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Assessment of Large Tumor Shrinkage Using Hypofractionated Gamma Knife Radiosurgery

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Abstract

Background The Gamma Knife (GK) is a radio surgical method to treat malignant and benign brain tumours, atrioventricular malformations (AVM), and functional disorders.

Objective To investigate the tumor shrinkage after six months of GK with hypofractionation.

Methods A study at Dr. Saad Al-Witry Hospital for Neurosciences and Al-Altaj Hospital involved 50 patients with large brain tumors. Each patients underwent a magnetic resonance imaging and computed tomography images before and after treatment.

Results The mean dose distribution was higher in metastasis. After irradiation, gliosis around the tumor was observed, with 86% showing a positive response to radiation treatment. The results of tumor shrinkage were classified according to the number of treatment fractions, with highly significant shrinkage observed in those treated in three fractions and those treated after four fractions.

Conclusion The hypo fractionated GK appears to be a viable and effective method of treating various brain tumors that are benign or malignant. The method has a favorable outcome that involves both a decrease in tumor size and a minimum of side effects.

Keywords Large brain tumor, volumetric change, gradient index (GI), gamma knife, stereotactic

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List of abbreviations: AVM = Atrioventricular malformations, CBCT = Cone beam computed tomography, CT = Computed tomography, GI = Gradient index, GK = Gamma Knife, GKRS = Gamma knife radiosurgery, LGK = Leksell Gamma Knife, MRI = Magnetic resonance imaging

Introduction

The Leksell gamma knife (LGK) Icon is a teletherapy tool designed for targeted radiation of anatomical structures used to treat various medical conditions such as arteriovenous malformations, metastatic tumors, and other malignancies [(1)]. The 2016-released LGK Icon uses the same radiation unit as its predecessor, with eight motorised sectors distributed among 192 sealed ^{60}CO sources. The machine uses the largest collimator size available, 16 mm, for calibration purposes [(2)]. An elliptical polystyrene phantom from Elekta AB is calibrated, with an 80 mm radius around the phantom [(3)].

Hypofractionation is a method of dosing patients with a fraction of the total dose required to treat a cancer over several days [(4-16)]. It combines radiosurgical and fractionated treatment methods, allowing for the irradiation of large, complex lesions while minimizing the radiation dose absorbed by surrounding radiosensitive tissues [17]. This treatment is particularly beneficial for patients who are too young, frail, or have large, poorly located anomalies. It is often required for cancers larger than 3 cm in diameter or 10 cm^3 in volume, as well as those near radiation-sensitive essential tissues. Fractionation radiobiology supports this strategy, aiming to reduce radiation exposure while controlling tumors [18].

This research aimed to assess the outcome shrinkage of the hypofractionated treatment of the Gamma Knife (GK) for particularly large tumors (more than 5 cm).

Methods

The study was conducted in the Al-Taj Privet Center of GK and Dr. Saad Al-Witry Hospital for Neurosciences. The duration of the study was from December 2023 to July 2024. The Institutional Review Board (IRB) of the Medical College, Al-Nahrain University approved the study. The study was designed for 50 patients with large brain tumors. Ethical consent was taken from each participant.

Following the patient's diagnosis and before GK therapy, a Philips Achieva 3 Tesla or 1.5 Tesla magnetic resonance imaging (MRI) model was used to get three-dimensional comprehensive anatomical pictures of the tumor. The next step is to acquire the head's bone and solid structures using the Cone Beam Computed Tomography (CBCT) attached to the GK equipment. The Leksell frame was used to get the patients ready for imaging.

Patients' tumor sizes, locations, and tolerance levels determine how radiation treatments are divided and administered using the GK radiosurgery equipment at Saad Al-Witry Hospital and Al-Taj Hospital. Depending on the size and grade of the tumor, patients may have hypo-RS (multi-session) or single-session therapy.

Neurosurgeons use high-resolution CT and MRI scans to determine the tumor's volume, augmented with contrast. The brain, optic nerves, retinas, and brain stem are shaped during treatment. After six months, researchers examine the patient's brain using MRI to determine the cancer's reduction and the impact of gamma radiation dose on tumor volume, using a 3 Tesla Philips MRI equipment.

In the same process, the shift in tumor volume could be ascertained. After about six months of radiosurgery, tumor volumes of all patients were compared by comparing MRI scans and taking note of any changes in the measured volumes caused by the effects of the gamma irradiation doses.

Statistical analysis

Statistical analysis was performed using statistical package for social sciences (SPSS) version 28. Student t-test used for showing differences and comparing between two groups which is pre and post treatment in this study. The P value considered as a significant if its ≤0.05.

Results

The characteristics of patients included in this study are shown in table (1). The mean age of patients included in the study was 48.46±13.89 years and ranged from 15 to 85 years. Six brain lesions treated with hypofractionation are meningioma, glioma, Schwannoma, arteriovenous malformations (AVM), pituitary adenoma, and metastasis; the age of patients age was divided according to the tumor types, which are 51.08±13.01, 46.4±16.47, 46.66±13.04, 27.33±12.50, 45, and 47 years, respectively. The females [34 (68%)] treated with hypofractionation; GK had a higher prevalence than males [12 (32%)]. The distribution of patients in this study is 34 (68%), 5 (10%), 6 (12%), 3 (6%), 1 (2%), and 1 (2%) for meningioma, glioma, Schwannoma, AVM, pituitary adenoma, and metastasis, respectively.

The dose received to organs at risks such as brain stem and pituitary glands shown in table (2).

Table 1. The characteristics of patients treated with hypofractionation gamma knife

Characteristic	
Age (years)	48.46±13.89 (15-85)
Tumor dose (Gy)	
Meningioma	51.08±13.01
Glioma	46.4±16.47
Schwannoma	46.66±13.04
Arteriovenous Malformations (AVM)	27.33±12.50
Pituitary adenoma	45
Metastasis	47
Gender	
Male	16 (32%)
Female	34 (68%)

Table 2. Dose to the organs at risks (OARs)

OARs	**Mean Dose (Gy)**
Brainstem	4.95± 0.81
Pituitary gland	24.25 ± 5.87

The dosimetric evaluation of the plans for patients treated with a hypofractionation GK is shown in table (3); it lists the parameters used in this study's assessment. The parameters for all tumor types are total dose (Gy), which was 15.42±3.50 Gy and ranged from 8-24 Gy. The dose per day (Gy) ranged from 3 to 8 depending on the tumor size and type. The fractions included in this study ranged from 2-5 fractions.

The mean dose (Gy) was 12.99±8.19 Gy, ranging from 1.6 to 27.3 Gy. The maximum Dose was 30.47 ± 16.24 Gy and ranged from 8 to 100 Gy. At the same time, the minimum dose reached by the tumor was 4.37±4.81, ranging from 0 to 14.7 Gy. The integral dose in milli Joule (mJ) was 949.82±103.53 mJ, ranging from 68.3 to 4614.3 mJ. The gradient index (GI) was 2.66±0.14, ranging from 2.33 to 2.93. The mean value for the tumor coverage was 0.94±0.02, ranging from 0.88 to 1. In contrast, the mean selectivity value is 0.83±0.13, ranging from 0.15 to 0.97. The number of shots that cover the tumor ranged from 2 to 55. The mean radiation treatment time was 23.11±7.91 minutes, ranging from 3.6 to 49 minutes.

After irradiation, gliosis around the tumor indicates that the cancer has a radiation response. The results from two expert radiologists' evaluations show that 43 (86%) had a positive occurrence of gliosis as a response to radiation treatment, while only 7 (14%) showed a negative sign of gliosis with a p-value <0.0001, as shown in figure (1).

Table 3. The Plan Evaluation of patients treated with hypofractionation gamma knife

Characteristic	values
Total dose (Gy)	15.42±3.50 (4-24)
Dose per day (Gy)	3-8
Fractions	(2-5)
Mean (Gy)	12.99±8.19 (1.6-27.3)
Max (Gy)	30.47±16.24 (8-100)
Min (Gy)	4.37±4.81 (0-14.7)
Integral dose (mJ)	949.82±103.53 (68.3-4614.3)
Gradient index (GI)	2.66±0.14 (2.33-2.93)
Coverage	0.94±0.02 (0.88-1)
Selectivity	0.83±0.13 (0.15-0.97)
Shot no.	(2-55)
Time (min)	23.11±7.91 (3.6-49)

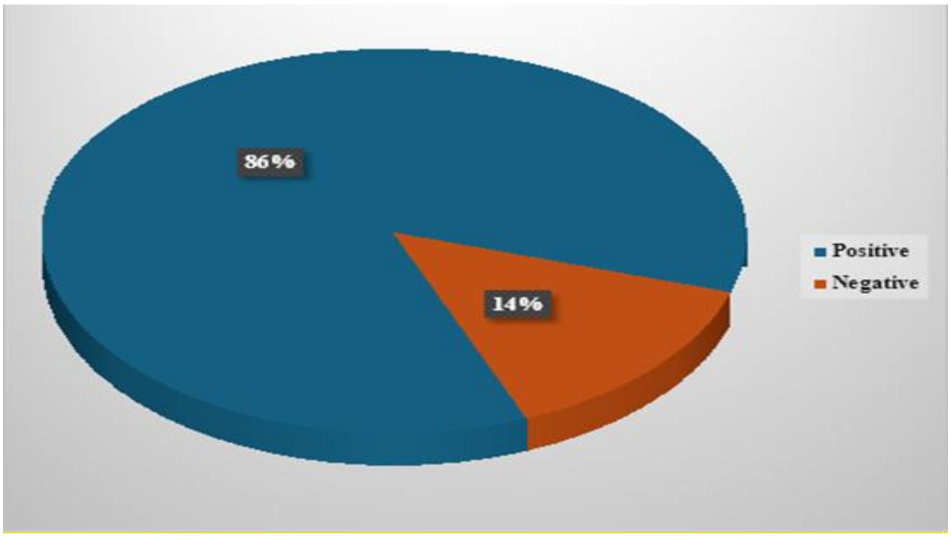

Figure 1. The percentage of patients who showed gliosis of brain tumors after six months of gamma knife treatment

The results of tumor shrinkage for patients included in this study are classified according to the number fractions of the treatment, as illustrated in table (4). The hypofractionated GK does look to be a feasible and efficient approach to managing assorted benign or malignant brain tumors. The method has a positive outcome in which the size of the tumor is reduced and the side effects are at the lowest. Definite future investigations with more patients as participants are needed to confirm these conclusions and observe outcomes of distinct fractionation schedules concerning the tumor control duration and patient survival.

Table 4. Comparison of the shrinkage of brain tumors before and after six months of gamma knife treatment according to the number of fractions

Number of Fractions	Pre-Treatment	6 Months Post-Treatment	P value
Two Fractions	2.63±1.45	2.44±1.41	0.0775
Three Fractions	3.33±1.06	2.95±1.03	<0.001*
Four Fractions	3.27±1.55	3.05±1.46	0.005*
Five Fractions	0.90	0.01	NA

* Significant difference if the P value ≤0.05

Discussion

The use of hypofractionated radiation in treating large brain tumors with GK resulted in substantial variations in the rate at which the dosage decreases (as measured by the GI values) compared to the coverage of the target volume and the conformity of the dose. GK consistently achieved a more pronounced decrease in radiation dosage outside the target area and yielded superior preservation of the normal brain, even though it delivered a higher dose to the core target. [19,20]. These findings were consistent with previous studies that used similar platform delivery to treat several lesions in intermediate-sized targets. It was seen that GK treatment resulted in a far sharper decrease in radiation dosage, therefore minimising damage to the healthy brain tissue around the target area, as proposed by Dong et al. [21].

Although irradiation has shown to be effective in neuro-oncology, there is a substantial risk of radiation-related consequences. Additionally, radio-surgical techniques greatly influence how much radiation to normal brain tissue can be tolerated [22].

This study revealed the importance of low rates of temporary gamma knife radiosurgery (GKRS)-related problems, quickly and readily addressed with steroids and long-term local tumor control, were seen in all patients treated with hypofractionated GKRS was found in retrospective observational research, Inserra et al. [23] detailed their experience treating 41 patients with hypofractionated GKRS for a range of benign and malignant intracranial tumors. They treated patients with hypofractionated GKRS and investigated if it was a safe and effective treatment option.

The strong conformance of GK may be attributed to its mechanical design. GK might achieve target conformity by using spherical focusing with more non-coplanar fields. Consequently, the dosage distribution in three dimensions was mostly spherical or ellipsoidal, which significantly restricted the accuracy of targeting irregularly shaped areas, leading to a poor conformity index. Gliosis around the tumor after irradiation indicated a positive response to radiation therapy. The present study stratified tumor volume reduction according to the number of hypofractionated treatment sessions. While no statistically significant reduction was observed immediately after irradiation, a significant decrease in tumor volume became evident six months post-treatment. A study by Dong et al. [21] found a substantial increase in cancer shrinking following six months of therapy. They saw time-dependent volumetric diminishment of glioblastoma stereotactic radiosurgery with hypofractionation in large or complicated lesions in the brain. This delayed tumor response aligns with present study findings. Pinzi et al. [18] also revealed that tumor regression results in a gradual manner, spread over many months, especially in larger lesions, e.g., larger than 3 cm or near eloquent structures, and it also highlighted the biological latency nature of radiation-induced cytotoxicity.

Future clinical trials should investigate crucial aspects, such as determining the optimal single-fraction equivalent doses of 10-Gy or 12-

Gy for different hypo-fractionated treatment plans. Additionally, it is important to assess the ongoing effectiveness of hypofractionated treatments, such as delivering 25 Gy in 5 fractions with a single-fraction equivalent dose. These examples provide a limited selection of the questions that must be resolved.

The research explores the role of gliosis as a biomarker of therapy response, highlighting its high prevalence. The present observation is in line with the study conducted by Walker et al. [22], which revealed that gliotic changes can reflect post radiation tissue remodeling and are related to tumor regression or effect of treatment, but not the progression of the disease. Similarly, Inserra et al. [23] reported the percent rate of gliosis in an extensive proportion of patients who received the treatment of hypofractionated GKRS and connected this phenomenon with positive results of treatment. The diagnosis specificity of gliosis as biomarker however is at the current status limited and has to undergo further investigation to do the confirmation of the predictive value related to long-term tumor control. Future studies should confirm gliosis and other indicators, and larger patient cohorts could provide more comprehensive insights into the safety and effectiveness of hypofractionated GK radiosurgery, ensuring statistical robustness.

In conclusions, the study demonstrates that hypofractionated GK radiosurgery is a successful treatment for various brain tumors, as evidenced by the presence of gliosis around the malignancy after six months of radiation treatment. Hypofractionated radiosurgery, specifically employing the GK, is more efficient for maintaining healthy brain tissue while delivering the necessary radiation dosage for treating large or complicated brain lesions. Meningioma responds more positively to hypofractionation than AVM.

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Author contribution

Kadhem: collecting data, writing the paper, statistical analysis. Dr. Ahmed: reviewing and editing. Dr. Hamandi: Objective of the study, review and editing.

Conflict of interest

The authors declare there is no conflict of interest.

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