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Research Paper

The Impact of Gamma Knife Radiosurgery on Survival Period of Patients with Brain Gliomas

Ahmed A Salam Al Atraqchi

ABSTRACT:

BACKGROUND:

Brain Glioma is one of the most common brain tumors that starts in the Glial cells of the brain which are the supportive tissue of the brain. Gliomas compromise about thirty percent of all brain tumors.

OBJECTIVE:

Evaluate the outcome of gamma knife radiosurgery as an effective treatment modality in the management of brain glioma.

PATIENTS AND METHODS:

A clinical retrospective study performed and conducted at Neurosciences hospital between January 2017 and November 2018. The cases conducted were 40 cases, 33 patients were undergone craniotomy prior to radiosurgery and the remaining 7 patients had radiosurgery with gamma knife as the first modality of treatment.

RESULTS:

Gamma Knife Radiosurgery has showed a good effect on tumor growth control and improving clinical outcome. In high grade glioma Gamma Knife Radiosurgery showed a good noticeable efficacy on prolongation of survival period and tumor control.

CONCLUSION:

Gamma Knife Radiosurgery gained an important role in the treatment of glioma in the last two decades in selected cases.

KEYWORDS: Gamma Knife, Glioma, Radiosurgery

Consultant Neurosurgeon, Saad Al- Witry Neuroscience Hospital/ Baghdad, Iraq

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INTRODUCTION:

A glioma is a type of tumor that starts in the glial cells of the brain or the spine which is the supportive tissue of the brain. This tissue helps to keep the neurons in place and functioning well. [1] Gliomas comprise about 30 percent of all brain tumors and central nervous system tumors, and 80 percent of all malignant brain tumors[2]. Gliomas could be classified by cell type, by grade, and by location. Thus, its categorized according to the specific type of cell with which they share histological features, but not necessarily from which they originate into: Ependymomas, Astrocytoma, Oligodendrogliomas, Brainstem glioma, Mixed gliomas and others.[3] Furthermore, WHO were classify Gliomas to low and high-grade depending on their differentiation. [4,5]

A person with a brain tumor may experience various signs and symptoms. Hence, the most common symptoms include headaches and seizures. Other signs and symptoms, such as loss of speech or vision, are possible and depend on the location of the tumor. [6]

Various forms of glioma respond to different approach of treatment, which may include surgery, radiation therapy, chemotherapy, or just observation. [7]

The most recent technique is Stereotactic radiosurgery (Gamma knife). Radiosurgery is surgery using radiation that is the destruction of precisely selected areas of tissue using ionizing radiation rather than excision with a blade.

Radiosurgery was originally defined by the Swedish neurosurgeon Lars Leksell as "a single high dose fraction of radiation, stereotactically directed to an intracranial region of interest".[2]

Radiosurgery is performed by a multidisciplinary team of neurosurgeons, radiation oncologists and medical physicists to operate and maintain highly sophisticated, highly precise and complex instruments, including medical linear accelerators, the Gamma Knife unit and the Cyber knife unit. The highly precise irradiation of targets within the brain and spine is planned using information from medical images that are obtained via computed tomography, magnetic resonance imaging, and angiography.

Gamma Knife radiosurgery has proven effective for patients with benign or malignant brain tumors up to 4 cm (1.6 in) in size. Acute complications following Gamma Knife radiosurgery are rare, and complications are related to the condition being treated. [8,9]

AIM OF THE STUDY:

To evaluate and assess the outcome of the glioma tumors treated by radiosurgery (Gamma knife radiosurgery)

PATIENTS AND METHODS:

This is a clinical retrospective study performed and conducted at neurosciences hospital between January 2017 and November 2018. Forty patients with brain glioma were enrolled in this study. All are harboring a radiologically or histologically diagnosed brain glioma, having radiosurgery by Gamma knife as primary treatment as well as a second therapy after previous treatment (craniotomy with tumor debulking). 30 patients (75%) had craniotomy surgery with tumor debulking (biopsy confirming the diagnosis), 10 patients (25%) treated with gamma knife as the first line of treatment (diagnosis was done using radiological and clinical evidences). The age of the selected patients ranged from 35-60 years old with the average age of 45 years old , 22 (55%) of them were females and the other 18 (45%) patients were males.

All patients were contacted and accepted to take part in the study.

Neuroradiological evaluation was performed by a team of neuroradiologists. Morphological parameters and tumor size were estimated from pre-treatment magnetic resonance imaging (MRI) tests using the Gamma Plan software. Tumor size was known by contouring the lesion on different slices, checking contrast enhanced T1 weighted, FLAIR and T2-weighed MRI axial views by the treating neurosurgeon with the attendance of a neuroradiologist, using the "volume" bar in the "measurements" bar of gamma knife operating system.

Radio surgical technique:

Leksell Gamma Knife Perfexion was used in performing the Gamma knife radiosurgery.

MRI compatible frame was used to fix the patient's head. Brain views were obtained using a high resolution 3Tesla MRI scanner. The level of the frame on the head is fixed to meet the exact site of the brain glioma attended for exposure. The frame is fixed to the patient's head by four screws after the infiltration of local anesthetic to minimize the pain feeling.

a 1-mm axial slice thickness T1-weighted with and without contrast-enhancement, combined with FLAIR and T2-weighted sequences.

Leksell gamma plan (elekta) is used to plan the treatment, all the doses applied to the drawn volume as well as all the treating plan variables need to be approved by the neurosurgeon (A.B. Elekta, Stockholm, Sweden, 2014).

When the targeted tumor near an eloquent area of the brain this area should be protected by blocks used to minimize the radiation to a level tolerated by this vital area. The dose delivered to an eloquent area measured precisely before the final approval of the treatment session.

The follow up started from the time of the treatment session to 6 months and 12 months following the starting day.

Radiological evaluation at follow-up

All the follow up neuroradiological views were carefully examined by the senior in charge and the department neuroradiologist. The tumor was considered unchanged in this research when the size of the tumor was +/- 15% of the starting size while tumor progression was considered when tumor size increased more than 15% of its pretreatment size.

RESULTS:

The age of the selected patients ranged from 35-60 years old with the average age of 4 years old, 22 (55%) of them were females and the other 18 (45%) were males.

The clinical presentation of the selected patients varied from signs and symptoms of raised intracranial pressure, epilepsy, weakness and cognitive disabilities.

The patient characteristics and the clinical presentation are shown in table 1.

Table 1:Patients' characteristics.

Characteristics		No. (%)
Gender (n° of GKRS=40)	male	18(45)
	female	22(55)
Age (n° of GKRS=40)		
	25 - 40	16 (40)
	> 40	24 (60)
Clinical presentation (n° of GKRS=40)		
	Epilepsy	11 (27.5)
	Headache/Vomiting	15 (37.5)
	Paresis	9 (22.5)
	Cerebellar Deficits	5 (12.5)

Tumor location and histology

Tumor location divided in this research into two major compartments according to the site of the tumor was being supra or infratentorial, As 28 cases the location of the tumor was supratentorial and the remaining 12 cases was infratentorial, then sub divided according to the area involved within these two compartments.

Table 2: Location of the selected lesions.

Tumor Location (total no. of cases = 40)		No. (%)
Supratentorial		28 (70%)
	Parietal Lobe	9 (32.1%)
	Frontal Lobe	10 (35.7%)
	Temporal Lobe	6 (21.4%)
	Thalamus	1 (3.5%)
	Lateral Ventricle	2 (7.1%)
Inrfatentorial		12(30%)
	Cerebellum	8 (66.6%)
	Brainstem	1 (8.3%)
	4th Ventricle	3 (25%)

Among the patients selected 33 (82.5%) patients had their diagnosis confirmed histopathologically and the other 7 (17.5%) patients were diagnosed on basis of MRI findings either being unfit for major surgeries (high morbidity) or their lesions were in an eloquent areas. Among these 7 patients with no histopathology, one patient had his tumor in brainstem and the other 6 patients presented with very high mortality and morbidity making major long surgeries very risky. Based on their radiological evidences 3 patients dealt with as low-grade glioma and the remaining 4 patients as high-grade Glioma.

Table 3: Histopathology confirmed diagnosis results.

Histopathology	No. (%)
WHO grade 1	5 (12.5)
WHO grade 2	6 (15)
WHO grade 3	13 (32.5)
WHO grade 4	16 (40)

Tumor and treatment characteristics:

The maximum volume of the selected lesions was 3.1 cm3 with average volume of 2.8 cm3.

The maximum dose delivered to these lesions was between 25 and 40 Gy with average of 30 Gy in 50% isodose.

Previous treatments:

33 (82.5%) of the selected patients had treatment before the GKRS,

5 (15.1%) of them had surgical resection with histopathological based diagnosis while 3 (9.0%) of them had surgical resection followed by radiotherapy, the remaining 25 (75.7%) patients had surgical resection, radiotherapy followed by 8 cycles of chemotherapy.

7 (17.5%) patients had GKRS as the primary treatment modality.

Among the 33 patients who had some kind of treatment before the GKRS 19 of them was treated on residual tumors (subtotal resection) while the other 14 patients treated from tumor recurrence.

The time interval between the first line tumor (surgery, radiotherapy) and the GKRS ranged from 6-12 months in 26 patients, in the remaining 7 patients the interval was > 12 months.

Tumor control

After the histopathological and the radiological diagnosis of patients in this research, our 40 patients now classified into two studying group, Group 1 which includes 11 (27.5%) patients represents the patients with low grade glioma (grade 1 and grade 2 gliomas) and group 2 including the remaining 29 (72.5) represents patients with high grade glioma (grade 3 and grade 4 gliomas).

In group 1 patients tumor control was achieved in 3 (27.2%) patients after 6 months (tumor size decreased by more than 20% of its original size), no changes in the size of the tumor (within +/- 15% of its original size) was observed in 6 (54.5%) patients while 2 (18.1%) patients had their tumors increased in size (more than 20% of its original size).

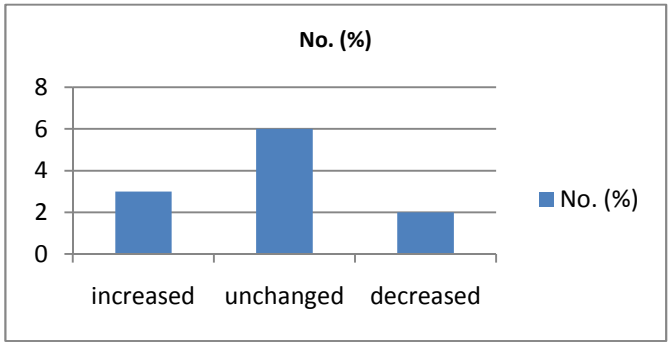

Figure 1: Tumor control after 6 months in Group 1 patients.

In last follow up after 12 months from the time of GKRS tumor control was achieved in 6 (54.5%) patients while tumor size remained unchanged in 1 (9.0%) patient, tumor progression was noticed in 4 (36.3%) patients.

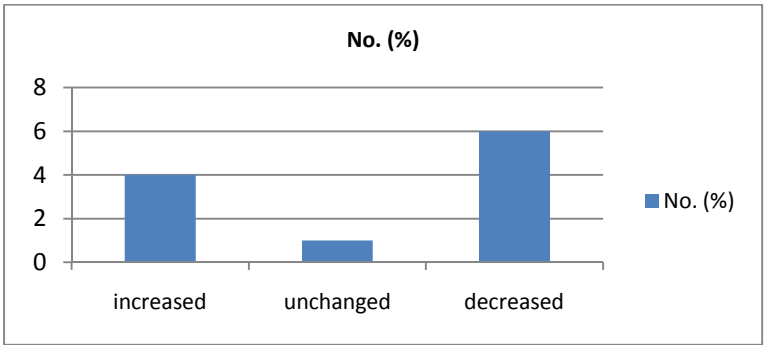

Figure 2: Tumor control after one year in group 1 patients.

In Group 2, After 6 months, tumor control was achieved in 11 (37%) patients, while tumor size unchanged in 14(49%) patients. Tumor progression was noticed in 4 (14%) patients.

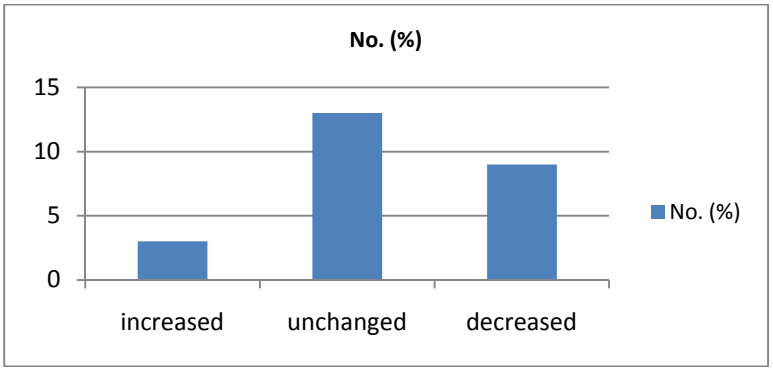

Figure 3: Tumor control after 6 months in group 2 patients.

At the end of our follow up (12 months) tumor control was achieved in 16 (56%) patients, no obvious change in tumor size was noticed in 4(14%) patients while 9(31%) had their tumor increased in size.

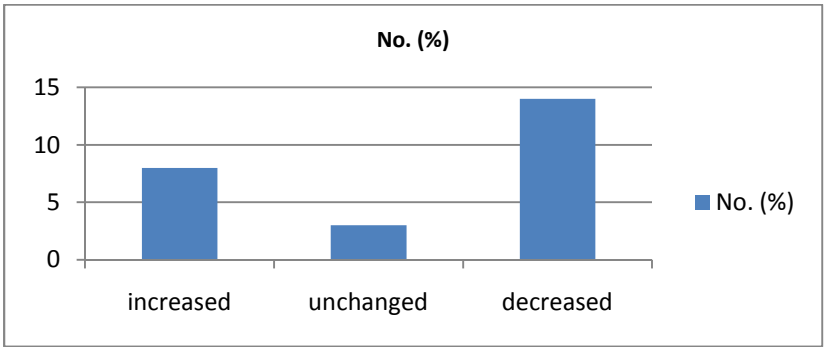

Figure 4: Tumor control after 12 months in group 2 patients.

Clinical Outcome

we assessed the clinical status in all of our patients focusing on the main three presenting features which was epilepsy, signs of raised intracranial pressure (headache, nausea and vomiting) and cerebellar deficits as 5 patients 6 patients of those presented with paresis died during the follow up period.

11 patients in our research presented with epilepsy as the presenting feature, at the last follow up control 4 (36.3%) patients were clinically stable, 6 (54.5%) patients improved clinically which was considered in any patient with decreased number of attacks or the duration of the attack while 1 (9.0%) patient registered as deterioration (increased number and intensity of the attack and needed dose adjustment with addition of another anti-epileptic drug).

Table 4: Clinical outcome in epilepsy patients

clinical outcome	No. (%)
improved	6 (54.5)
unchanged (stable)	4 (36.3)
deteriorated	1 (9.0)

15 patients presented with signs of raised intracranial pressure (headache and vomiting), at the end of the follow up control after 12 months 6(40%) patients were clinically stable, 7(46.6%) patients showed acceptable improvement and the remaining 2(13.3%) showed clinical deterioration.

Table 5: Clinical outcome in patients with raised intracranial pressure.

clinical outcome	No. (%)
improved	7 (46.6)
unchanged (stable)	6 (40)
deteriorated	2 (13.3)

Moreover 5 patients in our study presented with cerebellar signs +/ paresis with axia, gait disturbances and diplopia).

At the end of the follow up control 3(60%) patients were clinically stable the remaining 2 patients 1(20%) of them showed good clinical improvement while the last 1(20%) patient showed clinical deterioration.

Table 6:Clinical outcome in patients with cerebellar signs +/or paresis.

clinical outcome	No. (%)
improved	1 (20)
unchanged (stable)	3 (60)
deteriorated	1 (20)

Mortality

40 patients were included in this research all of them were diagnosed with glioma either by histopathology or by radiological evidence.

7(17.5%) were unfortunately dead during a follow up period of 12 months.

Four of them were diagnosed with high grade glioma depending on their clinical and radiological evidences as they were unfit for long major surgery like craniotomy and treated with gamma knife as the primary treatment modality.

2 patients were diagnosed by histopathological evidence to have high grade glioma and they had radiotherapy and chemotherapy before the GKRS.

The last one diagnosed to have brainstem glioma (low grade) radiologically.

5(71.4%) patients died during the first follow up control of 6 months while the remaining 2(28.6%) died during the second follow up control.
6(20.6%) patients died in group 2 patients in which all the patients were diagnosed with high grade gliomas (29 patients) and only 1(9.09%) patient died in group 1 patients (the patients with diagnosis of low-grade glioma) total number of patients in this group was 11 patients.

Table 7: Mortality rates in group 1 and 2 patients.

Group	no. of patients	No.(%) of deaths after 6 month.	No.(%) of deaths after 12 month.	total deaths
1	11	0 (0)	1 (9.09)	1 (9.09%)
2	29	5 (17.24)	1 (3.44)	6 (20.6%)

DISCUSSION:

Brain Glioma is one of the commonest brain tumors that affect all age groups especially in middle and old ages. To date, there is no definite agreement about the treatment of glioma, surgery considered as the first line of treatment sometimes followed by radiotherapy and chemotherapy, the regime of the treatment of glioma is set according to the grade , site of the tumor and the general condition of the patient. [10]
Gamma Knife Radiosurgery took an important role in the treatment of glioma in selected cases in the last two decades. In our research we divided the patients to LOW (grade 1 and grade 2) and HIGH (grade 3 and grad 4) grades. We assessed the effect of Gamma Knife on the size of the tumor, the clinical outcome and the mortality in patients.
In the first group of patients with low grade glioma which included 11 patients, tumor control and improvement in clinical outcome was achieved in 54.5% with mortality in one patient after one year. Such findings are in complete agreement with Larson *etal* 2002 and Kong *etal* 2008.[11,12]
Moreover, in the second group patients with high grade glioma tumor control and improvement in patient's survival period was achieved in 56% of our patients with a mortality of 13% of our patients in this group. Confidently, such outcome is in harmony with various pervious reports, they stated that Gamma Knife Radiosurgery plays an important role in the prolongation of patient's survival period and tumor control especially following treatment with whole brain radiosurgery. [13,14,15]

CONCLUSION:

The efficacy of GKRS in the treatment of low-grade glioma showed a good effect on the tumor growth control and improving clinical outcome while in high grade gliomas especially on those who had whole brain radiotherapy, chemotherapy prior to gamma knife establish a good noticeable efficacy on prolongation of survival period and tumor control.

Recommendations

1. To increase the spectrum of the study
2. Introducing tumor staging technique in Gamma knife perfixion version + fractionation technique in Gamma knife Icon version

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