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Staged Volume Gamma Knife Stereotactic Radiosurgery for Large Skull Base Benign Meningiomas: Feasibility and Safety

Sara El-Sherif [1], Hoda Abdelbaky [1], Reem M. Emad Eldin [1,2], Wael A. Reda [2], Amr M. N. El-Shehaby [2,3], Yasser Abdelazim[1]

[1] Radiation Oncology Department, National Cancer Institute, Cairo University;

[2] Gamma Knife Center Cairo, Nasser Institute Hospital;

[3] Neurosurgery Departments, Faculty of Medicine, Ain Shams University, Cairo.

Corresponding author: Sara El-Sherif

Email: Sara.elsherif@nci.cu.edu.eg

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Abstract:

Background: Worldwide Meningioma Accounts for Approximately Up to 30% Of Primary Intracranial Tumor in Adult (1) and About 20%~30% Of Them Occurs in The Skull Base. Most Are Benign and Slow-Growing Tumors. (2) Although The Mainstay Treatment in Most of Cases Is Surgical Resection, Many Patients with Large and Critically Located Meningioma often Fail to Achieve Complete Resection Without Significant Neurologic Deficit Due To The Frequent Involvement Of Cavernous Sinus Or Cranial Nerve, Or Close Proximity To Optic Nerve Or Chiasm (3) The Progression Rate After Incomplete Resection Has Been Reported To Be 30% At 5 Years, 60% At 10 Years, And 90% At 15 Years. (4) The Success of Stereotactic Radiosurgery (SRS) Confirmed By Series With Excellent Long Term Results Has Led To A Shift In The Treatment Paradigms From Radical Surgery to a Combined Surgical/ Radio-surgical Approach Or Even SRS As Primary Therapy. (5) Several Studies Concluded That Radiosurgery Is Able to Control Growth of Tumors In 80-100 % of Cases of Skull Base Meningioma (SBM). (6) However, In Cases Where the Tumor Is Large and Close to Critical Structures Like Optic Apparatus, Auditory Apparatus and Brain Stem, Physicians Face A Clinical Dilemma As High-Dose Radiation Exposure Can Lead To Neuritis And Irreversible Deterioration In Function. (7) So, The Concept Of Staged Volume SRS Was Emerged. The aim of This Study to Assess Safety Of Staged Volume Gamma Knife (GK) In Large Skull Base Benign Meningiomas With Size ≥ 10 Cc.

Patients And Methods: This is a Single Arm Study Included 245 Patients With Large Skull Base Benign Meningiomas Underwent Staged Volume GK Treated In The Period From February 2010 To February 2021. **Results**: The Median Age of The Patients Was 49 Years. Seventy Eight Percent Were Females While Twenty Two Percent Were Males. The Median Treated Volume Was 23.2 Cc (Range,8.4-82 Cc), 13 % Received 3 Stages Of Treatment While The Rest 87% Were Staged Into 2 Sessions. After Median Follow Up Of 46 Months (Range,8-157 Months); 49% Had Stable Clinical Symptoms, 41% Had Improved Clinical Symptoms And Only 10 % Had Worsened Clinical Manifestations. Adverse Radiation Events (ARE) On Near-By Organs 6%. **Conclusions**: The Data From Our Series Justify A Clear Recommendation In Favor Of Staged SRS, With Or Without Previous Surgery, For Large Meningiomas In Delicate Locations Compared With Open Surgery Alone Or Conventional Radiotherapy. By Yielding Low Toxicity And Appropriate Safety Of Treatment.

Keywords: Meningioma -Large– Gk- Gamma Knife- staged volume- SRS- Radiosurgery- Skull Base- Toxicity- Safety- Adverse events.

1. Introduction

Meningiomas are the most common primary neoplasms of the central nervous system (CNS) accounting for 37% of them (8) While a minority of meningiomas exhibit aggressive behavior classified as World Health Organization (WHO) grades II and III, more than 80% are WHO grade I, commonly referred to as benign (8).

Skull base meningiomas, originating from the Dura mater of various cranial structures such as the clivus, petrous bone, sinuses, tentorium, sphenoid bone, olfactory groove, and optic nerve sheath, collectively constitute about 35 % of all intracranial meningiomas. (9)

While biopsy or resection remains the definitive method for confirming diagnosis through histopathologic analysis, the typical radiologic appearance often provides adequate diagnostic information and remains the primary approach for meningioma diagnosis with 62% of cases are diagnosed radiologically (10) MRI typically reveals a well-circumscribed lesion with homogeneous enhancement at the dural base. Benign meningiomas typically exhibit a thickened, contrast-enhancing dural tail and appear isointense to gray matter on non-contrast sequences (10)

Although the mainstay treatment in most of meningioma cases is surgical resection, skull base tumors necessitate advanced surgical techniques to access them safely without extensive brain retraction or injury, many patients with large and critically located meningioma often fail to achieve complete resection without significant neurologic deficit (11) Numerous single-institution studies with extended follow-up periods have indicated that the 5-year local progression rate following STR of benign meningiomas ranges from 37% to 62%, while the 10-year local progression rate can be as high as 52% to 100 (12) (13) (14)

There has been some debate regarding whether patients with meningioma post-STR should undergo active surveillance or adjuvant radiation therapy. Some studies suggest that small residual tumors can be monitored with PFS rates. For instance, a 2010 analysis by Sughrue et al. reported an 81% 5-year PFS rate following Simpson Grade IV resection (15)Consequently, patients of advanced age or with multiple comorbidities and small residual tumors may not experience recurrence or significant tumor growth that leads to symptoms. However, others advocate for adjuvant radiation therapy, particularly in younger patients or those with tumor locations prone to symptomatic progression. (12) (14)

The success of stereotactic radiosurgery (SRS) confirmed by series with excellent long term results (5) has led to a shift in the treatment paradigms from radical surgery to a combined surgical/ radiosurgical approach or even SRS as primary therapy. However, in cases where the tumor is large and close to critical structures like optic apparatus, auditory apparatus and brain stem, physicians face a clinical dilemma as high-dose radiation exposure can lead to neuritis and irreversible deterioration in function. For example, vision can be preserved by limiting the maximum radiation exposure of the optic pathway to 8-10 Gy per SRS session while unfortunately; the minimum effective dose for the treatment of benign skull base meningioma is 11-13 Gy (7)

To address this dilemma, multistation SRS, which includes staged radiosurgery, was emerged. This can involve repeated sessions focusing on different areas of one target (volume staging) or treating the same target with large time intervals (dose staging) (16)

Volume-staged radiosurgery may be advantageous over dose-staged radiosurgery, as benign tumors are thought to respond better to higher doses per fraction. Reports on dose-staging for large meningiomas have shown 93%-100% tumor control, 61%-93% favorable clinical outcomes, and AREs in 7%-26% of cases, with a mean follow-up of 38-50 months (17) (18).

Reports on volume-staging for large meningiomas have demonstrated 86%-100% tumor control, 45%-100% favorable clinical outcomes, and AREs in 0%-15% of cases, with a mean follow-up of 39-101 months (19) (20) (21)

PATIENTS AND METHODS

This is a single arm study included 245 patients with large skull base benign meningiomas underwent staged volume GK treated in the period from February 2010 to February 2021.

1-Inclusion Criteria

Patients with pathological or radiological diagnosis of large volume skull base benign meningiomas>10 cc.

2-Exclusion Criteria

1- Prior cranial radiation.
2- Atypical or malignant meningiomas.
3- Multiple meningiomas.
4- NF-2 associated meningiomas.

3-End Point

To safety of staged volume GKRS for large skull based benign meningioma.

4-Statistical Methods

Data was analyzed using IBM SPSS Statistics Version 22. Data was tested for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Quantitative data was presented as mean and standard deviation. Qualitative data was presented as number and percentage. Comparing categorical variables was done by using chi-square test or fissure exact as appropriate. For normally distributed, Independent sample T test was used to compare numerical variables between two groups and ANOVA test to compare between more than two groups. P value set significant at 0.05 levels. All tests were two tailed.

5- Pre-Treatment Evaluation of the Patients

All patients were subjected to full history and physical examination including neurological examination.

Baseline MRI brain with I.V gadolinium contrast with 2 mm slice thickness was obtained and baseline visual field or audiometry with speech discrimination as indicated by lesion location.

6-Treatment Strategy

After application of Leksell GK stereotactic fram and defining the stereotactic position of the patient's skull, thin slice MRI with gadolinium contrast was done for the patient while MRI indicator box was in use.

GK-SRS plan was done using version 5.31 developed by Elekta by defining the near-by organ at risks and delineation of the target. The staging of the volume was based on the proximity to organ at risks. The volume was staged into 2 or 3 stages with 3-6 months interval between sessions according to its size and we choose the first volume by weighing the risk of wait till the next session and the risk of edema and according to the patient symptoms and this was individualized per each patient.

The doses were dependent on location and volume that will be treated. Doses at the margin were ranging from 9 to 14 in each treatment session procedure. The treatment plan then was evaluated to meet the constraints of organs OAR including maximum point to any part of visual apparatus 8 Gy and maximum point to any part of brain stem not above 12 Gy and also the dose-volume histogram (DVH) was evaluated for coverage of the defined target.

7-Follow Up

Patients were followed up after the treatment at 6 and 12 months and 24 months and then annually by:

1- Clinical assessment (symptoms, signs).
2- Gadolinium-enhanced MRI for assessment of size of the lesion and presence of edema
3- Visual field or audiometry with speech discrimination as was indicated.

RESULTS

A total of 245 patients were included in our study. The median age of the patients was 49years (range, 14-77). One hundred and ninety two (78%) patients were females while fifty three (22%) patients were males.

Only three patients were discovered accidentally during routine brain imaging for other reasons, while rest of the patients had a variety of clinical symptoms. Median duration of symptoms was 12 months (range, 1-120 months).

The main presenting symptoms were diminished vision in 73 patients (30%), facial numbness in 62 patients (25%) and ataxia in 52 patients (21%).

Baseline clinical data are shown in table (1).

Table 1: showing baseline clinical presentation of the patients.

Presenting symptom	Number of patients	Percentage of patients
Diminished vision	73	29.8%
Facial numbness	62	25.3%
Ataxia	52	21.2%
Headache	50	20.4%
Proptosis	44	18.0%
Hearing defect	41	16.7%
Fits	32	13.1%
Bulbar symptoms	28	11.4%
Ocular muscle palsy	23	9.4%
Ptosis	22	9.0%
Diplopia	21	8.6%
Vertigo	21	8.6%
Tinnitus	18	7.3%
Motor weakness	17	6.9%
Facial pain	16	6.5%
Facial weakness	13	5.3%
Ocular pain	10	4.1%
Hemihypothesia	8	3.3%
Increased ICT	6	2.4%
Facial twitches	3	1.2%

Of the 245 patients included in the study; 202 patients (82%) had CN affection. The most common cranial nerve affected was optic nerve in 137 patients (56%), followed by vestibulo-cochlear nerve in 65 patients (26.5%) followed by oculomotor nerve in 40 patients (16%). The percentage of presenting CN affection is presented in figure 1.

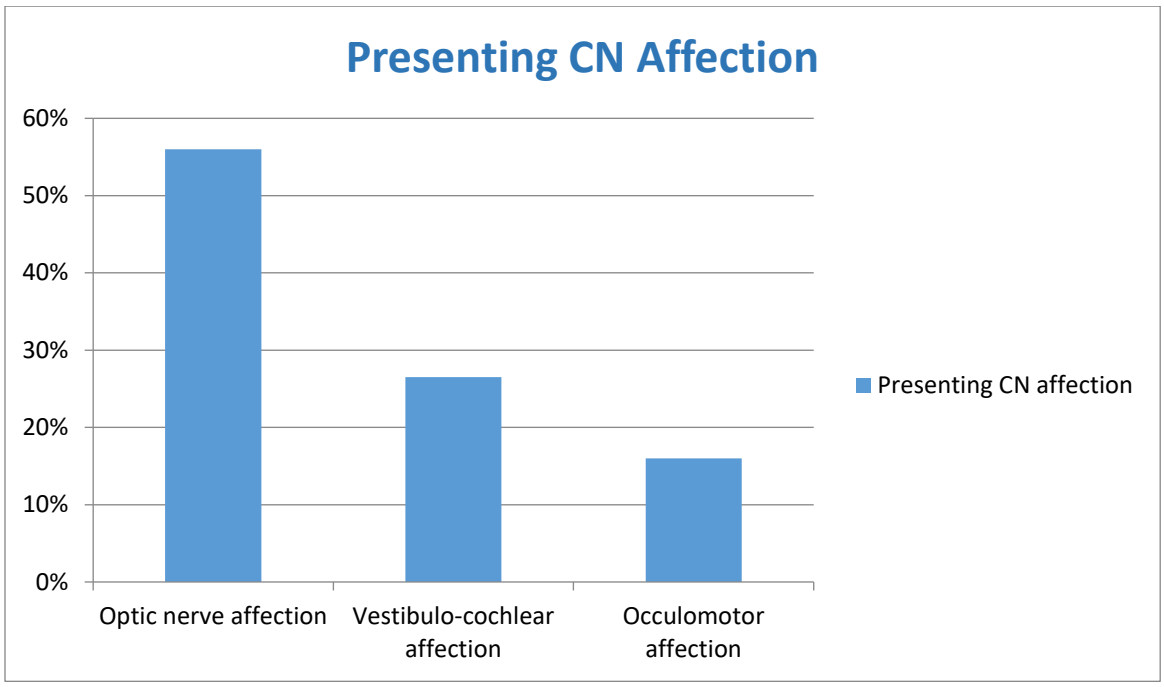

Fig.1: Showing the percentage of presenting cranial nerve affection

The most common tumor location was parasellar region in 80 patients (32.7%) followed by sphenoid location in 49 patients (20%) then petroclival location in 47 patients (19.2%). One hundred and twenty seven patients (52%) had left sided location and 99 patients (40%) had right sided lesions while 19 patients (8%) had midline lesion. Tumor locations are shown in table 2

Table 2: Showing the incidence of location of the tumor in our patients.

Tumor location	Number of patients	Percentage of patients
Parasellar	80	32.7%
Sphenoid	49	20%
Petroclival	47	19.2%
CPA	27	11%

Petrous	8	3.3%
Olfactory	8	3.3%
Suprasellar	7	2.9%
Cavernous	4	1.6%
Clinoid	4	1.6%
Foramen magnum	3	1.2%
Clival	3	1.2%
Temporal	1	0.4%
Sellar	1	0.4%
Orbital	1	0.4%
Jugular	1	0.4%
Optic nerve	1	0.4%

At baseline 201 patients were tested for visual field due to proximity of their tumors to optic apparatus; 137 patients (68%) had initial field defects, while 64 (32%) patients had normal initial visual field.

Only 112 patients had baseline hearing evaluation -by audiometry and speech discrimination- due to related location of the tumor to the posterior fossa or petrous location; 36 patients (32%) had non serviceable hearing and the remaining 76 patients (68%) had serviceable hearing.

Only 45 patients (18.4%) underwent partial resection of the lesion before GK treatment while 200 patients (81.6%) did not undergo any surgical intervention. Of the forty five patients who underwent surgery; the median time between surgery and first GK session was 10 months (range, 2-144 months).

The diagnosis was radiological for 241 patients (98.4%) while only 4 patients (1.6%) underwent biopsy for diagnostic reason.

Of the entire cohort; 25 patients (10.2%) had pre-GK VP shunt insertion to bypass the CSF outflow obstruction, while the rest 220 patients (89.8%) did not need this intervention

The median treated total tumor volume was 23.2 cc (range, 8.4-82 cc).

Thirty one patients (13%) received three treatment sessions, while 214 patients (87%) were treated in two treatment sessions.

Median time between first and second sessions was 4.2 months (range, 1.7-39 months) and between second and third sessions was 3.8 months (range, 2.3-17.8months). The dosimetric data for each session is summarized in table 3.

Table 3: Showing dosimetric data for treatment sessions

Treatment dosimetric parameters		**First session**	**Second session**	**Third session**
Prescription dose	**Mean ± SD**	11.32±0.64	11.11±0.70	10.72±0.73
	Median	11	11	11
	Range(Min-Max)	9-14	9-14	9-12

Prescription isodose	**Mean ± SD**	49.94±0.96	50	50.62±3.53
	Median	50	50	50
	Range(Min-Max)	35-50	50-50	50-70
Cover	**Mean ± SD**	97.21±2.48	96.85±2.571	97.9±1.75
	Median	98	98	98
	Range(Min-Max)	86-100	83-100	94-100
Minimum dose	**Mean±SD**	8.27±1.15	8.2±1.2	8.20±1.01
	Range(Min-Max)	8.4	8.2	8.19
	Range(Min-Max)	2-10	1.5-11.9	6.1-10.1
Maximum dose	**Mean±SD**	22.79±1.58	22.2±1.5	21.32±1.95
	Median	22.1	22	22
	Range(Min-Max)	18-34.3	16.4-28.4	14.4-24.2
Mean dose	**Mean ± SD**	15.55±1.07	15.27±1.25	14.88±1.24
	Median	15.5	15.2	14.9
	Range(Min-Max)	6.6-18.8	6.6-19.39	12.20-17.30
Target volume in cc	**Mean ± SD**	12.66±4.56	11.05±5.28	12.20±6.03
	Median	12.6	10.4	13.50
	Range(Min-Max)	2.4-30	0.30-32.20	0.9-22
Max to visual pathway	**Mean ± SD**	7.46±1.25	7.15±1.91	6.43±2.48
	Median	7.8	8	7.8
	Range(Min-Max)	2.-10.3	1.2-9.1	1.5-9.1
Integral dose	**Mean ± SD**	196.17±69.55	167.0±79.0	182.44±92.62
	Median	195.9	162.4	202.75
	Range(Min-Max)	38-497	4.3-489.1	11.3-370.8
Number of shots	**Mean ± SD**	21.73±7.30	21.37±7.64	20.22±6.16
	Median	21	21	20
	Range(Min-Max)	4-45	5-43	8-37
Time of beam on min	**Mean ± SD**	39.86±11.87	38.51±11.23	36.02±8.87
	Median	39.3	37.9	35.65
	Range(Min-Max)	11.2-107.6	17-90	17.7-52.5

Clinical Outcome

After a median follow up period of 46 months (range, 8-157 months), 119 patients (49%) had stable clinical symptoms, 101 patients (41%) had improved symptoms and 25 patients (10%) had worsened clinical manifestation either aggrevation of pre-existing symptoms or development of new ones.(Fig.2)

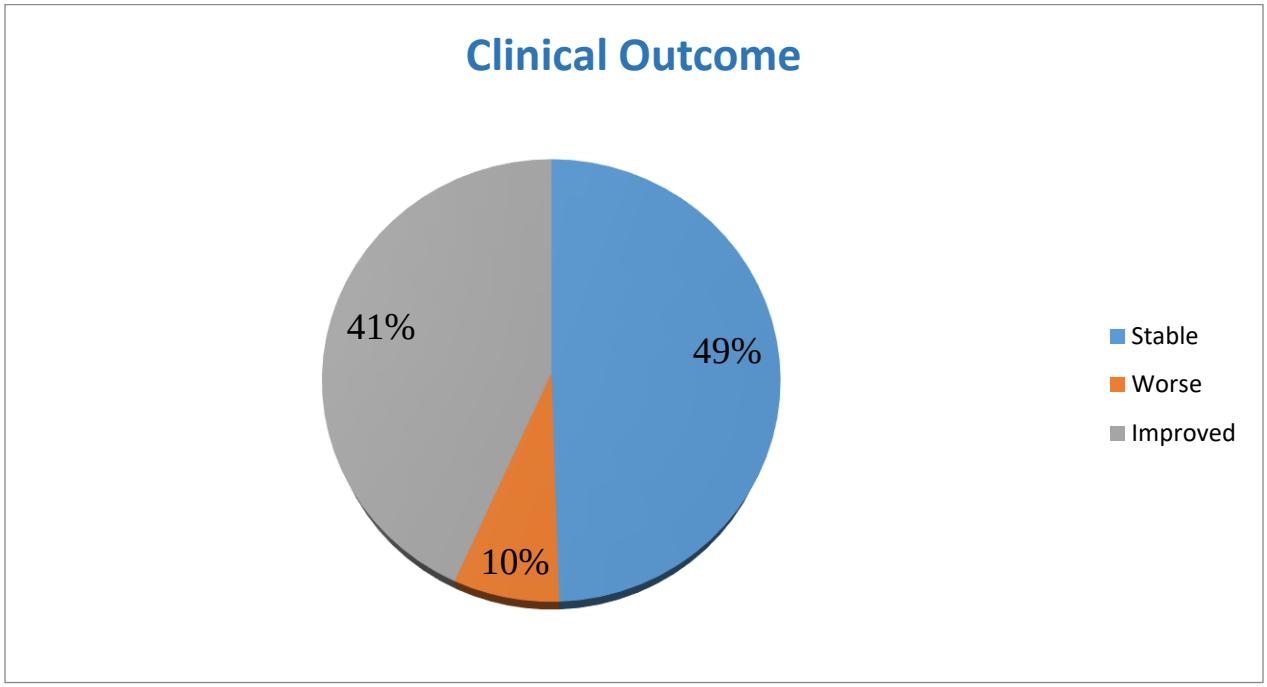

Fig.2: Showing Percentage of patients with different clinical outcomes

Adverse Radiation Events

Out of the 201 patients who had visual field assessment post treatment, only 13 patients (6%) had worse visual field outcome. One hundred and ten patients were assessed for hearing changes by audiometry with speech discrimination after treatment and compared to initial evaluation, of them only 2 patients (2%) had worse hearing outcomes after treatment.

So, total adverse events occurred only in 15 patients (6%) in total cohort

DISCUSSION

Traditionally, meningiomas are treated with upfront surgery aiming for gross total resection. (22)

However, gross total resection is often not feasible due to critical location of the tumor and close proximity to critical structures. SRS has offered an excellent and safe alternative to surgery, especially for tumors that are challenging to resect due to their location such as the SBM (23) (24)

Published studies addressing the long-term outcomes of radiosurgery for SBM have reported tumor control rates between 89 to 98 % with acceptable complication rates between 4 to14 % (25) (26) (27) (28)

The treatment of SBM by SRS has been challenging as the lesion is usually intimately related to critical neural structures which are sensitive to radiation injury like optic pathway structures that

have limited tolerance below the needed doses to control the tumor, being the dose limiting organs for radiation doses (21)

Also stratifying meningiomas by size leads to different GK planning and outcomes, especially in skull base lesions. (29)

With large-sized meningioma, the need of higher dose is higher which is associated with substantial risk of nearby critical structures injury and rendering decision process very challenging, leading to emergence of the concept of volume-staged SRS. Using a staged approach, the putative advantage of SRS steep radiation fall off can be maintained in the treatment of larger tumors, protecting nearby critical structures from radiation damage. (19) (30)

In our study we considered the meningioma lesion to be large volume if ≥ 10cc or diameter of ≥3 cm, we included 245 patients. The majority of the cohort was female representing 78% with median age of 49 years. The majority of our patients underwent upfront GK treatment with radiological diagnosis (82%) while only 18% of the patients underwent STR with histologically confirmed grade I meningioma. In comparison to Stark et.al study which included 75 patients with almost the same inclusion criteria to ours except for definition of large volume which was considered as tumor volume ≥8cc or diameter ≥2.5 cm. Stark et.al assessed the outcome of treatment of large SBM with single session GKRS. The majority of Stark's cohort was also female representing 68% with median age 55 years. The majority of patients -60%-underwent STR before SRS. The mean tumor volume in our study was 23.2 cc and the mean treating dose was ranging from 10.7-11.3 Gy while the volume was 14.1 cc in Strake's cohort and the mean dose was 13.5 Gy. Despite of treating larger volumes and with doses less than used in Strake's study we reported lesser neurological worse outcome at median FU 3.8 years which was 6 % compared to 17 % in Starke's cohort at 5 years for volumes ≥ 8cc. (31)

In another smaller series of 20 patients with a longer median follow up of 7.5 years and larger tumor volumes(median 33.3 cm3 , range 13.6-79.8 cm3) conducted by Haselsberger et al. They reported an excellent tumor control with staged GKRS for large benign meningiomas. Of their 20 patients with treatment volumes between 5.4 and 43 cm3 (median 19 cc), tumor control was achieved in 90% of cases (25% tumor regression, 65% stable size). Two patients (10%) experienced tumor progression outlying the planning target volumes and were treated by an additional radiosurgical procedure. Thereafter tumor volume decreased in one patient and remained stable in the second one. Clinically, nine patients (45%) improved within the time of follow-up and 11 (55%) remained unchanged. (20)

Recently, Su et al. described a volume-staged GKRS technique called the "snowman-shape" design .They adopted this technique for four patients with large skull base meningiomas involving the optical structures with the upper part compressing the visual pathway whereas the basal part pushes the brain stem inferiorly. They treated the large basal portion with a median prescribed dose of 13.5 Gy (range,12-15 Gy), and the upper part of the tumor, close to the optic apparatus, using a median dose of 9 Gy (range, 8-10 Gy) and the 2 sessions were separated by at least 3 months duration. The median tumor volume was 17.7 mL (range: 5.3-69.4 mL) treating almost ¾ of the initial tumor volume in the first session and the rest in the second one. They achieved 100 % tumor control without adverse radiation injury with 100.5 months' follow-up. The difference between their strategy and ours was that they mandated treatment of the lower portion of the tumor first, while we might start with treatment of the tumor close to critical structures. Although we do not disagree with their strategy of first irradiating the basal tumor close to the tumor attachment with

vascular supply, we were considering the potential risk for clinical deterioration during the wait for the second GKRS treatment due to tumor growth (21)

Another recent study conducted by Iwai was published and showed the results of treatment of 27 patients with large SMB, with 3 patients excluded from the analysis as they did not meet the minimum follow up period. Females were represented as 62.5% of the total cohort with median age 64.5 years. The most common locations were parasellar, cavernous sinus, and petroclival. The most commonly affected CN were II, III, IV, V and VI. The parasellar location was also the most common presenting location in our study represented 33% followed by sphenoid location 20% then petroclival location 19%. And the most commonly affected CNs in our cohort were CN II, VIII and III respectively. Only 50 % of Iwai's cohort had histologically proven WHO grade I and the rest were included based on neuroimaging criteria of grade I meningioma. They used definition of large volume as ≥ 4 cm in maximal diameter with median tumor volume of 27.5 cc (range 14.7-49.5 cc). Iwai's patients almost had the same features of our patients. Their patients were treated with staged volume GK in 2 sessions with 3-9 months interval between the 2 sessions. In our cohort 12.7% of the patients were staged on 3 volumes with median time between the treatment sessions 3-4 months. The used median radiation dose by Iwai was 10 Gy (range, 8-12 Gy). The minimum time of follow up was 6 months like our study and the median time of follow up was 84 months. The incidence of permanent radiation injury was 4 % compared 6 % worsening of pre-existing neurological deficit in our cohort. (32) Summary of results of our study and other previous studies are compared in table 4.

Different techniques of radiation were also tested in terms of safety l in treatment of large and critically located SBM. In 2011 Valentina and her colleagues conducted a prospective study of 178 patients published in 2022 evaluating the hypo-fractionated radiosurgery (hypo-RS) for large size (diameter ≥3 cm) and/ or critically located (< 3 mm from critical structures) grade 1 meningioma using 25 Gy in 5 fractions using cyber knife. Their median target volume was 14 cc (range, 0.76-126 cc) which was smaller than our study which was 23.2cm3 (range, 8.4-82 cm3). Despite including very small volumes started of less than 1cc their patients experienced more frequent treatment toxicity including trigeminal numbness and visual impairment which was shown in 12.7 % of the total cohort and this is almost double incidence of our study which was 6 % in the form of deterioration of already affected visual field or hearing. This difference in toxicity favoring our technique of staged volume GK can be explained by the characteristic of rapid and steep fall off of the GK used in our study (33)

Table 4: showing summary of different studies compared to ours in terms of number of patients, total tumor volume, prescribed doses, median follow up duration and ARE.

Study	No. of Patients	Tumor volume,cc	Dose (Gy),Mean	Median follow up duration, Months	ARE (%)
Haselsberger et al., 2009	20	33.3	12	90	-
Starke et al., 2015	75	14.1	13.5	60	17%
Su etal.,2017	4	17.7	9-13.5	100.5	-
Iwai etal.,2019	27	27.5	10	84	4%

Pinzi etal.,2022	178	14	25	53	12.7%
Current study	245	23.2	10.7-11.3	46	6%

LIMITATIONS

Limitations of our study include that most of our patients were included based on radiological diagnosis without histological confirmation and also limited time for follow up.

CONCLUSIONS

In summary, we consider our volume-staged GKRS protocol for large volume meningioma to be safe, especially given the sharp decline in radiation dose, which has significant advantages for benign SBM; however, a long-term follow-up is needed to confirm safety of our approach in terms of delayed radiation injury to surrounding critical structures.

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