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Fractionated Gamma Knife Surgery: Long-Term Results and Patient Outcomes for Intracranial Lesions

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Abstract

Background: Fractionated gamma knife surgery (f-GKS) is an effective and safe procedure for treating various intracranial lesions, including pituitary adenomas and meningiomas. It offers noninvasive treatment with short hospitalization periods. This study aims to assess the long-term outcomes of f-GKS in patients at the Iran Gamma Knife Center (IGKC).

Methods: This cross-sectional study examined patients who underwent at least 2 GKS sessions between 2011 and 2018. Lesion sizes in 2-dimensional slices were compared before and after the procedure. Data were analyzed using descriptive statistics in SPSS software Version 22.

Results: The study included 106 patients (32 male, 74 female), with a mean age of 49.95 ± 16.6 years. The follow-up period was 24.98 ± 19.01 months. The most common pathology was meningioma, with f-GKS typically performed 3 times at 1-day intervals. The median change in lesion area was 185.67 mm². Out of 36 patients at the last visit, 26 (72.2%) showed improved prognosis. The maximum radiation dose used was 13.05 ± 5.21 Gy. The pathology coverage was 98.69% ± 2.15%, with a mean and mode of 99%.

Conclusion: In this study, we examined various factors, including lesion levels from brain Magnetic Resonance Imaging findings, patient prognosis, and changes after f-GKS. Our results confirm those of previous studies, highlighting the significant role of noninvasive GKS in improving patient prognosis and reducing tumor size.

Keywords: Radiosurgery, Gamma Knife Surgery, Fractionated Gamma Knife Surgery, Brain Neoplasms, Meningioma, Skull Base

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Introduction

Gamma knife surgery (GKS) is a modern, effective, and safe radiosurgical method for treating various intracranial lesions. This technique is utilized for the treatment of many types of brain lesions, including pituitary adenomas, meningiomas, and others. Advantages include its noninvasive nature and the minimal duration of the procedure (1, 2).

GKS employs 201 focused cobalt-60 sources to deliver highly precise gamma radiation to intracranial targets, including deep or surgically inaccessible lesions. The system's design ensures the convergence of gamma beams at a single focal point (3, 4), maximizing dose delivery to the lesion while sparing surrounding healthy tissue. During treatment planning, the target is positioned at the isocenter of the collimator helmet, enabling submillimeter accuracy for optimal therapeutic effect and minimal off-target exposure (5).

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↑What is "already known" in this topic:
Fractionated gamma knife surgery (f-GKS) is a well-established noninvasive approach for treating inoperable or recurrent intracranial tumors, offering high tumor control with reduced toxicity through multisession dose delivery.

→What this article adds:
This study presents the long-term outcomes of f-GKS for brain tumors, demonstrating significant lesion reduction and an improved prognosis, while confirming optimal dosimetric parameters for clinical application.

The gamma knife method is currently used to treat various benign brain tumors (including acoustic neuroma/schwannoma, meningioma, pituitary adenomas, hemangioblastoma, chordoma, and pineal tumors), malignant brain tumors (including metastases, glial tumors, ocular melanoma, and craniopharyngioma), brain vascular abnormalities (including arteriovenous and cavernous malformations), functional nerve diseases, and treatment-resistant pain (6). The integration of computed tomography (CT) scans and magnetic resonance imaging (MRI) has significantly enhanced the planning and implementation of GK treatments. This advanced technology is utilized by numerous medical centers worldwide (7, 8).

Fractionated gamma knife surgery (f-GKS) involves multiple sessions, typically a minimum of two. Studies indicate that f-GKS is significantly more effective than the single-session GKS method (1, 2). While single-session GKS achieves high local control rates for small, well-defined tumors, multisession or f-GKS offers a safer alternative for larger lesions or those adjacent to critical structures, as it distributes radiation doses across multiple sessions to mitigate toxicity risks while maintaining therapeutic efficacy (9).

In this study, we examined the long-term outcomes of patients with brain lesions of varying sizes and locations who underwent f-GKS. We assessed factors such as improvement in neurological symptoms and changes in tumor size.

Methods

Study Design

This cross-sectional study was conducted at the Iran Gamma Knife Center (IGKC) after obtaining approval from the institutional ethics committee. The adoption of fractionated f-GKS at IGKC originated from concerns regarding the high toxicity risks of single-dose regimens for tumors in critical regions, particularly orbital/optic nerve lesions, where conventional single-session dosing risked damage to adjacent structures. Building on prior surgical experiences and the published study by Kurt et al (10), the decision was made to divide the total dose into 3 fractions to mitigate toxicity. Following favorable outcomes, the protocol was expanded to include tumors in other brain regions, demonstrating superior safety and efficacy compared to single-dose GKS in complex cases. We analyzed data from patients with intracranial lesions who underwent a minimum of 2 sessions of f-GKS between 2011 and 2018. Eligible participants were required to have a confirmed diagnosis of brain lesions (via histology or pretreatment MRI), documented completion of ≥2 f-GKS sessions with dosimetric records, and at least 1 posttreatment clinical follow-up for symptom or neurological assessment. Patients were excluded if their medical records lacked essential baseline variables (eg, lesion size/location), if they received fewer than 2 f-GKS sessions, or if informed consent was unavailable. All patients provided written informed consent after comprehensive counseling on alternative therapies and their risks/benefits. The treatment protocol consisted of 3 radiation doses, each delivered at 24-hour intervals. Dose parameters were individualized based on lesion size, proximity to critical structures, and prior irradiation history. To ensure consistent targeting, a stereotactic frame remained affixed to the patient's head for 48 hours during the multisession protocol, as per the technical specifications of the gamma knife model C (201 cobalt-60 sources) at IGKC. After the final fraction, the frame was removed, and patients were discharged with follow-up instructions.

Data Collection

Data were collected using a researcher-compiled checklist, approved by respected professors. Variables included age, sex, brain lesion volume, lesion location and position, the interval between the first and second GKS, and between the second and third GKS, the time from pathology identification to GKS, dosimetric characteristics used in GKS, and changes in neurological symptoms.

Sample Size

The sample size was determined by a census, reviewing all patient files with brain masses referred to IGKC who underwent f-GKS between 2011 and 2018.

Data Analysis

Data were analyzed using SPSS software Version 22) (IBM). Descriptive statistics (mean ± SD, median, frequencies, and percentages) summarized demographic, dosimetric, and outcome variables (eg, lesion size change, radiation dose). Given the retrospective cross-sectional design and exploratory analysis of routinely collected data, inferential statistics (e.g, regression models to control for confounders such as prior interventions or lesion location) were not employed.

Results

In this study, out of 106 patients, 32 (30.2%) were male and 74 (68.2%) were female. The mean age of the patients was 49.95 ± 16.06 years, and the age range was 7 to 80 years (mode = 57, median = 52 years), indicating a distribution with a skewness of –0.5.

Among 104 patients with available data, 50 (48.1%) had no history of previous neurosurgery. A total of 38 patients (36.5%) had undergone 1 last neurological intervention, 10 patients (9.6%) had 2, 5 patients (4.8%) had 3, and 1 patient (1%) had a history of 4 previous interventions.

The mean follow-up period was 24.98 ± 19.01 months, and the median was 24 months. The mean interval between pathology diagnosis and GKS was 38.70 months, with a median of 24 months, a mode of 12 months, a minimum of 0 months, and a maximum of 360 months.

Radio-Surgical Dosimetry

For each procedure, the prescription dose was individualized in collaboration with experts from IGKS, taking into account lesion characteristics (e.g, size, location, proximity to critical structures), pathology type, and prior treatment history. The mean maximum dose delivered to the lesion was 13.05 ± 5.21 Gy (range: 6.66–45 Gy; median/mode: 12 Gy). Tumor coverage—defined as the percentage of the lesion volume receiving at least the prescription dose—was calculated using the treatment planning system. Coverage was near-complete in most cases, with a mean of 98.69% ±

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Table 1. Radiosurgical Dosimetry Data Used in This Study

Statistical index	*Pathology Coverage* (%)	*Maximal Dose*	*Marginal Dose* (Gy)	*Iso dose* (%)	*Iso center*
Mean	8.6311	13.0543	7.5728	54.5673	98.6923
Median	9.0000	12.0000	6.0000	50.0000	99.0000
Mode	9.00	12.00	6.00	50.00	99.00
Standard Deviation	3.46690	5.21476	6.67429	7.83416	2.15909
Minimum	1.00	6.66	4.00	40.00	83.00
Maximum	18.00	45.00	70.00	80.00	100.00

2.15% (range: 83%–100%; median/mode: 99%) (Table 1).

Pathology

The most common pathology type among the subjects was meningioma, accounting for 53 cases (50%). The subsequent most frequent pathology was adenoma, with 15 cases (14.2%). Following this, we had metastasis, glioma, craniopharyngioma, and other pathologies as shown in Figure 1.

The Locations of Brain Lesions

In 46 patients (43.4%), brain lesions were multifocal, involving multiple regions rather than confined to a single anatomic location. The most commonly known locations were the pituitary gland (13.2%), right optic sheath (6.6%), sella and suprasellar (6.6%), right cavernous sinus (5.7%), right optic nerve (5.7%), left cavernous sinus (4.7%), and left optic nerve (5.7%) (Figure 2).

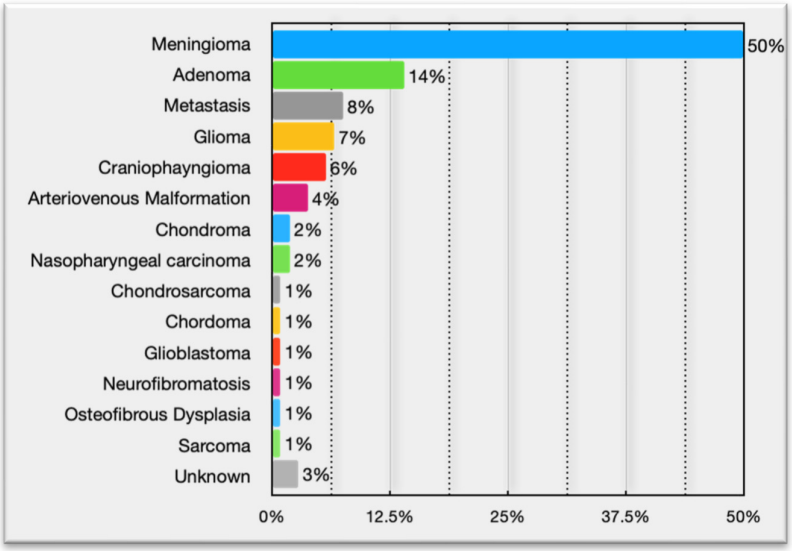

Figure 1. Distribution of pathology types among study patients (N = 106)

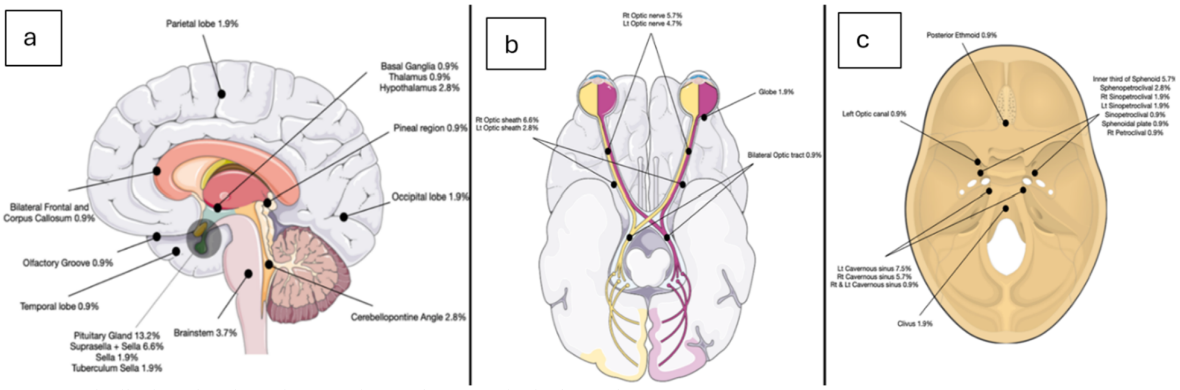

Figure 2. Distribution of Brain Lesion Locations and Frequencies in the Study
(A) Mid-sagittal MRI section: Lesion prevalence across key regions, including the pituitary gland (13.2%), suprasellar/sellar areas (6.6%), and the Brainstem (3.7%). (B) Visual pathway: Lesions along the optic nerve, chiasm, and tracts. Right Optic sheath (6.6%), right optic nerve (5.7%), and left optic nerve (4.7%) were the most commonly affected sites. (C) Skull base bone view: Proximity of lesions to critical neurovascular structures. Percentages reflect the proportion of patients with lesions in each anatomical site (N = 106). Anatomical templates adapted from (21, 22).

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Time Interval Between the First, Second, and Third GKS

The strategy for performing f-GKS involved 3 GKS sessions with 1-day intervals. However, due to issues such as patient unavailability and distance, this strategy could not be applied to a minimal number of patients. In 100 patients (95.3%), the interval between the first and second sessions was 1 day. Similarly, in 99 patients (93.4%), the interval between the second and third sessions was also 1 day. Five patients underwent only 2 GKS, making the interval between the second and third GKS irrelevant for them (Figure 3).

Lesion Size

In this study, the largest lesion size on pre-GKS and the final follow-up brain MRI was evaluated. The lesion size was determined by identifying the MRI slice (axial, coronal, or sagittal) displaying the largest diameter of the lesion. The longest diameter and its longest perpendicular diameter within the same slice were multiplied to calculate the surface area (mm²). Due to the incomplete availability of the final MRI scans, data from only 36 patients were analyzed. Volumetric analysis was not performed in this study; all assessments were based on 2-dimensional measurements derived from the largest identifiable cross-sectional diameters across any imaging plane (Figure 4).

In 29 out of 36 patients (80.6%), the lesion size decreased, while in the remaining 7 patients, the lesion size increased. The average change in lesion size was 185.67 mm², with the most significant reduction of 981.64 mm²

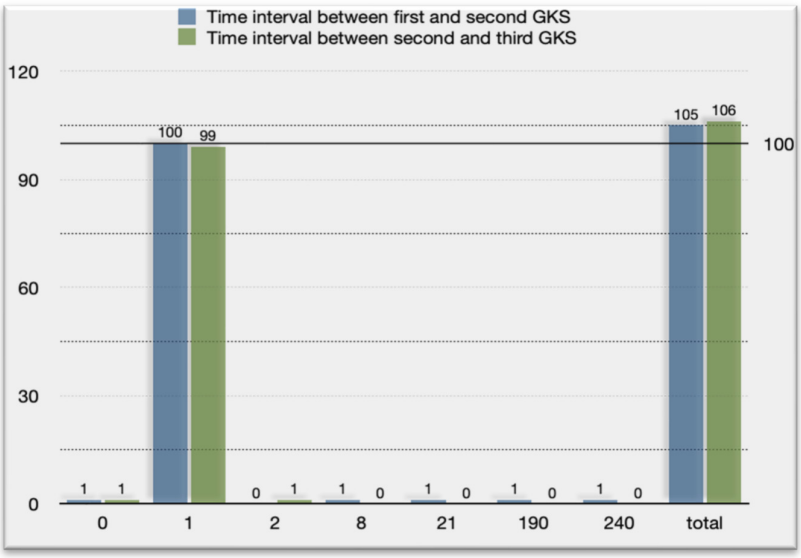

Figure 3. Time intervals between GKS sessions

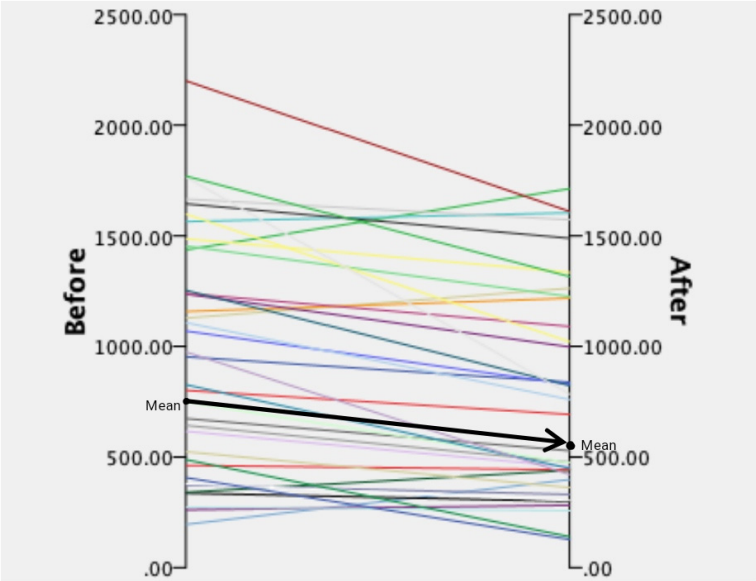

Figure 4. Lesion sizes before and after GKS

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Table 2. Lesion Sizes Before and After f-GKS

Statistical index	Lesion size before GKS (mm²)	Lesion size at last follow-up (mm²)
Mean	973.44	787.76
Standard Deviation	534.98	476.99
Minimum	195.64	127.41
Maximum	2200.15	1713.12
Total (n)	36	36

and the largest increase of 276.48 mm² (Table 2).

Prognosis

Out of the 36 patients who attended the final follow-up visit, 26 (72.2%) showed an improved prognosis based on symptom relief and neurologic assessments. Improvements were noted in vision quality (86.7%), headaches (63.6%), dysfunction of the visual muscles (75%), facial pain and paresthesia (66.7%), dizziness (66.7%), ptosis (80%), seizures (66.7%), decreased level of consciousness, et cetera (Figure 5 and Table 3).

Discussion

GKS has become one of the primary and most significant management strategies for patients with meningioma (16,17). However, reports on long-term tumor control and neurological outcomes remain limited. The tumor control rate within the first 5 years post-GKS for various patients with benign meningiomas is reported to be between 90% and 100% (3-5, 11-16).

Advantages of this method include the ability to treat inoperable lesions, eliminating the need for head shaving or skull opening; no requirement for anesthesia; prevention of typical surgical complications, such as infection and adhesions; a short treatment process lasting several hours; no recovery period; and lower costs (17). The risk of side effects with GKS is very low compared to open surgery, external radiotherapy, and similar treatments. However, in some cases, patients may experience mild side effects such as headaches, dizziness, nausea, and vomiting for a few days posttreatment (14, 15).

Our study contributes to the growing body of literature on the clinical effectiveness of fractionated f-GKS for treating meningiomas. The findings from our study, which included 106 patients (32 males and 74 females), with a mean age of 49.95 years (range, 7 to 80 years), align closely with the results from several previous studies, further supporting the efficacy and safety of f-GKS for this patient population. The average lesion size before f-GKS was 185.67 mm² with a standard deviation of 249.02 mm², and the maximum decrease observed was 981.64 mm².

In comparison with the 2014 study by Tae Keun Jee et al, which evaluated the efficacy and safety of f-GKS for perioptic lesions in 38 patients (with a mean tumor volume of 3.851 cm³ and a follow-up period of 38.2 months), our study similarly demonstrated significant tumor control and positive outcomes in visual prognosis. Jee et al. reported a tumor control rate of 94.6% and visual improvement in 43.2% of patients. In contrast, our study found that 80.6% of patients experienced a reduction in lesion size, and 72.2% had improved prognosis (1). These findings collectively emphasize the reliability of f-GKS in managing both

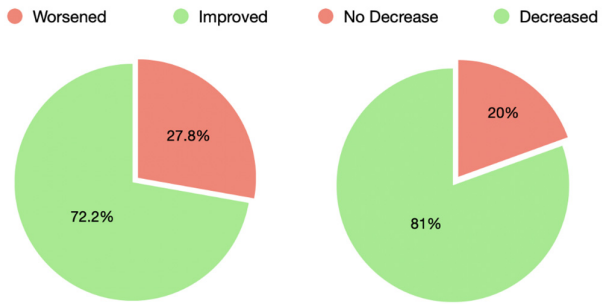

Figure 5. (A) Prognosis. (B) Decrease in lesion size.

Table 3. Improvement in the Signs and Symptoms of Patients

Signs & Symptoms	Total Presentation	Evaluated in the study	Improvement
Visual Disorder	53	30	26 (86.7%)
Headache	31	11	7 (63.6%)
Ptosis	6	5	4 (80%)
Proptosis	6	3	2 (66.7%)
Oculomotor Dysfunction	6	4	3 (75%)
Seizure	5	3	2 (66.7%)
Ataxia	5	-	-
Dizziness	4	3	2 (66.7%)
Pareshesia	4	3	2 (66.7%)
Vomiting	4	-	-
Acromegaly	4	-	-

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meningiomas and perioptic lesions.

The outcomes reported by Hamilton et al in 2017 for optic nerve meningioma treated with f-GKS showed stability or improvement in visual acuity and fields in a majority of the 41 patients (with an average age of 56 years and follow-up periods of 3.8 years for visual and 4.4 years for radiological follow-ups). Hamilton et al reported that visual acuity remained stable in 65%, improved in 27%, and declined in 8% of patients, while visual fields were stable in 70%, improved in 21%, and reduced in 9%. Our study's results are consistent with these findings, as a significant proportion of our patients (72.2%) showed improved prognosis and reduced lesion sizes (2). The consistency across studies underscores the efficacy of f-GKS in achieving tumor control and preserving or enhancing visual function.

Han et al (2016) investigated the effectiveness and safety of GKS for large intracranial meningiomas in 70 patients (42 treated with 1-session GKS and 28 with f-GKS). The study reported a median tumor volume of 15.2 cm^3 for the 1-session group and 21 cm^3 for the f-GKS group. They concluded that f-GKS is suitable for large-volume meningiomas, offering a better 5-year tumor control rate (92.9% vs 88.1%) and fewer complications compared to one-session GKS (P = 0.017) (17). Our study's findings support this conclusion, as we observed significant improvements in prognosis and reduction in lesion size in our patients, highlighting the suitability of f-GKS for larger meningiomas.

Kondziolka's 2014 study on long-term GKS outcomes for meningiomas reported on 290 patients treated between 1987 and 1997, with a mean tumor volume of 5.5 mL and an average age of 61 years. Kondziolka et al found that 91% of tumors were controlled, with 26 patients showing delayed growth and 44 experiencing regional progression. They also reported 10- and 20-year tumor survival rates of 87.7% and 87.2%, respectively. Of the 234 patients with symptoms before treatment, 26% showed improvement, 54% had no change, and 20% experienced worsening symptoms (18). Our study found similar outcomes, with 80.6% of patients experiencing a reduction in lesion size and 72.2% showing improved prognosis. These parallel findings validate the use of f-GKS as a reliable treatment modality for meningiomas.

The systematic review by Nida Fatima, Antonio Meola, and colleagues included 496 patients (69.3% female and 30.6% male) with a median age of 60 years, focusing on the effectiveness and safety of stereotactic radiosurgery (SRS) for large intracranial meningiomas (LIMs). Their review reported high radiographic tumor control rates (84% to 100%) and clinical improvement in a significant proportion of patients, with 45.1% showing improvement and 15.7% deteriorating after SRS (19). Our study demonstrated similar outcomes, with f-GKS effectively reducing lesion volumes and improving prognosis in the majority of patients, supporting the broader applicability and success of SRS techniques for meningiomas.

Lastly, the study by Ganz et al evaluated the safety and efficacy of GKS for large meningiomas in 97 patients (70 females and 27 males), with a mean age of 48.1 years and a mean tumor volume of 15.9 cm^3. The results showed that none of the tumors continued to grow, with 27 tumors decreasing in size and 72 remaining unchanged (20). Our study corroborates these results, as we observed a notable reduction in lesion sizes and improved prognosis in our patient cohort.

In medical prognostic studies, one possible reason for the lower improvement in patient outcomes compared to previous studies could be the significantly higher volume of end-stage brain lesions examined in this study. This factor can influence the overall results and potentially reduce the observed improvements.

Another reason for the lower percentage of prognoses in this study compared to other studies is that access to the gamma knife is less convenient in other centers. Thus, this treatment has been used for multiple lesions with smaller sizes and less aggression. It is also possible that this treatment was applied to patients in the early stages of the disease. However, in our study, due to the referral nature of the Iran Gamma Knife center, mostly end-stage patients from various parts of the country were treated with this method. These patients had no other treatment options available except f-GKS. Therefore, observing a lower percentage of prognosis is expected.

In conclusion, our study reinforces the positive outcomes associated with f-GKS for meningiomas, corroborating the findings of previous research. The high rates of tumor control, lesion size reduction, and improved patient prognosis emphasize the clinical effectiveness of f-GKS as a treatment option for meningiomas. Further studies with more extended follow-up periods are warranted to confirm these findings and to explore the long-term benefits and potential complications associated with this technique.

Limitations and Future Research

This study's limitations include its single-center, Iran-based design, which limits generalizability, and the absence of a control group to isolate the efficacy of f-GKS. Retrospective data collection risks inaccuracies, while the modest sample size (N = 106) and incomplete follow-up (eg, only 36 post-MRIs) constrain statistical power and longitudinal insights. Future work should prioritize multicenter collaborations to enhance diversity, incorporate control groups (eg, single-session GKS/surgery), and adopt prospective digital registries for robust data collection. Expanding sample sizes, extending follow-up periods, and integrating multidisciplinary expertise (eg, radiology, psychology) would clarify long-term outcomes, optimize protocols, and strengthen f-GKS's role as a standardized, evidence-based treatment for intracranial lesions.

This research demonstrates the technical limitations of fractionated GKS with the older model "C" system, particularly the need for extended frame fixation. Nevertheless, the newly established Gamma Knife Center at Yas Hospital in Iran, which features the frameless Icon model, allows for patient-friendly fractionation. Current research at this facility seeks to refine protocols for complex lesions.

Conclusion

In this study, we examined various factors, including lesion levels from brain MRI findings, patient prognosis, and changes after f-GKS. Our results confirm those of previous

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studies, highlighting the significant role of noninvasive GKS in improving patient prognosis and reducing tumor size.

Authors' Contributions

Farid Kazemi Gazik contributed to the conception of the study, data collection, and initial drafting of the manuscript. Taghi Aghajanlou was involved in methodology development, data analysis, and interpretation of the results. Narges Mirzania supervised the project, critically revised the manuscript, and served as the corresponding author. Ali Ariyaei Motahar assisted with statistical analysis and manuscript editing. Amin Jahanbakhsi contributed to the literature review, data acquisition, and gave final approval of the manuscript. All authors reviewed and approved the final version of the paper.

Ethical Considerations

Informed consent was obtained from all patients after a comprehensive explanation of all available treatment options, including single-session GKS and more invasive surgical methods. Patients voluntarily chose f-GKS based on this counseling. Additional safeguards included maintaining patient data confidentiality, securing approval from the Iran University of Medical Sciences (IUMS) and project managers for data usage, allowing participants to withdraw from the study at any time, and ensuring that no costs were imposed on participants.

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Conflict of Interests

The authors declare that they have no competing interests.

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