# Hypofractionated Gamma Knife Radiosurgery in Big Tumors

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**KEYWORDS**

Big Brain Tumor, Volumetric Change, Gradient Index (GI), Gamma Knife, Stereotactic.

**ABSTRACT**

**Objective:** This research aimed to determine the most effective dosages and achieve improved outcomes without surgical intervention, discomfort, or blood loss. Its objective was also to regulate the formation of both benign and malignant tumours and reduce tumour size. **Patients and Methods:** A study involving 50 patients at Dr. Saad Al-Witry Hospital for Neurosciences and Al-Altaj Hospital examined brain tumours using MRI models, CBCT, and a gamma knife device. Patients with large tumours were included, while those receiving single fractions of treatment and pregnant women were excluded. Patients were prepared using Leksell frames, thermoplastic masks, and personalised stereotactic masks. Gamma Knife radiosurgery sessions were administered based on tumour size, location, and patient tolerance. **Results:** This study analysed the use of hypofractionation gamma knife treatment for six brain tumours: Meningioma, Glioma, Schwannoma, Arteriovenous Malformations (AVM), Pituitary Adenoma, and Metastasis. The mean dose distribution was higher in metastasis, followed by AVM, meningioma, glioma, schwannoma, and pituitary adenoma. The maximum dose was found in metastasis, followed by meningioma, glioma, pituitary adenoma, AVM, and schwannoma. The coverage of the target reached excellent value for metastasis, followed by AVM and pituitary adenoma. The beam on time for the treatment was highest in meningioma. Following six months of treatment, the study found a significant difference in tumour volume before and after six months. The highest reduction was observed in meningioma cases, followed by glioma and vestibular schwannoma. A study involving ten patients showed a significant reduction in tumours after a year of gamma knife treatment, with meningioma cases showing the highest reduction. **Conclusion:** The study found that metastasis was the most common cancer, followed by meningioma, glioma, schwannoma, AVM, and schwannoma. After six months, meningioma showed the highest reduction, and meningioma showed a better response to hypofractionation, followed by AVM.

## 1. Introduction

The term "radiation" encompasses the whole electromagnetic spectrum and all known atomic and subatomic particles. Two ways that radiation may be distinguished from one another are ionising and non-ionising. Upon passing across a medium, radiation can ionise atoms and molecules (1–11).

Stereotactic radiosurgery is a minimally invasive procedure used to treat intracranial tissues or lesions that are difficult to reach or unsuitable for traditional surgery. The original technique, which used probes and electrodes, paved the way for modern radio surgery. The design of the instrument, with the target at the centre of a semicircular arc, allowed for precise targeting with narrow beams of radiation (12). Radiosurgery is a neurosurgical procedure that involves delivering radiation through a stereotactic approach. The term stereotaxis originates from the Greek words stereo, meaning three-dimensional, and taxis, meaning orderly arrangement (13). The Gamma Knife was designed for precision in treating brain conditions, using multiple narrow radiation beams targeted at a specific area without incisions. Despite its name, there is no actual knife involved. Patients typically undergo treatment and are discharged within a day, allowing them to resume their normal activities quickly. This method is a proven alternative to traditional brain surgery and whole-brain radiation therapy, offering accurate and precise results for complex brain conditions. Renowned medical centres worldwide prefer the Gamma Knife for its documented patient treatment success (14). The principal radiation of the Gamma knife concentrates inside a target in the brain while avoiding radiation surrounding healthy tissue. The Gamma knife accomplishes this by mechanically focusing 192 or 201 radiation sources, which allows the brain to be shaped into an extremely defined irradiated volume (15).

This study aimed to get optimal doses and better results without surgery, pain, or even blood, as well as control benign and malignant tumour growth and minimise the tumour size.

## Patients and Methods:

This cross-sectional study was performed in Dr. Saad Al-Witry Hospital for Neurosciences and Al-Altaj Hospital for six months (from January 2024 to July 2024). The Institution Review Board (IRB) of the Al-Nahrain University College of Medicine approved this study. Fifty patients with different types of brain tumours were selected for this study. These tumours are big noncancerous (benign) and cancerous (malignant) brain tumours, Arteriovenous malformation (AVM), neuroma, acoustic neuroma, and pituitary tumours. All patients with big tumours were included in this study. All patients with single sessions and pregnant women were excluded from this study.

After patients' diagnoses and being forwarded to the gamma knife treatment, a magnetic resonance imaging (MRI) model, Achieva 3 Tesla or 1.5 Tesla, manufactured by Philips, was used to acquire three-dimensional detailed anatomical images for the tumour. Then, the Cone Beam Computed Tomography (CBCT) mounted to the gamma knife device is used to acquire the bone and solid structures of the head. The Leksell frame was performed to prepare the patients for imaging.

Patients with a condition are fitted with a thermoplastic mask made of Poly Methyl Methylate Acrylate (PMMA), a water-equivalent material. A custom-fit mask is created before the first treatment or the same day, holding the head still during imaging and treatment. The mask is heated to 76 $^{0}$C and placed across the face, exposing the nose for easy breathing. The mask adapter is equipped with multiple markers, tracking patient movements at a rate of 20Hz to minimise interference from noise and camera movements.

The patient is secured with a thermoplastic mask, ensuring minimal interference with nose movements. The HDMM system is a non-rigid treatment method that uses an infrared stereoscopic camera to track patient movement during treatment. The patient is secured with a thermoplastic mask, which has a large opening for the nose to minimise interference. The system uses a gating function to restart treatment if the patient returns to the correct position within a set time frame or pauses until the operator resumes it. The infrared camera is attached to an arm on a couch that can be folded up for storage. After six months, the tumour volume was evaluated using MRI imaging for the patient's head at AL-Taj Hospital and Saad AL-Witry Hospital. The tumour volumes were compared before and after radiosurgery for about six months and one year, observing differences in measured volumes due to the doses of gamma irradiation. Data analysis was performed using the statistical package SPSS-28, with simple measures of percentage, mean, standard deviation, and range. The significance of the difference was tested using the students' or the paired test. A scattering distribution curve was used for correlation, and statistical significance was considered when the p-value was equal to or less than 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 tumours treated with hypofractionation are Meningioma, Glioma, Schwannoma, Arteriovenous Malformations (AVM), Pituitary Adenoma, and Metastasis. The age of patients age was divided according to the tumour 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 Gamma Knife had a higher prevalence than males (12 (32%)), as shown in Figure (1). 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, Arteriovenous Malformations (AVM), Pituitary Adenoma, and Metastasis, respectively, as shown in Figure (2).

**Table (1): The characteristics of patients treated with hypofractionation Gamma Knife**

| Characteristic |
|---|

| | |
|---|---|
| **Age (years)** | 48.46 ± 13.89 (15 – 85) |
| **Gender** | |
| **Male** | 16 (32%) |
| **Female** | 34 (68%) |
| **Type of Tumors** | |
| **Meningioma** | 34 (68%) |
| **Glioma** | 5 (10%) |
| **Schwannoma** | 6 (12%) |
| **Arteriovenous Malformations (AVM)** | 3 (6%) |
| **Pituitary Adenoma** | 1 (2%) |
| **Metastasis** | 1 (2%) |

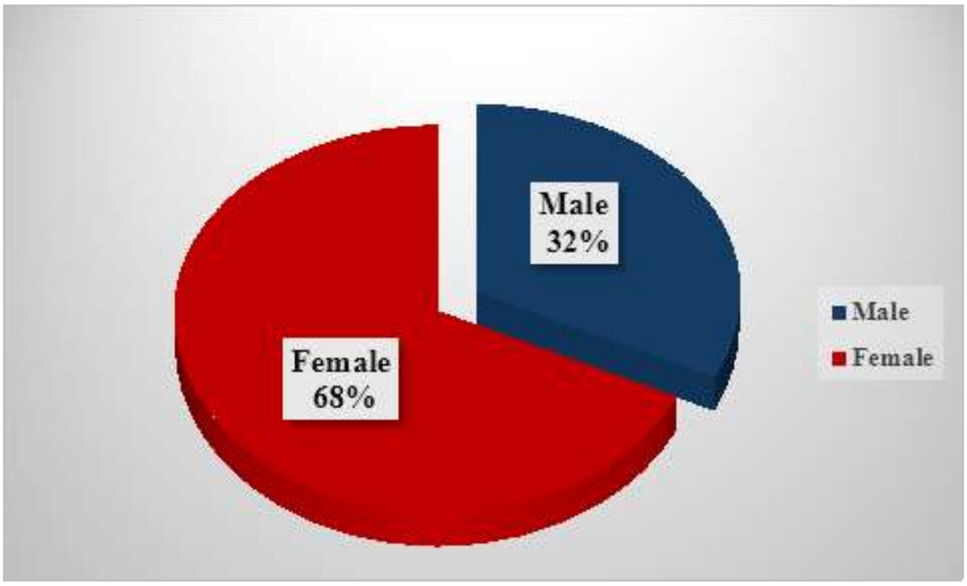


**Figure (1): Gender Distribution Treated with Hypofractionation Gamma Knife**

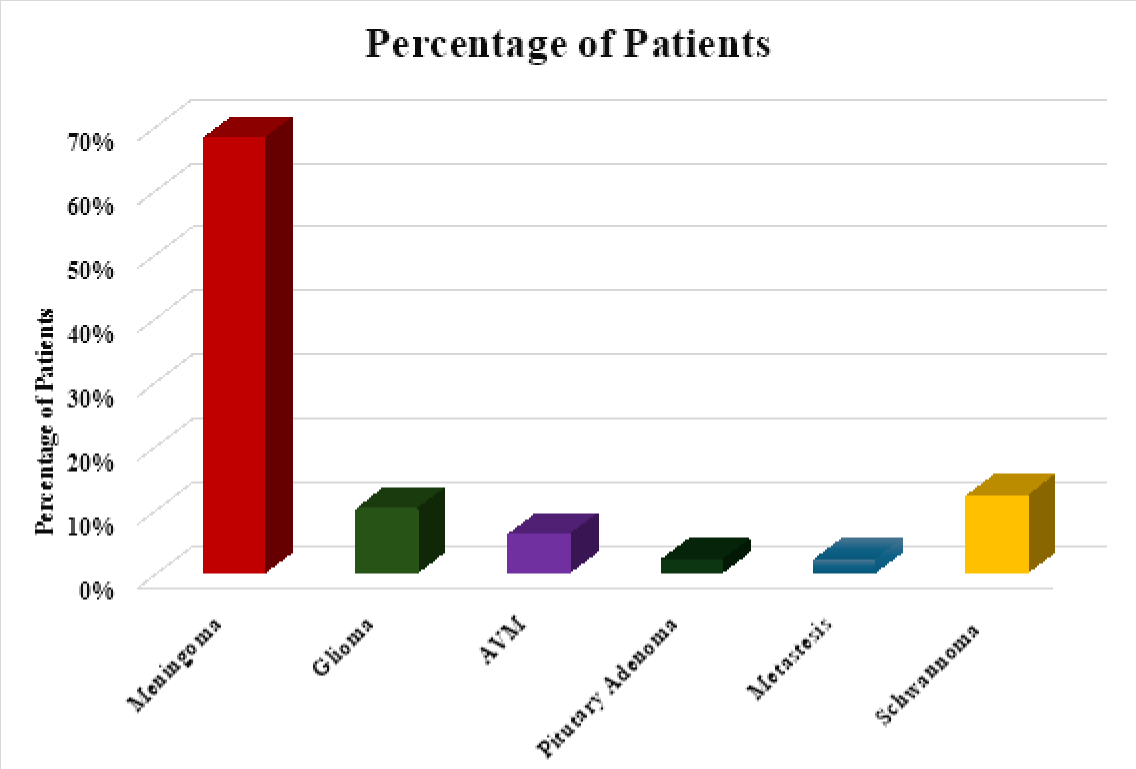


**Figure (2): Percentage of Patients Treated with Hypofractionation Gamma Knife.**

The evaluation parameters of the plans for patients treated with hypofractionated gamma knife were measured and listed in Table (2). The total Dose per day and fractionation were higher in metastasis, followed by AVM, meningioma, glioma, schwannoma, and pituitary adenoma. The mean dose distribution was higher in pituitary adenoma, followed by AVM, meningioma, glioma, metastasis, and less Dose for schwannoma. The maximum dose was found in metastasis, followed by meningioma, glioma, pituitary adenoma, AVM, and schwannoma. The minimum Dose reached the target volume was higher in AVM, followed by pituitary adenoma, meningioma, glioma, and schwannoma, and finally, it was zero in the metastasis. The integral Dose was higher in metastasis, followed by glioma, meningioma, schwannoma, AVM, and pituitary adenoma. The gradient index (GI) was higher in metastasis, followed by glioma, schwannoma, meningioma, AVM, and pituitary adenoma. The coverage of the target reached excellent value for metastasis, followed by AVM and pituitary adenoma. The coverage was almost equal for Meningioma, Glioma, and Schwannoma. The selectivity reached the best values for pituitary adenoma, followed by glioma and schwannoma equally, then meningioma, and finally, the AVM. The number of shots given per session was higher in metastasis, followed by meningioma, schwannoma, glioma, pituitary adenoma, and finally, the AVM. Finally, the beam on time for the treatment was the highest in meningioma, followed by pituitary adenoma, metastasis, glioma, schwannoma, and AVM.

**Table (2): The Plan Evaluation of patients treated with hypofractionation Gamma Knife according to the tumour type**

| Parameters | Meningioma | Glioma | Schwannoma | Arteriovenous Malformations (AVM) | Pituitary Adenoma | Metastasis |
|---|---|---|---|---|---|---|
| Total Dose (Gy) | 15.47 ± 3.48 (4 – 20) | 15.2 ± 2.94 (12 – 20) | 12.83 ± 1.32 (12 – 15) | 18.66 ± 1.15 (18 – 20) | 12 | 24 |
| Dose per Day (Gy) | 4 – 8 | 3 – 8 | 3.5 – 5 | 5 – 6 | 4 | 6 |
| Fractions | 2 – 4 | 2 – 3 | 3 | 3 – 5 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mean (Gy) | 14.17 ± 8.11 (1.6 – 27.3) | 12.98 ± 9.70 (4.7 – 26.5) | 5.05 ± 1.13 (3.7 – 6.7) | 14.8 ± 11.6 (2.7 – 26) | 17.2 | 10.9 |
| Max (Gy) | 32.06 ± 18.67 (8 – 100) | 30.4 ± 5.03 (24 – 40) | 22.83 ± 3.64 (15.6 – 25.9) | 23.8 ± 11.48 (13.2 – 36) | 24 | 49 |
| Min (Gy) | 4.77 ± 1.75 (0 – 14.7) | 3.82 ± 5.03 (0 – 10) | 0.55 ± 0.03 (0 – 1.1) | 8.9 ± 1.70 (0.7 – 13.2) | 7.6 | 0 |
| Integral Dose (mJ) | 892.09 ± 122.99 (68.3 – 3661.9) | 1430.18 ± 173.96 (265.8 – 3111.9) | 799.53 ± 192.98 (200.7 – 2130.8) | 150.33 ± 42.38 (101.4 – 175.8) | 148.8 | 4614.3 |
| Gradient Index (GI) | 2.65 ± 0.15 (0.15 – 0.97) | 2.72 ± 0.16 (2.54 – 2.93) | 2.66 ± 0.12 (2.42 – 2.77) | 2.66 ± 0.08 (2.59 – 2.75) | 2.53 | 2.82 |
| Coverage | 0.93 ± 0.02 (0.89 – 1) | 0.93 ± 0.03 (0.88 – 0.96) | 0.93 ± 0.02 (0.90 – 0.96) | 0.95 ± 0.02 (0.93 – 0.97) | 0.94 | 1 |
| Selectivity | 0.83 ± 0.15 (0.15 – 0.97) | 0.86 ± 0.06 (0.79 – 0.93) | 0.86 ± 0.07 (0.74 – 0.94) | 0.79 ± 0.08 (0.71 – 0.87) | 0.88 | 0.84 |
| Shot No. | 2 – 55 | 13 – 30 | 16 – 33 | 5 – 14 | 23 | 48 |
| Time (min) | 24.53 ± 8.63 (3.6 – 49) | 21.78 ± 2.54 (19.4 – 25.3) | 19.73 ± 5.93 (11.7 – 27.2) | 16.1 ± 7.57 (7.5 – 21.8) | 23.92 | 22.2 |

The volumetric change after and before six months of follow-up of patients was measured and shown in Table (3) and Figure (3). The statistical analysis shows a significant difference in tumour volume before and after six months of treatment by hypofractionation Gamma Knife. The highest significance difference was found in meningioma, glioma, and schwannoma. Excellent results were found in AVM, where the tumour had disappeared. There was noticeable shrinkage in pituitary adenoma and metastasis tumours, but no statistical analysis was performed because they are single cases. For all of the tumours treated with hypo fractionation, the statistical analysis shows a higher significant shrinkage of tumours due to gamma knife irradiation after six months of treatment.

**Table (3): Comparison of the Shrinkage of Brain Tumors Before and After Six Months of Gamma Knife Treatment**

| Tumor | Pre-Treatment | 6 Months Post-Treatment | *p*-value |
|---|---|---|---|
| **Meningioma** | 3.61 ± 0.80 | 3.27 ± 0.74 | <0.0001* |
| **Glioma** | 3.38 ± 1.13 | 3.10 ± 1.06 | 0.04511* |
| **Schwannoma** | 3.32 ± 0.53 | 3.07 ± 0.38 | 0.0817* |
| **Arteriovenous Malformations (AVM)** | 1.22 ± 0.54 | 0 (disappeared) | NA |
| **Pituitary Adenoma** | 3.03 | 2.99 | NA |
| **Metastasis** | 3.32 ± 1.66 | 3.07 ±0.5 | NA |
| **All tumours** | 3.39 ± 0.95 | 3.031 ± 1.04 | <0.0001* |
| * **Significant difference if the *p*-value ≤0.05** | | | |

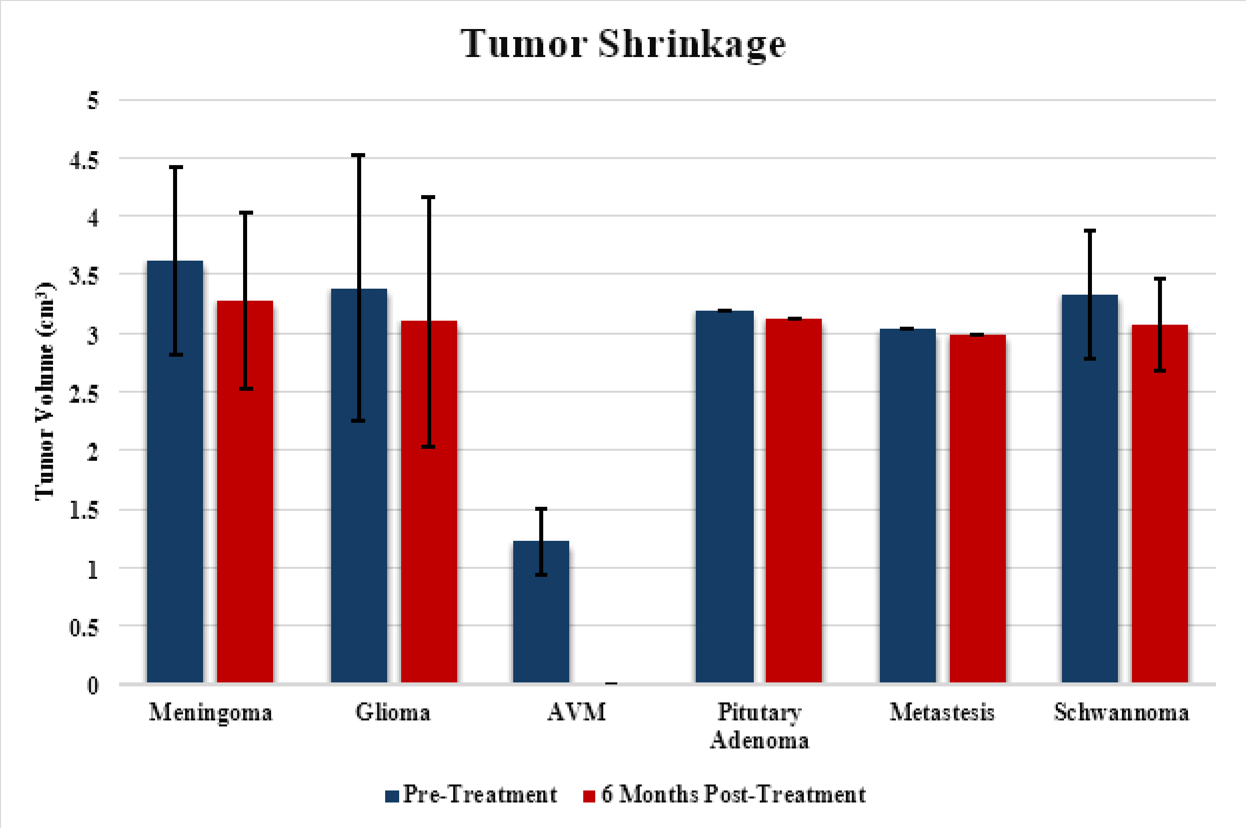


**Figure (3): The Shrinkage of Brain Tumors Before and After Six Months of Gamma Knife Treatment**

A follow-up after one year of the study was assessed for only ten patients and presented in Table (4). Six have meningioma, two have glioma, and two have vestibular schwannoma. The statistical analysis shows a highly significant reduction in tumours after one year of gamma knife treatment. The highest reduction was observed in meningioma cases, followed by glioma and vestibular schwannoma.

**Table (4): Comparison of the Shrinkage of Brain Tumors Before and After one year of Gamma Knife Treatment**

| Tumor | Pre-Treatment | One Year Post-Treatment | *p*-value |
|---|---|---|---|
| **Meningioma** | 3.61 ± 0.80 | 0.51 ± 0.11 | <0.0001* |
| **Glioma** | 3.38 ± 1.13 | 1.02 ± 0.06 | <0.0001* |
| **Schwannoma** | 3.32 ± 0.53 | 1.43 ± 0.45 | <0.0001* |
| *** Significant difference if the *p*-value ≤0.05** | | | |

## Discussion

Hypofractionated radiotherapy of large brain tumours in GK treatment resulted in large statistically significant differences in dose fall-off (e.g., as indicated by the GI values for equivalent target volume coverage and dose conformity). Despite a greater central target dose, GK consistently produced sharper dose fall-off and better normal brain-sparing results(16,17). These findings agreed with studies that treated multiple lesions with these platform deliveries for treating intermediate-sized targets, where GK produced noticeably sharper dose fall-off in sparing the normal brain tissue surrounding the target (18).

The objective of this research was to determine the most effective dosage and achieve improved outcomes without the need for surgery, discomfort, or blood loss. Additionally, the study attempted to regulate the development of both benign and malignant tumours, intending to reduce tumour size.

The study involved patients aged 15-85 with six types of brain tumours: Meningioma, Glioma, Schwannoma, Arteriovenous Malformations (AVM), Pituitary Adenoma, and Metastasis. The age range was 45-47 years. Females had a higher frequency of hypofractionation Gamma Knife treatment (68%) than males (32%).

This study analysed the treatment plans for patients undergoing hypofractionated gamma knife therapy. It was found that the highest daily dose and fractionation were found in metastasis, followed by AVM, meningioma, Glioma, schwannoma, and pituitary adenoma. The average dosage distribution was highest in pituitary adenoma, followed by arteriovenous malformation (AVM), meningioma, Glioma, and metastasis. Schwannoma had a lower dose distribution. The minimal dose required for achieving the goal volume was highest in AVM, followed by pituitary adenoma, meningioma, Glioma, and schwannoma. The treatment achieved high coverage for metastases, followed by AVM and pituitary adenoma. The number of administered doses per fraction was highest in metastasis cases. The therapy beam's duration (beam on time) was the longest for meningioma.

The results of our coverage for the tumour for hypofractionation in gamma knife disagreed with the research of Dong et al. (18). They performed a comparative study for the hypofractionation technique in multi-modalities of SRS. They found that the pituitary adenomas had the greatest average dose, while metastases had the highest maximum dose. These findings emphasise the importance of tailoring dosimetric planning to maximise treatment effectiveness while minimising negative side effects. Our study shows that the metastasis had the highest coverage. They studied hypofractionation using the Linac and Gamma Knife, while we studied the Gamma knife only.

This study, which assessed tumour volume before and after six months of treatment with hypofractionation Gamma Knife, revealed significant differences in tumour volume. The most notable difference was seen in meningioma, Glioma, and schwannoma. AVM showed exceptional outcomes, while pituitary adenoma and metastatic tumours showed reduction.

The study's results show that the three commercially accessible SRS solutions can produce designs that meet clinical standards. The findings of this investigation have unveiled a plethora of intriguing data. GK offered several benefits in dosimetry and biology, but this came at the expense of the lengthiest treatment duration.

For the dosimetric indexes with statistical differences, the relative performance of GK was unrelated to the PTV volume. The relative advantages of the three-conformity index (CI) techniques depended on the PTV volume. To the best of our knowledge, the first report for hypofractionation of gamma knife was performed by Duan et al. in 2021(3), quantified the quality and biological differences, including CI among GK, Cone-VMAT, and MCL-CRT to treat single small brain metastasis only. Despite these statistical differences, the clinical relevance and impact of such differences remain to be determined. They agree with our study addressing the importance of CI in hypofractionation gamma knife. The difference is that the studied metastasis only, and our study involved seven types of tumours.

This research showed that GK fractionation strategies yielded comparable targets or gradient index (GI) in multiple brain metastases or big intracranial tumours. The significant decrease in GK effectiveness was due to its physical architecture, which enabled the concentration of thousands of non-coplanar beams onto a single target. These findings agree with the research of Siberian et al. (7).

Moreover, Rahman et al. (19) agreed with our results regarding the importance of GI. They reported after a prospective study for hypofractionated stereotactic radiosurgery that the risk assessment research on the low-dose region in GI of healthy brain tissue in brain tumour patients treated with SRS revealed no elevated risk of developing cancer compared to the general population during five years.

When determining the best dosing and fractionation techniques, it is important to consider the dose to the target peripheral and the surrounding normal brain regions. In this research, the dose remains lower than the risk values. These results agreed with the research of Milano et al. (20) in 2024. We aimed to find standardised dosimetric and toxicity to improve the biological effects of tissue at risk after hypofractionation GK. Milano et al. performed an analysed study for the dosimetric and clinical predictors of radiation-induced optic nerve/chiasm neuropathy (RION) after hypofractionated (2-5 fractions) radiosurgery (SSRS) or single-fraction stereotactic radiosurgery (SRS). Their research on malignant tumours found no correlation between prior resection and RION risk in 76% of patients. However, a 10-fold greater incidence of RION was related to past irradiation in 6% of patients. The guideline for RION risk is 10 Gy in 1 fraction, but in patients without prior radiation treatment, maximum point doses are 12 Gy in 1 fraction, 20 Gy in 3 fractions, and 25 Gy in 5 fractions. A single-fraction dosage of 10 Gy was linked to a 1% risk of RION. Our research found that GK with hypofractionation is within these guidelines.

Due to significant shrinkage, the three-fraction schedule is recommended for most tumour types, but further research is needed to explore alternative schedules for specific tumour types or patient characteristics. Customised dosimetric planning ensures each patient's specific tumour characteristics are tailored to the total dose, daily dose, and fractions, maximising therapeutic effect and risk to healthy tissues (21).

Current and upcoming clinical trials should investigate several important issues, including the appropriate single-fractional equivalent doses of 10-Gy or 12-Gy for different hypo-fractional treatment plans, the continued validity of hypofractionated treatments such as 25 Gy delivered in 5 fractions with a single-fractional equivalent dose. These are just a few examples of the questions that must be addressed.

**Conclusion:**

The conclusion of this study demonstrates that hypofractionated Gamma Knife radiosurgery is a very effective therapeutic approach for a diverse range of brain tumours. The treatment significantly reduced tumour size for meningiomas, gliomas, schwannomas, and AVMs. A customised approach to fractionation and dosage may be used using dosimetric evaluation, ensuring effective tumour control while minimising adverse effects. After six months, the therapy showed a noteworthy decrease in tumour volume, with meningioma instances demonstrating the most substantial reduction. Hypofractionated radiosurgery using Gamma Knife (GK) is more effective in preserving healthy brain tissue while still achieving the appropriate radiation dose for large or complex brain lesions. Meningioma responds more favourably to hypofractionation than Arteriovenous Malformations (AVM).

**Conflict of interest:** there is no conflict of interest.

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