



## Gamma Knife Radiosurgery in the Management of Benign Skull Base Meningioma; Long-Term Outcome, Possible Prognostic Factors and Literature Review

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### Abstract

**Objective:** The current retrospective study reports and analyzes the clinical and radiological outcome in long-term follow-up of patients harboring benign WHO grade I skull base meningiomas after single-session gamma knife radiosurgery with the evaluation of possible prognostic factors and review of the literature.

**Patients and Methods:** This study was conducted on 252 patients harboring benign skull base meningiomas treated by GKRS at our center between 2005 to 2015 and were followed till the end of 2019, with a median follow-up period of 102 months (range 60 to 180). There were 197 females and 55 males. The median tumor volume was 4.4 cc; the median marginal prescription radiation dose was 13.5 Gy; the median isodose line was 40%.

**Results:** The overall tumor control rate at the last follow-up post-GKRS was 93%. Tumor progression and lost tumor control were detected in 7.14% of patients. The local tumor control progression-free rate at 3-, 5-, 10 and 12 year was 100%, 97.62%, 81.6% and 81% respectively.

**Conclusion:** In the short and long-term, single-session GKRS provides a highly durable and favorable rate of tumor control in the management of benign medium and small size skull base meningioma with improvement or maintenance of neurological function with low morbidity. GKRS can replace a complicated surgical resection in selected patients in critical locations and, in planned combined surgical and GKRS cooperation for larger tumors provides a documented long-term tumor control of residual and recurrence. Tumor volume variable stands as a reliable long-term prognostic factor for skull base meningioma tumor control post-GKRS.

**Keywords:** Gamma knife radiosurgery; Meningioma; Microsurgery; Radiosurgery; Skull base

### Abbreviations

CC: Cubic Centimeter; GKRS: Gamma Knife Radiosurgery; PIV: Prescription Isodose Volume; PPD: Peripheral Prescription Dose; TV: Tumor Volume; WHO: World Health Organization

### Introduction

Meningiomas account for approximately 12% to 20% of all primary intracranial tumors. The majority of meningiomas are benign lesions WHO Grade I Gross total resection has been traditionally referred to as the primary treatment option. However, lesions adjacent to critical neurovascular structures, especially skull base meningiomas, often do not allow for a safe, complete resection, leading to lower local tumor control and increased risk of tumor progression and recurrence [1-3].

The aim of microsurgery for skull base meningiomas is complete excision with minimal morbidity and mortality [4-8]. In recent series, total removal of basal meningiomas was achieved in 60% to 87.5% of patients. Between 30% and 56% of patients suffered postoperative complications [4,9-11]. The most common surgical sequela are new or deteriorated pre-existing cranial nerve deficits occurring temporarily in 20% to 44% and permanently in 16% to 56% of the meningioma patients. The postoperative mortality rate ranges from 0% to 9% (median 3.6%) [4,5,11-13]. The variation of total recurrence rates among the surgical series (from 0% to 17%, median 6.7%) is seemingly caused by the range of the follow up periods [4,5,10,14,15]. Furthermore, the recurrence/progression rates increase with the long duration of follow-up and seem to be influenced by tumor site and specific histopathological factors [2,5-9,15-17]. Microsurgery alone cannot be the

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ideal solution to treat all skull base meningiomas, and less invasive therapeutic options have been considered adjunctive and alternative primary treatment [1,6,11-14,17-19].

Radiation therapy for managing recurrent, partially removed, or unresectable benign meningiomas seem to prevent or delay progressive tumor growth at 5 years follows [20-23]. Complications following irradiation developed in 3.6% to 19% of the cases [6-8]. Permanent or transient cranial nerve deficits were found in 3.6% to 22% of irradiated cases, parenchymal radiation necrosis developed in 3.6% to 11.8%, and radiation-induced edema in 3.6% to 23.5% [20,23]. GKRS has begun to play an increasingly important role as a non-invasive alternative therapeutic modality for patients with skull base meningiomas [24-29]. GKRS aims to achieve long-term tumor control with maintenance of the patient's clinical status and prevention of new treatment-related morbidity [1,18,24-39]. Outcomes for benign skull base meningioma patients treated with radiosurgery, especially gamma knife surgery, appear favorable in short to intermediate follow-up; however, it is not clear if these favorable results in terms of tumor control and neurological condition are maintained beyond 5 years. [3,10,26,27,35,36].

In elderly or medically critical patients mainly, it must be considered whether the meningioma will likely cause serious problems in the natural course of the remaining years and if the risks will exceed the potential benefits offered [33,38,39].

### Aim of the Work

The current retrospective consecutive cohort study reports and analyzes the clinical and radiological outcomes in long-term follow-up after single-session Gamma knife radiosurgery in the management of benign WHO grade I skull base meningioma patients with evaluation of possible prognostic factors.

### Patients Populations and Methods

#### Patient's population

Between 2005 and 2015, 534 meningioma patients were treated with GKS at the International Medical Center (IMC), Gamma knife center, Cairo-Egypt. Skull base meningiomas represent 52% (n=278) of the treated various meningioma cases in the same period.

The current study is a retrospective outcome analysis for 252 cohort consecutive patients harboring benign single skull base meningioma treated with a single-session GKRS at our center with a median follow-up period of 102 months (range 60 to 180). Clinical and radiological follow-up data were available for the studied 252 patients from the beginning of 2005 till the end of 2019 or whenever failure of tumor control and or progression of patient's clinical condition is reported. Signed consents from all patients were obtained for using the medical data records and radiological images for research purposes as a standard policy in our Gamma Knife Center. Three patients had more than a single meningioma, 3 had a history of cancer breast, 4 with neurofibromatosis-II, 2 received prior radiotherapy, 1 with atypical meningioma, and 6 patients missed or not completed the follow-up, all were excluded from this study. Seven patients deceased during the follow-up period for causes unrelated to tumor progression those patients were also excluded from this study. There were 197 females and 55 males with a ratio of 3.5:1. The median age at GKRS was 49 years (range 20 to 80). For 188 patients (74.6%), GKRS was performed as a primary treatment and benign skull base meningioma diagnosis based on typical imaging findings,

**Table 1:** Patient's population, tumors characters and GKRS parameters.

| Characters                              | Value                |
|---|----------------------|
| <b>Sex</b>                              |                      |
| Females                                 | 197                  |
| Males                                   | 55                   |
| <b>Age (years)</b>                      |                      |
| Median                                  | 49                   |
| Range                                   | (20-80)              |
| <b>Skull base meningioma locations</b>  |                      |
| Cavernous sinus                         | 82                   |
| Cerebellopontine angle                  | 52                   |
| Petro-clival                            | 32                   |
| Sphenoidal ridge                        | 30                   |
| Clinoid                                 | 18                   |
| Petrous apex                            | 14                   |
| Olfactory groove                        | 10                   |
| Cranio-cervical                         | 4                    |
| Suprasellar                             | 6                    |
| Orbital                                 | 4                    |
| <b>Gamma knife surgery</b>              |                      |
| Primary                                 | 188                  |
| Adjuvant                                | 64                   |
| <b>Previous resection</b>               | 64                   |
| Partial                                 | 50                   |
| Subtotal                                | 14                   |
| <b>Tumor volume in (*cc)</b>            |                      |
| Median                                  | 4.4                  |
| Range                                   | (0.5-16.8 cc)        |
| <b>Median follow up period (months)</b> |                      |
| Median                                  | 102                  |
| Range                                   | (60-190)             |
| <b>GKS treatment parameters</b>         |                      |
| Peripheral dose (Gy). Median (range)    | 13.5 Gy (12-16)      |
| Isodose line %. Median (range)          | 40% (35-60)          |
| Maximum dose (Gy). Median (range)       | 33.8.24 Gy (24-42.9) |
| Tumor coverage %. Median (range)        | 94% (82-100)         |

\*cc: cubic centimeter

including a clear definition of the lesion, wide dural base, extra-axial location, uniform contrast enhancement, and sometimes intratumor calcification. GKRS performed as an adjuvant treatment for 64 patients (25.4%) who had a postoperative residual or recurrent tumor with histological confirmation of benign meningioma WHO grade I.

#### Tumor location

The treated benign skull base meningiomas were mainly located at the cavernous sinus in 82 patients, at the cerebellopontine angle region in 52, at petroclival location in 32, at the sphenoidal ridge in 30, clinoidal location in 18, the petrous apex in 14, at olfactory groove and Planum sphenoidal in 10, the craniocervical junction in 4, orbital in 4 and suprasellar in 6 patients Table 1.

#### Clinical presentation

Pre-GKRS neurological disorders and cranial nerves deficits

**Table 2:** Pre- and post-GKRS neurological and cranial nerve deficits.

| Neurological and cranial nerve deficits  | No. of patients Pre-GKRS | No. of patients Post-GKRS |        |  |
|--|--------------------------|---------------------------|--------|--|
|  |                          | Improved                  | Stable | Neurological and cranial nerve deficits post-GKS |
| Headache                                 | 68                       | 30                        | 38     | No new agonizing persistent headache             |
| Ocular movement disorders                | 64                       | 44                        | 20     | -  |
| visual acuity and/or visual field defect | 55                       | 5                         | 50     | 3 Permanent                                      |
| Trigeminal Paresthesia                   | 35                       | 7                         | 28     | 8  |
| Trigeminal neuralgia                     | 28                       | 4                         | 24     | 3 Controlled                                     |
| Facial nerve palsy                       | 6                        | -                         | 6      |  |
| Hearing affection up to loss             | 32                       | 2                         | 30     | 3 Permanent                                      |
| Bulbar symptoms                          | 7                        | 2                         | 5      | -  |
| Motor weakness                           | 12                       | 2                         | 10     | 4 (2 unrelated and 2 related to tumor Progress)  |
| Ataxia                                   | 18                       | 6                         | 12     | -  |
| Seizure activity                         | 10                       | 2                         | 8      | 2 Controlled                                     |
| Anosmia                                  | 6                        | 1                         | 5      | -  |
| Exophthalmos                             | 5                        | -                         | 5      | -  |
| Dizziness                                | 28                       | 8                         | 20     | -  |

were reported in 97% of patients (n=245), including intermittent headache in 68 patients, diplopia and ocular movement disorders in 64, trigeminal nerve affection in 63 patients (trigeminal neuralgia in 28 and trigeminal paresthesia in 35), visual acuity and visual field deterioration in 55 patients, hearing deterioration in 32, dizziness in 28, 12 patients presented with different degrees of motor weakness and 10 patients presented with seizures activity. Seven patients were discovered to have skull base meningioma accidentally or with minor symptoms Table 2.

### Gamma knife procedure and dosimetry parameters

The treatment was performed using Leksell Gamma Knife Model B followed by Model 4-C with APS (Elekta AB, Stockholm, Sweden). The Elekta Leksell G Stereotactic frame (Elektra Instruments) is attached first to the patient's head after applying local anesthesia and sometimes mild sedation. The Target tumor localization is achieved using high-resolution MRI (1.5 Tesla) with contrast enhancement obtaining T1 and T2 Axial and coronal-weighted sequences at 2-mm slice thickness or less without gap zero angles displaying the microanatomy of critical neurovascular anatomical structures. The responsible neurosurgeon determined treatment planning in accordance with a medical physicist using Elekta Leksell Gamma Plan version 10. A conformal GKRS planning is usually achieved by outlining the target with multiple isocenters to cover the tumor volume with the prescription isodose. The dose plan is then transferred to the operating console of the Leksell GK, where treatment is delivered. The Stereotactic frame was then removed after irradiation, and patients were discharged on the same day of treatment. The median tumor volume of the treated skull base meningioma was 4.4 cc (range 0.5 to 16.8), the median tumor marginal prescription radiation dose was 13.5 Gy (range 12 to 16), the median isodose line was 40% (range 35% to 60 %), the median % tumor coverage was 94% (range 82 to 100) and the median maximum radiation dose was 34 Gy (range 24 to 42.9).

### Follow-up

Clinical and radiological (MRI with contrast) evaluation obtained in the first follow-up routinely 6 months post-GKRS then annually in the first 5 years, followed by bi-annual after that or whenever clinically indicated. Clinical follow-up information was collected

retrospectively with a review of detailed patient records; besides, patients were contacted to provide structured follow-up information. The tumor growth response after GKRS was made primarily based on linear (2D) contrast-MRI and the radiological reports and discussed in a multidisciplinary session that included radiologist and gamma knife physician. We defined "tumor control" as tumor volume stable or reduction of at least >10% of the original volume and "lost tumor control" as a progression of tumor volume >10% of the original size. A favorable outcome is achieved whenever tumor growth is controlled (stable or regressed) and the neurological status is preserved or improved. The median radiological and clinical follow-up period after initial GKS was 102 months (range 60 to 180), including those with tumor progression and deceased patients due to lost tumor control.

### Literature search and review

A literature search on PubMed, Science Direct, and Scopus was performed using the following query terms: "Gamma Knife" [All Fields], "Stereotactic radiosurgery" [All Fields], "Skull base meningioma" [All Fields] and "Intracranial Meningioma" [All Fields]. Articles were included in the study contained patients who had undergone GKRS treatment for intracranial and skull base meningioma. Case reports were excluded. Crosschecking of the references for relevant articles was carried out.

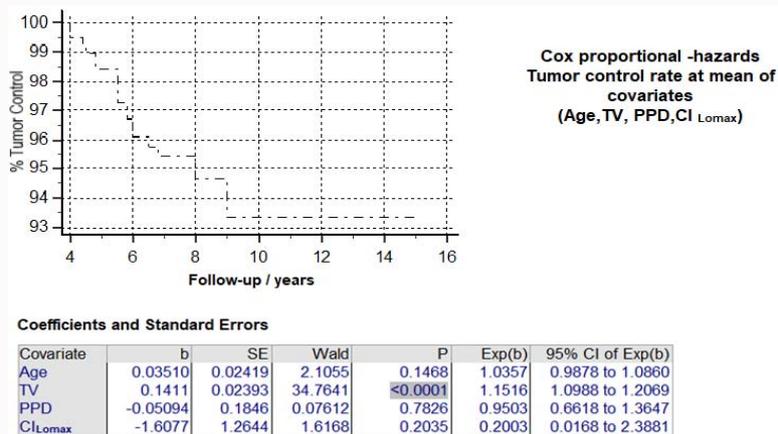
### Statistical analysis

Descriptive statistics were calculated for variables, including median and frequency distributions as appropriate. Kaplan-Meier plots [37] were used to estimate the local tumor control progression free rate assisted with MedCalc-software. For evaluating of possible predictable prognostic factors for tumor control, we used the Cox proportional-hazards regression curve displaying the effect of several variables [Age, Tumor Volume (TV), Peripheral Prescription Dose (PPD) and  $CI_{Lomax}$  conformity index], through follow-up time on tumor control rate at final outcome for detecting any possible tumor control prognostic factors.

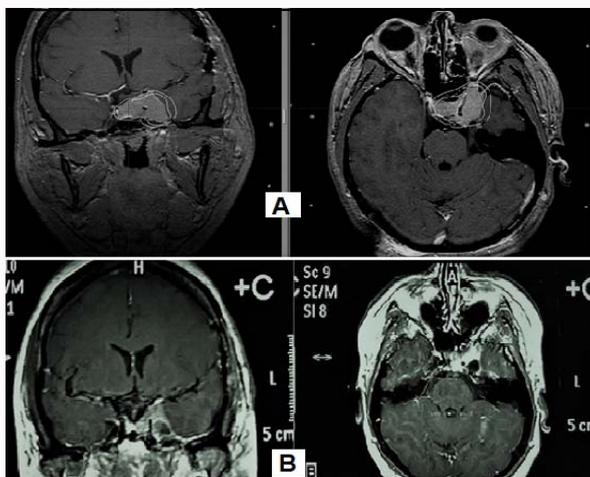
## Results

### Tumor control

246 patients were followed for =>5 years. 49 patients were followed for =>10 years, and 27 patients followed =>12 years. At the last follow-



**Figure 1:** Cox proportional-hazards regression curve displaying the effect of several variables [Age, Tumor Volume (TV), Peripheral Prescription Dose (PPD) and CI<sub>Lomax</sub> conformity index]. Through follow-up time on tumor control rate at final outcome for detecting possible tumor control prognostic factors.



**Figure 2:** Female patient 40 years old presented with left eye proptosis and left eye visual field defect. (A) Stereotactic Gamma plan coronal and axial sequences of recurrent post-operative left medial sphenoidal meningioma invaded the cavernous sinus of 7.5 cc treated with 14 Gy to 35% isodose line. (B) 144 months post-GKRS coronal and axial images revealed marked reduction in tumor size and clinically the patient was stable.

up, the overall tumor control was 93% (n=234). 183 patients (78%) had a stable tumor size, and 51 patients (22%) showed a decrease in tumor size. In this group, the median treated tumor volume was 3.87 cc (range 0.5 to 10.4), the median Peripheral Prescription Dose (PPD) was 14 Gy (range 12 to 16), and the median tumor coverage by the PPD was 95%. Lost tumor control post-GKRS was detected in 7.14% of patients (n=18). The median tumor volume in this group was 11.3 cc (range 6.6 to 16.8) treated with a median PPD of 12.5 Gy (range 12 to 15), the median tumor coverage was 82%.

74.6% of patients (n=188) had GKRS as a primary treatment with no previous surgical tumor resection; in this group, tumor control was achieved in 92% (173 patients). GKRS was performed as adjuvant therapy for 64 patients (25.4%) who underwent previous microsurgical resection; this group's tumor control rate was 93.8% (n=60).

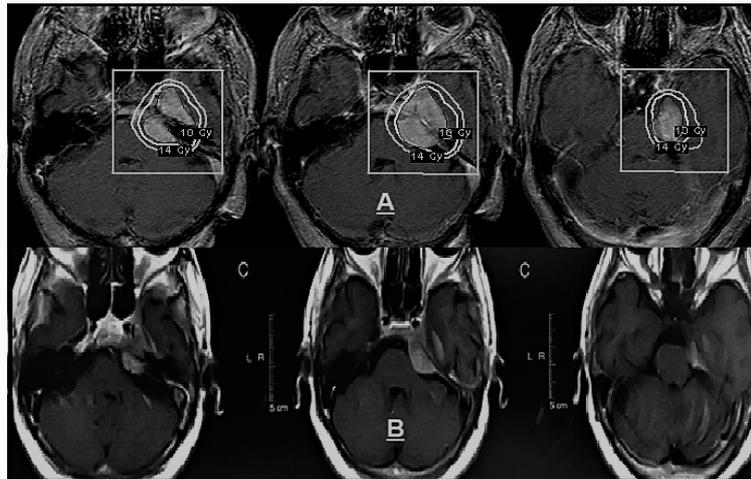
Post-GKRS 93% (n=234) did not require any further additional procedures. Because of lost tumor control and tumor progression, 4 patients had later open microsurgery at 58, 68, 70, and 72 months respectively, 2 required ventriculoperitoneal shunts, 3 underwent second Gamma Knife re-treatment, and 3 had fractionated conformal radiotherapy.

We used the Conformity Index (CI) proposed by Lomax and Scheib [7] to evaluate the stereotactic plan quality criterion regarding the tumor/radiation dose relationship.  $CI_{Lomax} = TV_{PIV} / TV$ , where  $TV_{PIV}$  stands for the target volume received at minimum the prescription isodose and TV is the tumor target volume. This conformity index can range from 0 to an optimum value of 1 when the target volume in its entirety receives at least the prescribed dose. For the 183 patients (78%) who achieved stable tumor size, the median treated tumor volume in this group was 3.87 cc (range 0.5 to 10.4), and the median  $CI_{Lomax}$  value was 0.95.

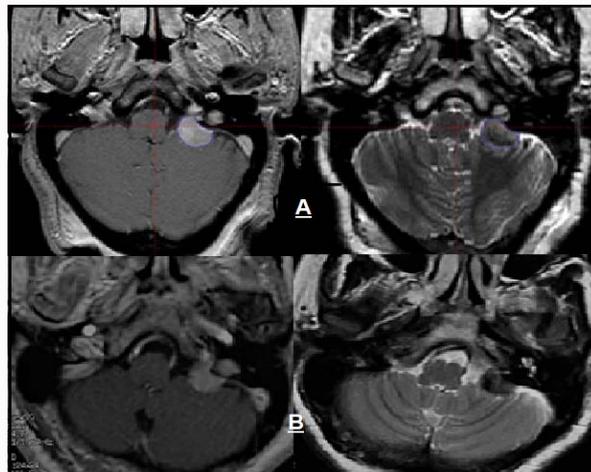
The overall tumor growth control in our study at last follow-up was 93% (n=234); in this group, the median treated tumor volume was 3.87 cc (range 0.5 to 10.4), the median peripheral prescription dose was 14 Gy (range 12 to 16), and median Lomax conformity index  $CI_{Lomax}$  value was 0.95. This better conformity demonstrates that most treated tumor volume received at least the PPD.

Tumor progression and lost tumor control after GKRS was detected in 7.14% of patients (n=18), the median tumor volume in this group was 11.3 cc (range 6.6 to 16.8), and the median  $CI_{Lomax}$  value was 0.82.

The local tumor control progression-free rate at 3-, 5-, 10, and 12



**Figure 3:** Female patient aged 61 years presented with headache, trigeminal neuralgia, 6<sup>th</sup> nerve palsy and diplopia (A) Gamma plan MRI axial contrast images showed large peritrochlear meningioma of 9.2 cc tumor volume (B) 132 months post-GKRS follow-up contrast-MRI axial sequences revealed tumor reduction. The patient diplopia and 6<sup>th</sup> nerve palsy subsided but still on medical treatment for trigeminal pain.



**Figure 4:** Female patient 44 years old presented with vertigo, headache and decreased hearing in left ear. (A) MRI contrast axial T1 and T2 sequences in Gamma plan of left cerebellopontine angle meningioma of 3.52 cc volume, treated with 12 Gy to 35% isodose curve. (B) 96 months post GKRS MRI contrast T1 and T2 revealed some tumor reduction. The patient was clinically stable.

years was 100%, 97.62%, 81.6%, and 81%, respectively.

We used the Cox proportional-hazards regression curve displaying the effect of several variables [Age, Tumor Volume (TV), Peripheral Prescription Dose (PPD) and  $CI_{Lomax}$  conformity index]. Through follow-up time on tumor control rate at final outcome for detecting any possible tumor control prognostic factors.

In our study's the tumor volume variable reached highly statistical significance ( $p < 0.0001$ ) as a reliable predictor prognostic factor regarding tumor control Figure 1.

### Clinical outcome

At last follow-up neurological evaluation revealed an overall control of clinical status in 92% (n=231), improvement in neurological status in 26% (n= 60) and stable clinical condition in 74% (n=171). Thirty patients with a pre-GKRS different form of headache improved post-GKRS, and 38 were stable, ocular movement disorders improved in 44 patients and were stable in 20. Trigeminal neuralgia improved in 4 and was stable in 24 patients with medication. Pre-GKRS Seizer improved in 2 patients. Bulbar symptoms improved partially in 2 and

were stable in 5 patients. Our study's overall survival rate at the last follow-up was 97.6% (n=246). Post-GKRS a decline in neurological function (side effect) was reported in 8% (n=21), 16 of them have lost tumor control during the period of follow-up. New onset of trigeminal neuralgia developed in 3 (14.3% of the 21 patients), additional trigeminal paresthesia, facial numbness in 8 (38%), deterioration of serviceable hearing in 3 (14.3%), increased seizure activity in 2 patients (9.5%) progressive deterioration of visual field in 3 patients (14.3%), and 2 patients developed new motor weakness (9.5%). Transient mild peritumoral edema was detected in 5 cases (2%) post-treatment, 4 of them had sphenoidal ridge, and one had olfactory groove meningioma. Clinically all of them developed new intermittent attacks of headache, and two also developed new onset of seizures' activity.

A favorable outcome (a combination of tumor control and clinical neurological improvement or stability) was achieved in 90% of treated patients (n=227). No Adverse Radiation Effects were reported among the treated cases. Illustrative cases are demonstrated in Figures 2-4.

**Table 3:** Summary of Gamma Knife radiosurgery-based series for skull base meningioma treatment.

| Reference                   | Number of pats* | Follow up mos*<br>Median (range) | Median tumor volume.cc* | Median peripheral prescription dose Gy | Actuarial 5 years *PFS%                  | Actuarial 10 years *PFS% | Clinical Complications % |
|-----------------------------|-----------------|----------------------------------|-------------------------|--|--|--------------------------|--------------------------|
| Aichholzer M, et al. [1].   | 46              | Mean 48 (36-76)                  | Not given               | 15.9 Gy (9-25 Gy)                      | 96                                       | N/A                      | 9                        |
| Eustacchio S, et al. [16].  | 121             | 82 (60-117)                      | 6.8 cc (0.5 - 89.9)     | 13 Gy (7-25 Gy)                        | Overall tumor control rate 93.3%         |                          | 3.3                      |
| Liscak R, et al. [45].      | 176             | 36 (6-110)                       | 5.3 cc (0.12-35.5)      | 11 Gy (6.5-20.4 Gy)                    | 98                                       | N/A                      | 11                       |
| Kreil W, et al. [40].       | 200             | 95 (60-144)                      | 6.5 cc (0.38-89.8)      | 12 Gy (7-25 Gy)                        | 98.5                                     | 97.2                     | 4.5                      |
| Iwai Y, et al. [27].        | 108             | Mean 86.1 (20-144)               | 8.1 cc (1.7-55.3)       | 12 Gy (8-12 Gy)                        | 93%                                      | 83                       | 6.5                      |
| Han JH et al. [23].         | 98              | Mean 77                          | 6.6 cc (0.5-18.4)       | 12.6 Gy (7-20 Gy)                      | 90.2                                     | N/A                      | 15.9                     |
| Igaki HIROCHI, et al. [28]. | 98              | Mean 53.2 (12.2-204.4)           | 3.9 cc (0.3-45)         | 16 Gy (12-22.5 Gy)                     | 86.9                                     | 78.9                     | 3                        |
| Hayashi M, et al. [24].     | 66              | Mean 46 (26-80)                  | 6.6 cc (0.3-50.6)       | 12 Gy (10-14 Gy)                       | 99                                       | N/A                      | 1                        |
| Starke RM, et al. [67].     | 255             | 78 (6-252)                       | 5 cc (0.3-54.8)         | 14 Gy (8-30)                           | 99                                       | 79                       | 10                       |
| Cohen-Inbar, et al. [9].    | 135             | 102.5 (60.1-235.4)               | 4.7 cc (0.5-23)         | 15Gy (7.5-36)                          | 95.4                                     | 68.8                     | 11.9                     |
| Patibandla MR, et al. [55]. | 219             | 66 (18-298)                      | 4.9 cc (0.3-105)        | 14 Gy (5-35)                           | Overall tumor control rate 83.4% (n=183) |                          | 20.5                     |
| Faramand A, et al. [17].    | 150             | 75 (12-312)                      | 8.1 cc (0.3-42)         | 13 Gy (10-20)                          | 95                                       | 90                       | 10                       |

**Abbreviations:** \*cc-\*Cubic Centimetre; \*N/A: Data Not Available in the Publication; \*mos: Months; \*Pats: Patients; \*PFS: Progression Free Survival

### Mortality

A total of 7 patients deceased during the long-term follow-up post-GKRS due to tumor progression complications. There was no short-term treatment-related mortality.

### Discussion

Microsurgery alone still leaves skull base meningioma patients with a substantial recurrence or residual rate, considerable morbidity, and occasional mortality. Less invasive alternative strategies, including radiosurgery, should be considered in the therapeutic management of skull base meningiomas [1-4,10,14,17]. GKRS has begun to play an increasingly important role as a non-invasive alternative or adjuvant therapeutic modality for patients with skull base meningiomas. GKRS aims to achieve long-term tumor control by maintaining the patient's clinical status and preventing new treatment-related morbidity [18,19,30-34,39,40,43].

### Tumor control

The overall tumor control rate in our study at last follow-up was 93% (n=234); in this group, the median treated tumor volume was 3.87 cc the median peripheral prescription dose was 14 Gy (range 12 to 16), and median Lomax conformity index  $CI_{Lomax}$  value was 0.95. This better conformity demonstrates that most treated tumor volume received at least the PPD. We reported tumor progression in 18 patients (7.2%), with a median treated tumor volume was 11.3 cc (range 6.6 to 16.8 cc), treated with median PPD of 12.5 Gy (range 12 to 14), and median conformity index  $CI_{Lomax}$  value of 0.82. The insufficient dose-volume relation in this group seemingly resulted in inadequate peripheral prescription dose distribution and low tumor coverage; hence was seemingly responsible for the post-GKRS tumor progression. Earlier in our study, we treated benign skull base meningiomas with a tumor volume of >10 cc at a low peripheral prescription dose of 12 Gy because the large tumor volume resulted in a low percentage of tumor coverage of the prescription dose. This conclusion (Low-dose radiosurgery for meningiomas) was consistent with what has been described by Nakaya et al. [33] and Kreil et al. [38]. Statistically in our study the tumor volume variable reached statistical significance (<0.0001) and served as a reliable predictor prognostic factor regarding tumor control. However, any nearby critical neurovascular structures' radiation tolerance should be considered

for optimum clinical outcomes, even smaller tumor volumes.

DiBiase et al. [40-66] reported a 91.9% 5-year disease-free survival for patients with meningiomas less than 10 cc as opposed to 68% for larger tumors. Kondziolka et al. [67] reported excellent outcomes with GKRS for meningiomas up to a diameter of 3.0 cm or a volume of <7.5 cc. Likewise, other authors have found high local control and fewer radiation-related complications associated with the treatment of smaller meningiomas, including complications in 4.8% of patients harboring tumors of <3.2 cc but in 22.6% with 9.6 cm. [68-71].

Patients with sizeable extensive skull base meningioma or significant brain stem compression or significant optic pathway entrapment microsurgery are usually advised first for microsurgical removal if feasible or planned combined surgical decompression and GKRS cooperation. Alternative options as fractionated stereotactic or conformal radiation therapy should be discussed individually according to tumor factors (size and location) and patients' factors (age and presence of other comorbidities).

In the current study, the 10-years local tumor progression-free survival for the 49 patients who were followed >10 years was 81.6% (40/49) and for the 27 patients who are followed for 12 to 15 years was 81% (21/27). Bledsoe et al. [71] in their series of Long-term outcomes after gamma knife radiosurgery for benign meningiomas, reported tumor control rates were 99% and 92% at 3 years and 7 years, respectively. Kondziolka et al. [72] reported an overall tumor control rate of 91% with 10-year actuarial rates of freedom from tumor progression were  $87.7\% \pm 2.5\%$ , with a sustained long term tumor control [3,38,42,44,46,48]. This finding supports our results that tumor progression despite radiosurgery will typically be detected in the first decade after the procedure. However late recurrences cannot be ruled out and longer follow-up period is still needed.

### Post-GKRS clinical outcomes and side effects

The nerves controlling ocular muscles are presumed to tolerate doses even beyond 21 Gy [8,27,31,51,52]. consistent with our results, no new ocular muscle cranial nerves deficit was observed, and the doses to the 3<sup>rd</sup> nerve if detected in gamma plan MRI in coronal 1.2 mm thickness slices (e.g., in the cavernous sinus and petroclival meningiomas) did not exceed 15 Gy to 20 Gy. However, many series

reported that the fifth cranial nerve seems to tolerate doses of up to 20 Gy [31,50,52-54]. We reported new onset of trigeminal neuralgia treated at PPD ranged between 14 Gy to 16 Gy to the trigeminal nerve in 3 patients (two cerebellopontine angles and one petroclival meningioma). This could be attributed to the nature of meningioma tumors or prolonged nerve compression. The overall clinical status control rate in this study was 92% (n=231 patients), 26% of them (60/231) showed clinical improvement and 74% (171/231) were clinically stable.

A decline in neurological function at the last follow-up was reported in 8% (n=21); 16 of them have lost tumor growth control. The obtained complications rates in our study may be a little higher than mentioned by Kreil et al. [38], Igaki Hiroshi et al. [44], and Hayashi et al. [45], but it was consistent with other series with long-term follow-up, as reported by Liscak R [41], Starke et al. [46], Cohen-Inbar et al. [3], and Faramand A. et al. [48].

The majority of side effects reported in the current study (16/21) were unrelated to the GKRS treatment and appeared late, and were associated with tumor progression complications. Similar to the present study, where late clinical complications appeared in 76% of those who lost tumor growth control. Starke and colleagues [67] reported that tumor progression was present in 64% of patients with new or worsening neurological decline. In general, the reported risk for clinical side effects after Gamma Knife treatment ranged between 4% and 8% [8,30,33,34,54-58]. Lee and colleagues [35], who had summarized the radiosurgical experience in Pittsburgh after radiosurgery treatment of 964 patients with various types of intracranial meningiomas. The authors reported that the incidence of adverse radiation effects ranged from 5.7% to 16%, but that side effects were gradually reduced with better imaging and lower dosing in small-sized meningiomas, perilesional edema occurred in 6.1%. The large study from the Hospital Na Homolce in Prague published by Kollova et al. for various intracranial meningiomas had demonstrated perilesional edema after radiosurgery in 15.4% and temporary and permanent morbidity rates of 10.2% and 5.7%, respectively [60]. Virtually the same rate for the risk of edema (15%) was recently reported in large series by Jang (15%) [61] or by Hoe (15.3%) [62].

Transient peritumoral edema was detected in 5 (2%) early treated patients in our series (4 sphenoidal and one olfactory groove meningiomas) with large skull base meningioma >10 cc volume (approximately >3.2 cm in maximum diameters) treated with median PPD of 13 Gy (range 12 to 14) to the 35% isodose line. Clinically these patients developed a headache, two of them developed new onset of seizer's activity, and two have developed some weakness. We did not report such complication since we begin to treat skull base meningioma of <10 cc (approximately =< 3.2 cm in maximum diameters) at a median low peripheral prescription dose median of 12 Gy (range 12 to 14) at 50% isodose line. The low incidence of reported perilesional edema in our patients may be related to the location of treated meningiomas at the skull base and not including surface meningiomas, as reported by some authors [25,30,35]. Commonly, extensive intracranial meningiomas are considered unsuitable for GKRS because the radiobiological tolerance of the surrounding brain tissue for the currently prescribed single dose ranged between (12 Gy to 15 Gy), practical maximal volume limit to around <10 cc or =< 3 cm in maximum diameters [8,38,63-66].

Reviewing the literatures resulted into 12 large series of GKRS treatment for skull base meningiomas [1,9,16,17,23,24,27,28,40,45,

55,67]. The authors in 10 of these series reported a 5 years tumor progression-free survival ranged between 86.9% to 99% with a median follow up of 72 months and post-GKRS complications at a median rate of 9.5%, six of these series reported a 10 years tumor progression-free survival ranged between 68.8% to 97.2% with a median follow up of 82 months and with complications with a median rate of 8% Table 3.

The 3-, 5-, 10, and 12-year local tumor control progression-free rates in our series were 100%, 97.62%, 81.6%, and 81%, respectively, compared favorably with the results of other treatment methods, including microsurgery, conventional radiotherapy, and Linac based radiosurgery in selected patients [14,22,29,32,42-49,50]. With a long-term median follow-up of 102 months (range 60 to 180), the present study provides evidence for the durability and efficacy of GKRS in a long-term perspective.

## Study Strengths and Limitations

The strengths of the current study included a relatively homogenous sizeable patient population with regular follow-up documentation in addition to a long-term follow-up.

There are several limitations in our study that must be considered. The retrospective study's nature and difficulties of collecting data from elderly earlier treated patients. Additionally, the subject of changes in the GKRS device capabilities, sophisticated imaging tools, and gamma plans' continued development over time. Despite this continuous change, there was no significant difference in the GKS treatment parameters and basics. More extended follow-up periods are always needed for a better and conformal conclusion.

## Conclusion

Single-session GKRS provides a long-term, highly durable, and favorable rate of benign skull base meningioma control with improvement or maintenance of neurological function and acceptable low morbidity. The reported 5-year and 10-year local tumor control progression-free rates were 97.62% and 81.6%, respectively. In critical locations, stereotactic GKRS can replace a complicated surgical resection, and in planned combined microsurgery and GKRS cooperation for large skull base meningioma, the need for an aggressive tumor resection could be reduced as GKRS provides a documented long-term control of tumor residual and recurrence. Tumor volume stands as a reliable predictor factor for skull base meningioma tumor control outcome. The long natural history of benign skull base meningioma slow progression necessitates longer observation periods before any conclusion regarding the various treatment options.

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