10	20.0
WBRT			1	2.0
DXT			1	2.0
Surgery and chemotherapy			11	22.0
Surgery, chemotherapy and DXT			5	10.0
Surgery, chemotherapy and WBRT			4	8.0
Total			50	100.0

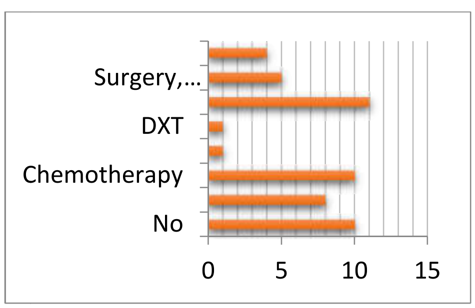

Figure 1: Previous treatment.

Mean Karnofsky Performance Score (KPS) pre-GKRS for patients with brain secondary metastasis was (61); 96% of them had Karnofsky Performance Score (KPS) of 70 and less. Mean Karnofsky Performance Score (KPS) post-GKRS of patients with brain secondary metastasis was (75); 14% of them improved, 10% not improved, 8% excluded from the study because of early death during follow up and 68% of them improved Karnofsky Performance Score (KPS) significantly more than 20.

Mean interval between previous treatment and GKRS was 17±14 weeks; 54% of patients had interval of 1-20 weeks, 20% of them had interval of 21-40 weeks, 6% of them had interval of 41-60 weeks and 20% of them had no previous treatment. (Table 5)

Table 5: KPS and time interval of patients with brain secondary metastasis pre and post GKRS.

Variable	No.	%
KPS Pre-GKRS mean±SD (61±9)		
≤70	48	96.0
>70	2	4.0
Total	50	100.0
KPS post GKRS mean±SD (75±25)		
Improved *	7	14.0
Not improved *	5	10.0
Excluded	4	8.0
Significantly improve *	34	68.0
Total	50	100.0
Time interval between previous treatment and GKRS mean±SD (17±14 weeks)		
1-20 weeks	27	54.0
21-40 weeks	10	20.0
41-60 weeks	3	6.0
No previous treatment	10	20.0
Total	50	100.0

* KPS clinical assessment

Mean tumor volume before treatment for patients with brain secondary metastasis was (6.2±2.3 cm^3) while mean tumor volume for same patients after GKRS treatment was (3.4±3.2 cm^3).

Local tumor recurrence for patients with brain secondary metastasis after GKRS therapy was observed in 16% of them, while the edema was observed among 20% of them.

The final outcome after GKRS treatment for patients with brain secondary metastasis was death in 20% of them and live status for 80% of them after 12 months follow up; half of death cases were related to brain metastasis progression in size, intra tumoral hemorrhage and seizures during clinical and radiological follow up and the other half were related to complication of systemic metastasis due to respiratory failure and other systemic organ failure detected by oncologist. (Table 6)

Table 6: GKRS therapy outcome of patients with brain secondary metastasis.

Variable	No.	%
Tumor volume before treatment mean±SD (6.2±2.3 cm^3)		
Tumor volume after GKRS mean±SD (3.4±3.2 cm^3)		
Local tumor recurrence		
Yes	8	16.0
No	42	84.0
Total	50	100.0
Edema after GKRS		
Yes	10	20.0
No	40	80.0
Total	50	100.0
Final outcome		
Dead	10	20.0
Alive	40	80.0
Total	50	100.0
Death cause		
Brain metastasis	5	50.0
Primary tumor	5	50.0
Total	10	100.0

Mean Karnofsky Performance Score (KPS) before treatment was (61) which was increased significantly after GKRS treatment to (75) (p<0.001) and mean tumor volume before treatment was (6.2 cm^3) which was significantly reduced to (3.4 cm^3) after GKRS treatment (p<0.001).

Table 7: Distribution of KPS and tumor volume before and after GKRS.

Variable	Before GKRS	After GKRS	P *
	Mean±SD	Mean±SD	
KPS	61±9	75±25	<0.001 ^{S}
Tumor volume	6.2±2.3	3.4±3.2	<0.001 ^{S}

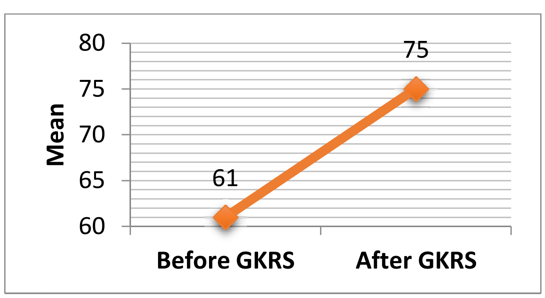

Figure 2: KPS mean distribution before and after GKRS.

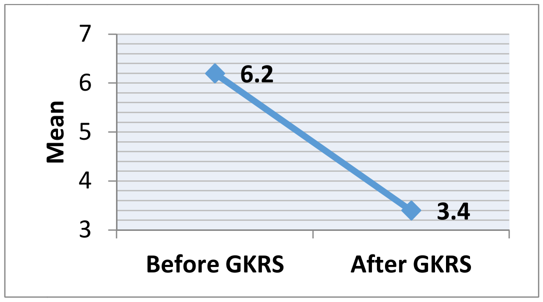

Figure 3: Tumor volume mean distribution before and after GKRS.

A significant association was observed between increased age of patients with brain secondary metastasis and death outcome (p=0.004). No significant differences were observed between dead patients with brain secondary metastasis and alive patients with brain secondary metastasis regarding gender (p=0.8). (Table 8 and Figure 4)

Table 8: Distribution of demographic characteristics according to final outcome after GKRS.

Variable	Final outcome				P Value
	Dead		Alive		
	No.	%	No.	%	
Age groups					0.004* Significant
≤65 years	3	30.0	31	77.5	
>65 years	7	70.0	9	22.5	
Gender					0.8* Not significant
Male	3	30.0	11	27.5	
Female	7	70.0	29	72.5	

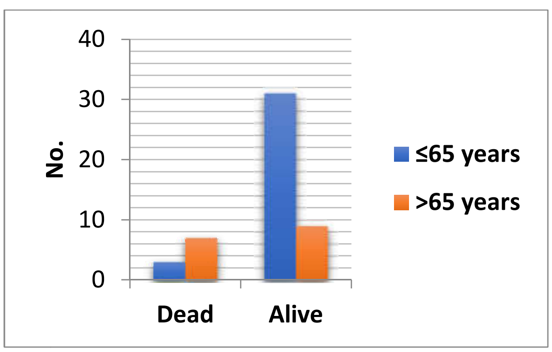

Figure 4: Distribution of age according to final outcome after GKRS.

Patients with previous surgery, chemotherapy and WBRT had significantly higher death rates (p=0.08). (***Table 9***)

Table 9: Distribution of previous treatment and interval according to final outcome after GKRS.

Variable	Final outcome				P Value
	Dead		Alive		
	No.	%	No.	%	
Previous treatment					0.08* *Significant*
No	0	-	10	25.0	
Surgery	0	-	8	20.0	
Chemotherapy	2	20.0	8	20.0	
WBRT	0	-	1	2.5	
DXT	1	10.0	0	-	
Surgery and chemotherapy	2	20.0	9	22.5	
Surgery, chemotherapy and DXT	2	20.0	3	7.5	
Surgery, chemotherapy and WBRT	3	30.0	1	2.5	

There was a highly significant association between significant improvement following GKRS treatment and alive outcome for patients with brain secondary metastasis ($p<0.001$). (Table 10 and Figure 5)

Table 10: Distribution of Karnofsky Performance Score (KPS) pre and post GKRS according to final outcome.

Variable	Final outcome				P Value
	Dead		Alive		
	No.	%	No.	%	
KPS Pre-GKRS					0.4* *Not significant*
≤70	10	100.0	38	95.0	
>70	0	-	2	5.0	
KPS post GKRS					<0.001* *Highly significant*
Improved	2	20.0	5	12.5	
Not improved	3	30.0	2	5.0	
Excluded	4	40.0	0	-	
Significantly Improved	1	10.0	33	82.5	

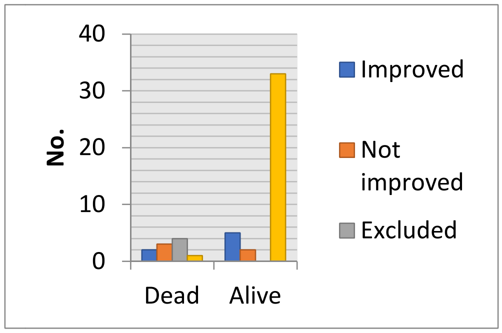

Figure 5: Distribution of post KPS results according to final outcome.

Mean tumor volume was significantly decreased among alive patients with brain secondary metastasis after GKRS therapy (p<0.001). (Table 11)

Table 11 : Distribution of GKRS outcomes according to final outcome.

Variable	Final outcome				P Value
	Dead		Alive		
	No.	%	No.	%	
Tumor volume after GKRS					<0.001** *Highly significant*
Mean±SD (cm^3)	6.4±3.1		2.6±2.7		

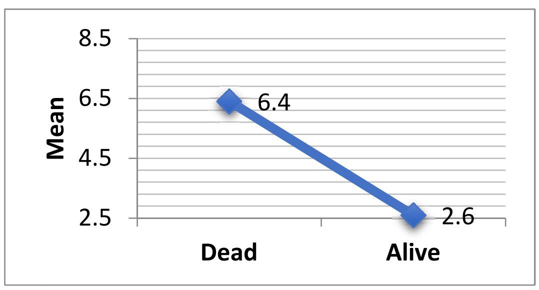

Figure 6: Tumor volume mean distribution after GKRS according to final outcome.

DISCUSSION:

The prognosis of secondary brain metastasis is different according to risk of primary tumor. The survival rate of brain metastasis is less than 6 months; however some patients have longer survival. Development of Gamma knife radiosurgery (GKRS) in management of secondary brain metastasis was helpful in survival improvement [5].

This study showed that 20% mortality rate after GKRS management of secondary brain metastasis after 12 months follow up; half of them related to primary tumors. This finding is close to results of Matsunaga et al [6] study in Japan which reported 20.7% mortality rate six months after application of GKRS in management of secondary brain metastasis. Another study conducted in by Lipptz et al [7] found that 22.7% of patients with secondary brain metastasis were died after treatment with Gamma knife radiosurgery. Jaboin et al [8] carried out a retrospective study on 100 patients with secondary brain metastasis and found that after median follow up of 18.25 months after GKRS, the survival rate was 38.6% while death rate 61.4%.

This study showed that half of the mortality was related to primary tumors related to brain metastasis progression in size, intra tumoral hemorrhage and seizures during clinical and radiological follow up and the other half were related to complication of systemic metastasis due to respiratory failure and other systemic organ failure, this finding is consistent with results of Ahluwalia et al [9] study in USA which revealed that GKRS is beneficial in reduction of mortality rates to range of 10-20% and half of dead cases are related to primary tumor not to brain metastasis. Another American study by Gatterbauer et al [10] stated that in spite of limited long-term survival of patients with brain secondary metastasis, some patients treated with GKRS have prolonged and good-quality survival. They also reported that extent of extracranial disease at the time of radiosurgery was predictive of outcome, but this does not necessarily mean that patients cannot live for years if treatment is effective [10].

In this study, the edema after GKRS was shown in 20% of patients with secondary brain metastasis. This finding is close to results of Lee et al [11] study in South Korea which found that edema after GKRS was shown among 22% of patients with secondary brain metastasis.

This study showed a significant increase in Karnofsky Performance Scale (KPS) of patients with secondary brain metastasis after treatment with GKRS ($p<0.001$). This finding coincides with results of Bir et al [12] study in USA which found that GKRS is an effective treatment option for secondary brain metastasis that offers tumor reduction and improvement in Karnofsky Performance Scale (KPS). In Japan, Matsunaga et al [13] reviewed the medical records of 177 patients with secondary brain metastasis treated with GKRS and found that GKRS is an effective and safe treatment modality of secondary brain metastasis and also reported a significant increase in KPS mean of patients after GKRS application. Previous study stated that Karnofsky Performance Scale (KPS) improvement is a predictor for GKRS therapy success of secondary brain tumor [14].

This study findings regarding tumor size is also similar to Huang et al [15] study in USA which reported a significant reduction in tumor volume and the tumor control rate was varied according to tumor volume and also revealed that risk-benefits ratio of GKRS in management of secondary brain metastasis is satisfactory.

Generally, this study confirmed the effectiveness of GKRS in elevating survival rate, improving the KPS and reducing the tumor volume of secondary brain metastasis which is consistent with many literatures [12-17].

In this study, there was a significant association between increased age of patients with brain secondary metastasis and death outcome after GKRS ($p=0.004$). This finding is similar to results of Matsunaga et al [13] study in Japan which stated that increased age, decline in KPS, extracranial metastasis and multiple brain metastasis were significant prognostic predictors of poor survival for secondary brain metastasis after GKRS. However, Park et al [16] study in South Korea found that GKRS use in elderly patients (≥70 years) is safe and effective in treating secondary brain metastasis. Despite effectiveness and safety of whole brain radiotherapy (WBRT) as treatment choice for secondary brain metastasis, many authors found a direct link between neurocognitive deterioration in elderly age patients with brain metastasis and use of WBRT [19-20]. For that, the GKRS was discovered in treating the secondary brain metastasis specifically in elderly age patients. Increased age is regarded as poor prognostic factor for survival in patients with secondary brain metastasis and this treatment option might be complicated by the fact that elderly patients often have multiple, concurrent diseases that can restrict their physiological reserve and physical functioning [18].

This study also showed also a significant association between previous surgery, chemotherapy and WBRT with a significantly higher death rate after GKRS ($p=0.02$) due to radiation necrosis, exposure eloquent area to radiation and side effect of chemotherapy. Similarly, Kawabe et al [19] retrospective study in Japan found that previous surgery or WBRT history of patients with secondary brain metastasis may be a prognostic factor for shortening of their survival.

This study revealed a highly significant association between significant improvement following GKRS treatment and alive outcome for patients with brain secondary metastasis ($p<0.001$). This finding is consistent with results of many literatures such as Shin et al [20 study in South Korea which reported that Karnofsky Performance Scale is after GKRS a significant prognostic factor for survival of patients with secondary brain metastasis. Inconsistently, Choi et al [21] study in South Korea found that pre-GKRS Karnofsky Performance Scale, pre-GKRS leptomeningeal seeding and multiple metastatic lesions were significant prognostic factors for poor survival of patients with secondary brain metastasis.

In current study, mean tumor volume was significantly decreased among alive patients with brain secondary metastasis after GKRS therapy ($p<0.001$). This finding is similar to results of study [22]

CONCLUSION:

The Gamma knife radiosurgery is an effective and safe treatment modality of secondary brain Metastasis.

The Gamma knife radiosurgery is effective in increasing the survival rate and Karnofsky performance scale in addition to reduction of the tumor size of patients with secondary brain metastasis.

The poor prognostic factors for Gamma knife radiosurgery in managing of secondary brain metastasis are advanced age, previous treatment, poor Karnofsky performance scale after Gamma knife radiosurgery and tumor volume.

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