Outcomes of Gamma Knife Surgery in the Treatment of Patients with Metastatic Brain Tumors

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ABSTRACT:

BACKGROUND:

Cerebral metastases are by far the most common intracranial tumors in adults. gamma knife radiosurgery has arguably been the most important advancement in the management of metastatic brain tumors since the 1980s.

OBJECTIVE:

To evaluate the effectiveness of gamma knife radiosurgery as a treatment of metastatic brain tumors.

METHODS:

This is a prospective study (the first trial in Iraq) of 27 patients (42 tumors) of brain metastasis between March 2016 and October 2017. Imaging follow up done in 6 months and 12 months, clinical follow up done in 3 weeks and 3 months.

RESULTS:

In the first six months 81.0% of the MBTs were regressed or remain stable in size. After 3 months post GKS, 81.5% patients showed neurological improvement. 82.4% of the patients<65 years old survive for 12 months and 85% of patients with KPS>70 survive for 12 months.

CONCLUSION:

The routine blood investigations, the gender and the location were of no significance on patients' general outcome or the tumor/edema response to gamma knife. Presence of extracranial metastasis, single or multiple MBTs found to have important effect on patients' survival.

KEY WORDS: Brain metastasis, Stereotactic radiosurgery, Gamma knife surgery .

INTRODUCTION:

The precise incidence and epidemiology of metastatic brain tumors is poorly studied and understood, however, it is estimated that approximately 1.4 million Americans are diagnosed with cancer every [(1)]. This percentage has been rising in recent years because of more aggressive treatment of the primary tumor with subsequent longer survival of patients[(2)]. Approximately 37–50% of solid tumor patients present with single brain metastases while roughly 50–63% have multiple tumors at initial presentation[(3)]. Cancers originating from the lung are responsible for approximately 30% to 60% of brain metastases. However, metastasis to the brain originating from melanoma, breast cancer, colorectal cancer, renal cell carcinoma, and carcinoma of multiple other origins are also frequently observed[(4)]. Patients who suffer from brain metastases have a poor prognosis and are estimated to survive 1 to 2 months when treated solely with corticosteroids[(5)]. Since its inception more than 60 years ago, SRS techniques and technology have evolved significantly, but its fundamental principles remain unchanged. In 2006, the American College of Radiology and the American Society for Radiation Oncology published practice guidelines for the performance of SRS[(6)] The Current American Society for Radiation Oncology evidence-based guideline for newly diagnosed brain metastases supports the use of stereotactic radiosurgery alone for patients with four or fewer tumors[(7)]. There is an ongoing debate about the optimal management of MBTs. Stereotactic radiosurgery has recently become more accepted as an alternative treatment because many patients with brain metastases are not optimal candidates for resection and some refuse an open procedure. In the last few decades, satisfactory radio-surgical outcomes in treating small to moderate-size MBTs have been reported after long-term follow-up[(8)].

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Radiosurgery is used typically to treat brain metastases that are 3 cm or smaller in maximum diameter. Nevertheless, in the RTOG 9508 study, the use of radiosurgery was permitted for one tumor that was up to 4 cm in diameter[9]. Stereotactic radiosurgery works well in treating patients with oligo-metastatic disease and small to moderate- size MBTs. It offers favorable local tumor control and often early volume reduction, depending on the particular type of carcinoma[10]. After radiosurgery, approximately 1.2% of patients with small to moderate-size MBTs undergo resection due to radiation necrosis and tumor progression[11]. A new Brain Metastases Treatment Guidelines Issued by the American Association of Neurological Surgeons & the Congress of Neurological Surgeons in 2009, discuss the role of SRS in the management of brain metastasis in more comprehensive way[12].

Unlike the traditional neurosurgical modalities, Stereotactic radiosurgery (SRS) is a noninvasive treatment regimen that has the ability to precisely target any region in the brain and can irradiate multiple lesions in the same treatment setting. Due to those advantages, the role of SRS in the treatment of patients with brain metastases is continuously increasing. The patient's skull is immobilized, allowing high dose of radiation to be delivered to the tumor volume with precision, while sparing the adjacent nervous tissue[13]

PATIENTS AND METHODS:

This is a clinical prospective study performed at neurosciences hospital; it is the first trial in Iraq to assess the effect of gamma knife radiosurgery in the treatment of metastatic brain tumors, cases collected between March 2016 and October 2017.

All cases were followed up clinically with neurologic examination after three weeks, then after eight weeks (3 months after GKS), then with three months interval; with general investigations performed in form of complete blood count (CBC), Erythrocyte sedimentation rate (ESR), Random blood sugar (RBS), Blood urea, Serum creatinine. Radiological assessment done after 6 and 12 months for the survived patients after gamma knife in form of brain MRI with gadolinium contrast enhancement.

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 and edema volumes calculated using the sum of the areas counted on each slice, multiplied by the slice thickness. The trapezoidal rule formula demonstrates that with accurate delineation on at least five slices, calculated volume would have an expected error rate of 10% or less. Therefore, this type of measurement generally has an uncertainty of 10% for tomographic imaging used for radiosurgery of a structural target such as a tumor.

Procedure

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

Patients were injected with local anesthesia, xylocaine with adrenaline 0.4% (3M) injected in the scalp in screws area, Leksell frame with four screws were applied to the patient, and the patient sent to the measurement room to obtain the exact distance from the skull to the gamma knife helmet, the patient then sent to obtain brain MRI with Gadolinium contrast enhancement. The MRI applied to the software and sent to the gamma knife computer, the surgeon will detect and target the brain lesion/s (MBTs), Dose of 15-25 grey applied to the lesion after checking the CAPs fit, measurements of fiducials (of copper sulfate), with shield protection (block) applied as Target, Sector, or collimator block to the brain stem, optic nerve, and eye lenses if they located adjacent to the lesion. The patients then enter in the Gamma Knife device and monitored by operating staff while he receiving the shoots … permission taken from the patient and operating staff and from the Neuroscience hospital and Gamma Knife department administration (figure 1-5).

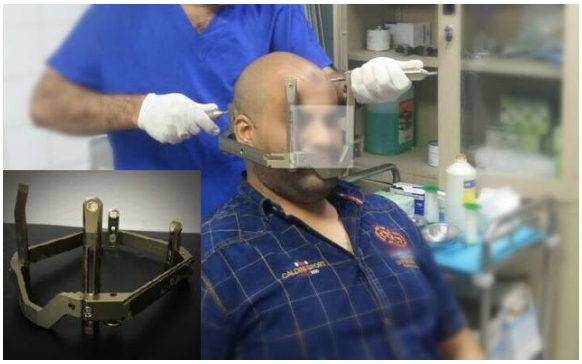

Figure 1 : Applying the Leksell four screws frame .

Figure 2: Obtaining dimensions from the Leksell helmet to the skull.

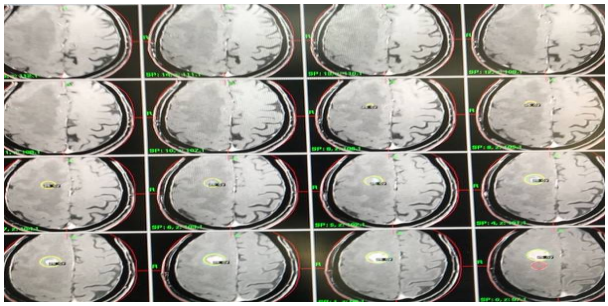

Figure 3: MRI with contrast sent to the gamma knife computer and targeting the MBTs done by neurosurgeon.

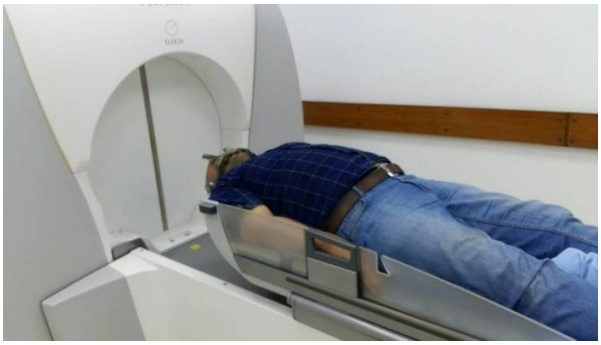

Figure 4 : Patients entered in the Gamma Knife device.

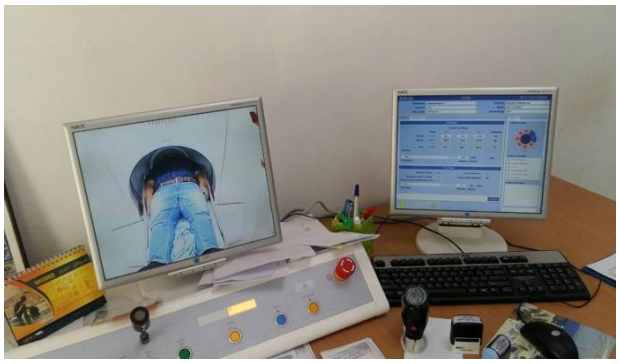

Figure 5: Monitoring of the patient via online camera and assessing the radiation dose and duration.

RESULTS:

The data collected for 27 patients and 42 tumors, the group included 12 male (44.4%) and 15 female (55.6%), the mean age was 48.81 years (range 27-67 years) with 17 patient (63%) <65 years old and 10 patients (37%) >65 years old. All the cases were patients with metastatic brain tumors that were proved to have a primary lesion. The lung cancer was the primary lesion in 100% of males and 13.3% of females (51.9% of the 27 patients). While the breast cancer was the primary lesion in 80% of females (44.4% of the 27 patients). Liver cancer appear to be the primary lesion in only one patient (3.7% of the 27 patients). Patients with lung and breast cancer were treated with surgery or chemotherapy or radiotherapy or combination of all or some of these treatment lines, the patient with liver cancer treated with surgery and chemotherapy. The largest tumor size in this study was 50mm in maximum diameter and the smallest size was 11mm in maximum diameter (the mean size was 25.63mm in maximum diameter) with 23 tumors (54.8%) were <30mm in maximum diameter and 19 tumors (45.2%) were >30mm in maximum diameter. 17 patients (63%) of this group were with single brain metastasis and 10 patients (37%) were with multiple metastasis, and the maximum tumors number in one patient were 4 tumors. Four patients (14.8%) were treated with WBRT+GKS, and five patients (18.5%) were underwent craniotomy (partial removal of the tumor) followed be WBRT and GKS, and in 18 patients (66.7%) the GKS was the only line of management. All the patients assessed according to the KARNOFSKY PERFORMANCE STATUS SCALE (KPS) (Table 1.5) with 7 patients (25.9%) were KPS<70 and 20 patients (74.1%) were KPS>70.

Presence of extracranial metastasis assessed, only 3 patients (11.1%) of the group had extracranial metastasis (the location of the extracranial metastasis is not known), while the remaining 24 patients (88.9%) had no extracranial metastasis.

Tumors locations are also assessed with the majority was in parietal lobe (28.6% of 42 tumors), cerebellar tumors were 19%, frontal and occipital lobes MBTs were 16.7% each, MBTs of temporal lobe were 9.5%, thalamus and basal ganglia MBTs were 9.5%, no MBTs found in insula.

The response of the tumor size and peritumoral edema after GKS:

The tumor volume and brain edema responses to GKS on MRI studies were classified into 3 categories (after period of 6 months, 12 months):

1) Decreased, if the area of tumor volume (on contrast-enhanced T1-weighted images) plus the peritumoral area of signal hyperintensity on T2-weighted images had lessened by more than 10% of its original size at the time of GKS
2) A stable volume, if the area was within 10% of the original size
3) Increased, if the volume had increased by more than 10%

The duration of post GKS imaging follow up for our patients in this study was 6 months and then after 12 months, in form of MRI with Gadolinium contrast enhancement. In the first follow up 24 MBTs showed regression, 10 MBTs were stable, and 8 MBTs were in progression regarding the tumor size control.

On the other hand, peritumoral edema regressed in 26 MBTs, remain stable in 9 MBTs, and progressed in 7 MBTs. Conclusively, in the first six months we have 81.0% of the MBTs that regressed or remain stable in size and 83.3% of MBTs that regressed or remain stable in peritumoral edema. For those patients who survive for more than 6 months (18 patients with 27 tumors) we evaluated the tumor response and peritumoral edema response after 6 months (one year after GKS). The follow up imaging show that 81.5% of the remaining 27 MBTs were regressed or stable in size, and 85.2% of them were regressed or stable in peritumoral edema. In addition, the patients with history of treatment with WBRT had worse tumor response and peritumoral edema response, the rate of tumor size control and edema control was 64.7%, 62.9%, respectively for patients treated with GKS alone, while it was 35.3%, 37.1% respectively in patients treated with WBRT+GKS. The results listed in Table 1 in details

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Table 1: Outcomes of the imaging assessment in 6 months and 12 months after GKS

	After 6 months evaluation (for 27 patients,42 MBTs)			After 12 months evaluation (for 18 patients,27 MBTs)
Variable	GKS	WBRT with GKS	Value	
Tumor size response				
Regression	17	7	24 (57.1%)	
Stable	5	5	10 (23.9%)	14 (51.9%)
Progression	3	5	8 (19.0%)	8 (29.6%)
				5 (18.5%)
Peritumoral edema response				
Regression				
Stable	18	8	26 (61.9%)	15 (55.6%)
Progression	4	5	9 (21.4%)	8 (29.6%)
	3	4	7 (16.7%)	4 (14.8%)
Total	25	17	42 (100%)	27 (100%)

It also appears that there is a relationship between the primary tumor histology and the tumor size control and peritumoral edema control, the patients with lung cancer found to be with favorable results with 92.3% of them showed regression and stability in tumor size response, and 88.5% of them showed regression and stability in peritumoral edema response. Table 2

Table 2: Relation between primary tumor histology and tumor size and peritumoral edema response to GKS.

Variable	Lung cancer	Breast cancer	Other (liver)	Total
Tumor size response				
Regression	18 (69.2%)	5 (33.3%)	1	24
Stable	6 (23.1%)	4 (26.7%)		10
Progression	2 (7.7%)	6 (40%)		8
Peritumoral edema response				
Regression				
Stable	17 (65.4%)	8 (53.3%)	1	26
Progression	6 (23.1%)	3 (20%)		9
	3 (11.5%)	4 (26.7%)		7
Total	26 (100%)	15 (100%)	1	42

The tumor size was evaluated as an important parameter to take in concern when talking about the tumor size and peritumoral edema response of MBTs to GKS, as we mentioned, large size tumors are the tumors with > 30mm in at least on diameter, small tumors are < 30mm in maximum diameter. In our group the small size MBTs showed 60.8%, 65.2% regression in tumor size, peritumoral edema respectively after 6 months post GKS, with 52.6%, 57.8% regression in tumor size, edema in large size MBTs.

The location of the MBTs was of no significance in tumor size response or peritumoral edema response, the same response seen in tumors of the frontal, parietal, temporal, thalamic and basal ganglia, and cerebellar tumors.

Clinical outcome after GKS:

Clinical evaluation done for all the patients after 3 weeks post GKS and there was no improvement or worsening in the neurological state, on the other hand, the general investigations were normal for all the patients. Clinical assessment that done after 8 weeks (after 3 months from the GKS) show neurological improvement in 22 patients (81.5%). In the next 3 months (6 months post GKS) the neurological outcome was improved in 20 patients of the 22 patients who were improved in the first clinical assessment, and two patients show clinical deterioration, and there was no improvement in other patients. In the last clinical assessment, we had 9 dead patients, and for the 18 survived patients there were 4 patients (22.2%) had new neurological symptoms or progression of existing neurological symptoms, those patients were treated with high dose steroid medication. See Table 3.

Table 3: Follow up of 27 patients in 3 weeks, 3 months, 6 months, and 12 months after GKS showing the percentage of neurological improvement after GKS.

Follow up	3 weeks	3 months	6 months	12 months
Improved	Non	22 (81.5%)	20 (74.1%)	14 (77.8%)
No improvement	27	5 (18.5%)	7 (25.9%)	4 (22.2%)
Death	Non	Non	Non	9 (00.0%)
Total	27	27 (100%)	27 (100%)	27 (100%)

According to our results the patients' age had a significant effect on patients' survival and outcome, with 60% of patients older than 65 years old died with 6 months, while 82.4% of the patients younger than 65 years old survive for 12 months.

DISCUSSION:

The standard treatment for patients with metastatic brain tumors includes resection, WBRT, single or multisession GKS, or combination of these modalities according to the clinical situation.

Tumor size and peritumoral edema response to GKS

In our study we obtain a results of 81.0% of the MBTs that regressed or remain stable in size and 83.3% of MBTs that regressed or remain stable in peritumoral edema, Yang et al.[14] noted that the local tumor control was 91.4% and the brain edema control rate was 81.4%, these results looks reasonable. While Cheng-Chia Lee et al.[15] found that 84.9% of the MBTs had regressed or remained While Ameer L. Elaimy and et al.[13] noted that treatment of patients with MBTs with SRS alone or stable, and 84.0% of the tumors had brain edema regression or were in stable condition.

For those patients who survive longer than 6 months, 81.5% of MBTs were regressed or stable in size, and 85.2% of them were regressed or stable in peritumoral edema. Cheng-Chia Lee et al.[15] noted that the percentage was 88.3%, 89.6% for tumor size, peritumoral edema respectively in a follow up at 3 months intervals. Although the results seems to be close, the difference in percentages may be due to the difference in number of patients in their study.

The history of treatment with previous WBRT gives worse effect for our patients regarding the tumor size and edema response, Both Yang et al.[14] and Han et al.[16] found that patients with no prior WBRT had a higher likelihood of tumor volume regression or stability than those who had been treated with WBRT.

SRS with WBRT gives equivalent results, they also found that SRS alone, or SRS with WBRT for

treatment of MBTs gives superior results compared with patients treated with WBRT alone. On the other hand, they noted that the number of MBTs in a patient can affect these results. Many prospective and retrospective studies reported non-significant tumor control and survival differences in patients treated with GKS with or without WBRT [17-24].

Large MBTs seems to be of good response when treated with GKS, our results showed that the large size tumors respond in 73.7% for tumor size control and 78.9% for peritumoral edema control, and the small size tumors respond by 86.9% for both tumors and peritumoral edema control. Han et al.[16] noted that 85% of patients with large MBTs showed good functional improvement or maintained their independent function status, this result reflect the good radiological response. Yang et al.[14] also noted a favorable results in tumor size and peritumoral edema control for tumors that were >30mm in diameter. These reports and our current study suggest that GKS can give local control and reduce peritumoral edema in selected patients with brain metastasis over 30mm in diameter.

According to our study, and the results noted by Cheng-Chia Lee et al.[15], the lung cancer as a primary origin of the MBTs gives favorable results in both tumor size control and brain edema control, the radiosensitivity of lung cancer makes those results reasonable. The others factors, including age, gender, numbers of intracranial metastases, extracranial metastasis, and radiation dose, were not related to local tumor control of brain metastasis after GKS.

Clinical outcome after GKS

All general investigations that done for all the patients were normal, and the few non-significant findings were of no relation to GKS. The neurological evaluation done after 3 months of GKS showed a result of 81.5% improvement, Yang et al.[14] noted that 74% of patients had improved symptoms. We have 33.3% of patients who were died in a period more than 6 months, the exact date and cause of death were not known as the patients were not regularly visit the hospital and the death occur at home. In the last clinical evaluation that done after 12 months of GKS the neurologic improvement for the survived patients was 77.8%.

The following factors found to be the more effective on patients survival;

In patients with multiple MBTs the GKS could be safely the first line of management, which showed a good tumor size control and peritumoral edema control.

1. **Age**, in patients with age >65 years the survival for 12 months was 40%, while in patients <65 years the rate was 82.4%.
2. **KPS**, patients with KPS <70 survived for 12 months in 14.3% of total group, while patients with KPS >70 survived for 12 months in a good percentage 85%.
3. **Presence of extracranial metastasis**, the survival rate for patients with extracranial metastasis was 33.3%, in patients with no extracranial metastasis the survival for 12 months was 70.8%.
4. **Single or multiple metastasis**, patients with multiple MBTs survived for 12 months in 40%, while single MBT the rate was 82.4%.

Other studies noted that there was a relation between some of these factors and patients survival in spite of differences in number of factors studied in each study, and in percentages between our study and their studies which mostly related to number of patients in each study. For example; the only effective factors in the study done by Cheng-Chia Lee et al.[15] were the pre-GKS KPS, control of systemic disease, and these factors found to play a significant role in survival not only in patients with large MBTs but also in small size tumors, too. While Han et al [16,25] noted that patients survival was related to control of primary lesion, size of MBTs, and the GKS dose. Ameer L. Elaimy et al.[13] noted that there was a relation between the patients' survival and the number, location, and size of the patient's metastases. The Radiation Therapy Oncology Group (RTOG) assigned that the prognosis of patients with MBTs after GKS and develop the RPA prognosis system[26], which based on: patients' age, KPS, control of primary disease, presence of extracranial metastasis.

CONCLUSION:

The GKS offers the patients with MBTs a viable, non-invasive treatment with 81.0% of the MBTs that regressed or remain stable in size and 83.3% of MBTs that regressed or remain stable in peritumoral edema. It gives patients with large MBTs >30mm who are not suitable candidates for surgery a reasonable benefit with tumor size and peritumoral edema control, increased survival rate, although the big tumor size could be a relative contraindication for GKS due to increased peritumoral edema after GKS.

The general blood investigation after 3 weeks of GKS are of no or very little value, as all investigations were normal in all the patients, there was no relation between clinical deterioration or improvement and the results of investigations. The WBRT treatment prior to GKS is accompanied with worse results when compared with treatment with GKS alone, the rate of tumor size control and edema control was 64.7%, 62.9%, respectively for patients treated with GKS alone, while it was 35.3%, 37.1% respectively in patients treated with WBRT+GKS. The histology of the primary tumor is a significant factor that affect the tumor and peritumoral edema control, as well as the clinical outcome.

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