

Stereotactic Gamma Knife surgery safety and efficacy in the management of symptomatic benign confined cavernous sinus meningioma

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Abstract

Background Considering the proximity to cranial nerves from II to VI and the internal carotid artery microsurgery for cavernous sinus meningioma (CSM) has its limits of complete resection, with high potential tumor recurrences, cranial nerve and vascular morbidity. Gamma Knife surgery (GKS) is an advanced modality as primary treatment for patients harboring symptomatic benign confined CSM as well as adjuvant therapy to postoperative residual tumor giving a high rate of tumor control, stabilizing or even improving clinical condition with low morbidity.

Materials and methods The aim of this study is to evaluate the safety and efficacy of GKS used in the management of 62 patients with symptomatic benign confined CSM < 3 cm in maximum diameters treated at the International Medical Centre (IMC), Cairo, Egypt, from 2005 to end of 2012, with mean follow-up period of 36 months (range, 24–96 months) by reviewing their clinical and radiological data. For 51 patients GKS was performed as a primary treatment. The diagnosis was based on typical clinical and imaging findings and in 11 patients GKS was used as adjuvant to post-operative tumor residual with histological confirmation.

Results There were 43 females and 19 males. The median age at the time of treatment was 48 years. The mean tumor volume

was 5.7 cc, the mean tumor marginal radiation dose was 14.4 Gy, the mean isodose line was 38 %, and the mean tumor coverage was 94.4 %. The optic pathway received <8 Gy and the brain stem <10 Gy. At most recent follow-up, 57 patients (92 %) had stable or improved cranial nerve deficits. Post-GKS cranial nerve complications were detected in five patients (8 %). Tumor volume was controlled in 60 patients (96 %) at most recent follow-up MRI; 12 patients had a reduction in tumor size and 42 had stable tumor size, while tumor size progression was detected in two patients. The tumor progression-free survival at 3 and 5 years in 40 patients who completed at least 5 years of follow-up was 95 %.

Conclusions Gamma Knife surgery is a safe and effective option for the treatment of cavernous sinus meningioma not only as an adjuvant to surgery but also as an alternative to surgical removal in tumors confined mainly to the cavernous sinus.

Keywords Gamma Knife surgery · Cavernous sinus · Cranial nerve · Meningioma · Radiosurgery

Abbreviations

GKS Gamma Knife surgery
CSM Cavernous sinus meningioma
SRS Stereotactic radiosurgery
WHO World Health Organization

Background

Meningiomas are the most common non-glioma tumors affecting the central nervous system and account for 13–26 % of all intracranial neoplasms. Cavernous sinus meningioma (CSMs)

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occur in 0.5 per 100,000 persons in general population. Over 90 % of tumors occurring in or invading the cavernous sinus are benign meningiomas. Tumors in the cavernous sinus are most frequent in the middle-aged, but still occur quite frequently in the older-age group. Female patients outnumber male patients by 2:1 [1–3].

Cavernous sinus meningiomas tend to cause symptoms by compressing or invading nearby neurovascular structures, as close proximity to cranial nerves II to VI and the ICA. CSMs often present with neurological deficit, commonly ocular movement deficits presenting with diplopia, ophthalmoplegia, and/or ptosis. Optic pathway compression or optic canal invasion can cause visual deficits up to a loss of visual acuity. Facial numbness, pain, and dysesthesias can result from compression of the trigeminal nerve. Pituitary stalk and gland dysfunction, though uncommon, can result from tumor compression. Patients with tumors arising from the sphenoid wing that infiltrate the cavernous sinus may present with seizures or hemiparesis. Finally, headaches are commonly associated with CSMs [3].

The management of symptomatic CSM includes close observation, surgical resection, radiosurgery, radiotherapy, and systemic therapy or a combination of these approaches depending upon patient-related factors (age, performance status, co-morbidities, and symptoms), and tumor features (size, localization, and histological grade [4, 5].

Despite improvements in the techniques and neurosurgeon skills, gross-total resection is still associated with significant morbidity. CSMs commonly invade bone, dura, dural sinuses, and even the carotid wall being almost impossible of total removal. After partial or subtotal CSM removal, the probability of recurrence remains significant (13 % at 3 years and 38 % at 5 years) [5, 6].

The inherently steep dose gradient produced by Gamma Knife surgery (GKS) affords physical protection of the normal tissue adjacent to the target lesion. For these reasons, application of SRS, particularly GKS to cavernous sinus meningioma, has been generally accepted as the primary treatment of tumors <3 cm in greatest dimension, not significantly compromising the optic pathway. Larger tumors >3 cm in maximum diameters or those with marked optic pathway compression benefits surgical debulking and optic nerve decompression followed by adjunctive Gamma Knife surgery (GKS) for residual or fractionated stereotactic radiosurgery or radiotherapy [7, 8].

Microsurgery and radiosurgery have recently been advocated as a combined therapy to achieve good control of tumor growth and favorable functional outcome of even some large CSM treatments [9, 10].

Gamma Knife surgery is an effective and safe option for the treatment of cavernous sinus meningioma not only as adjuvant to surgery but also as an alternative to surgical removal in selected patients [10–12].

Materials and methods

Objective The aim of this study is to evaluate the safety and efficacy of GKS in management of 62 consecutive patients having symptomatic benign confined cavernous sinus meningioma of <3 cm in maximum diameter, by retrospective reviewing of their clinical and radiological data at a mean follow-up period of 36 months (range, 24–96 months). Signed consents from all studied patients were obtained as the policy in our Gamma Knife center at the IMC requires that consent be obtained from any patients before their medical records and radiological images are used for research purposes.

Patient's population Between 2005 and the end of 2012, 62 patients harboring benign symptomatic confined cavernous sinus meningioma were treated with GKS at the International Medical Center (IMC), Cairo, Egypt, and completed at least 24 months follow-up with a mean follow-up period of 36 months (range, 24–96 months). Excluded were patients who did not complete at least 24 months of follow-up, those lost during follow-up, patients with multiple meningiomas, with neurofibromatosis type II, and those receiving prior radiotherapy. There were 43 females and 19 males. The median age at the time of GKS was 48 years (range, 26–74 years). For 51 patients, GKS was performed as a primary treatment and diagnosis was based on typical imaging findings (clear definition of the lesion with wide dural attachment and enhancement after contrast). GSK was used as an adjuvant treatment in the remaining 11 patients who had post-operative residual tumor all had histological confirmation of benign meningioma.

For larger extensive cavernous sinus meningioma that not confined to cavernous sinus with maximum diameters >3 cm especially those with significant visual affection microsurgery is advised first, to decompress the optic pathway and debulking the tumor followed by GKS for residual tumor or fractionated radiotherapy depending on patient's age, tumor location, extension, and tumor size.

Regarding the clinical manifestations pre-GKS, 37 patients presented with diplopia and ocular movement disorders, being the main neurological manifestation prior to treatment, there were 15 oculomotor palsy, and 26 abducens nerve palsy two patients presented with total ophthalmoplegia. Eleven patients presented with trigeminal hypoesthesia and 13 presented with trigeminal neuralgia. There were nine patients with minimal visual impairment.

Gamma Knife technique The Elekta Leksell Gamma Knife with automatic positing 4-C version system was used for the treatment of the studied 62 patients with confined cavernous sinus meningioma. The stereotactic coordinate frame was fixed to the patient's head after application of a local anesthesia and placed low, anterior, and to the side of the lesion. The

8-mm collimator was the commonly used helmet, and in cases where the optic pathway was in the vicinity of radiation, doses the 4-mm collimator was also used. The 72° angle was applied in many cases so that the radiation beams became parallel to the optic pathway, avoiding harming it. Target localization was achieved using high-resolution stereotactic MRI with contrast obtaining T1 and T2 coronal-weighted sequences, which displayed accurately the microanatomy for optic pathway and cranial nerves, at 2-mm slice thickness without gap and on zero angle, axial T1 sequence was performed as well. Treatment planning was performed with the Elekta Leksell Gamma Plan. In all of the treated 62 patients, the mean CSM volume was 5.7 cc (range, 1.8–12.4 cc). The mean tumor marginal radiation dose was <14.4 Gy, the mean isodose line was 38 % (range 35 to 50 %), and the mean tumor coverage was 94.4 % (range, 88–100 %). In all treated patients, tumor base was involved in the given radiation field, optic pathway received <8 Gy and brainstem radiation dose was <10 Gy.

Follow-up All studied patients were followed prospectively after the GKS with clinical examination, neuro-ophthalmological testing, and imaging (MRI with contrast) at each 6 months in the first year then yearly afterwards. The mean follow-up period was 36 months (range, 24–96 months). Tumor growth was considered controlled if its volume was unchanged or reduced in size.

Results

Considering post-GKS neurological outcome, 14 (38 %) of the 37 patients presented with eye movement deficits improved or recovered, 23 remained stable, and only one patient developed new sixth nerve palsy after 12 months post-GKS. None of the patients presenting with normal visual acuity and normal field of vision before treatment experienced visual deterioration after GKS. Among the nine patients presenting with minimal visual disturbances pre-GKS, two patients improved in visual field, six remained stable, and one developed additional visual deterioration with detectable tumor volume progression toward optic canal. In 13 patients that presented with trigeminal pain, seven improved, six were stable, and one developed new trigeminal pain after 6 months post-GKS. Among the 11 patients presenting with trigeminal hypoesthesia, seven remained unchanged, two improved, and two deteriorated. Generally, at the most recent follow-up, 57 patients (92 %) had stable or improved cranial nerve deficits, 38 % of those presented with ocular movement deficits improved, and 54 % of those with trigeminal neuralgia improved.

At the most recent follow-up MRI brain with contrast evaluation, tumor size was controlled in 60 patients (96 %), 12 of which had some reduction in tumor size and 48 showed stable

tumor sizes. Two patients showed tumor size progression at 12 and 18 months post-GKS, respectively. One was retreated with GKS and the other who developed additional visual field deterioration and was subjected to microsurgery. The tumor progression-free survival at 3 and 5 years in 40 patients who completed at least 5 years of follow-up was 95 % (Figs. 1 and 2).

Five patients (8 %) in our study developed new or worsened cranial nerve deficits related to post-Gamma Knife radiation, including trigeminal hypoesthesia in two patients, trigeminal pain in one, additional diplopia in one, and deterioration of affected visual field in one patient. All of these deficits

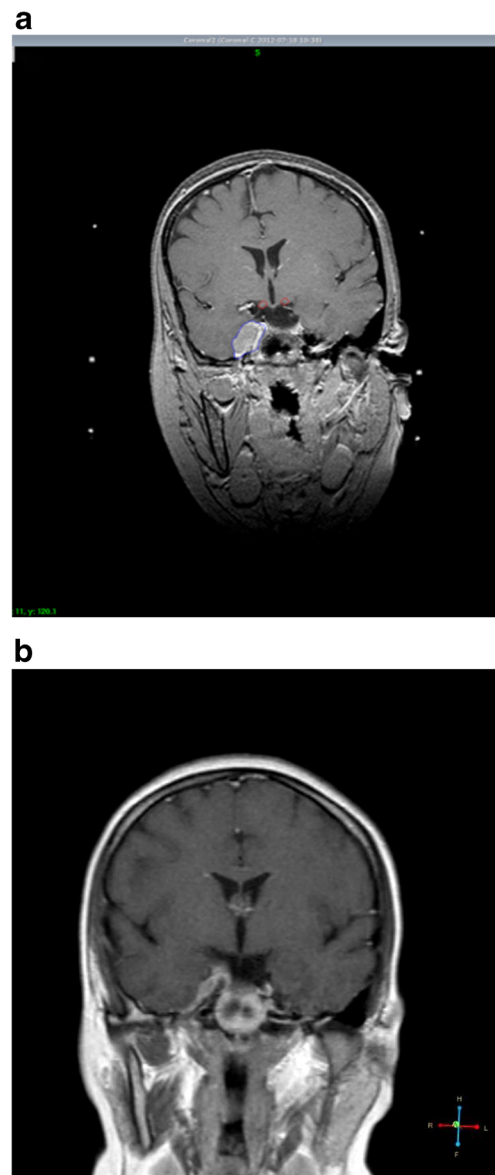


Fig. 1 T1-weighted enhanced coronal MRI (a) illustrating pre-GKS stereotactic MRI of right-side cavernous sinus meningioma in a 25-year-old woman with 2.9-cc tumor volume presenting with right ptosis and diplopia treated with 15 Gy marginal dose at 35 % isodose curve with 99 % tumor coverage with the prescription dose. (b) Eight-year post-GKS MRI showing a marked reduction in tumor volume. The patient showed significant clinical improvement

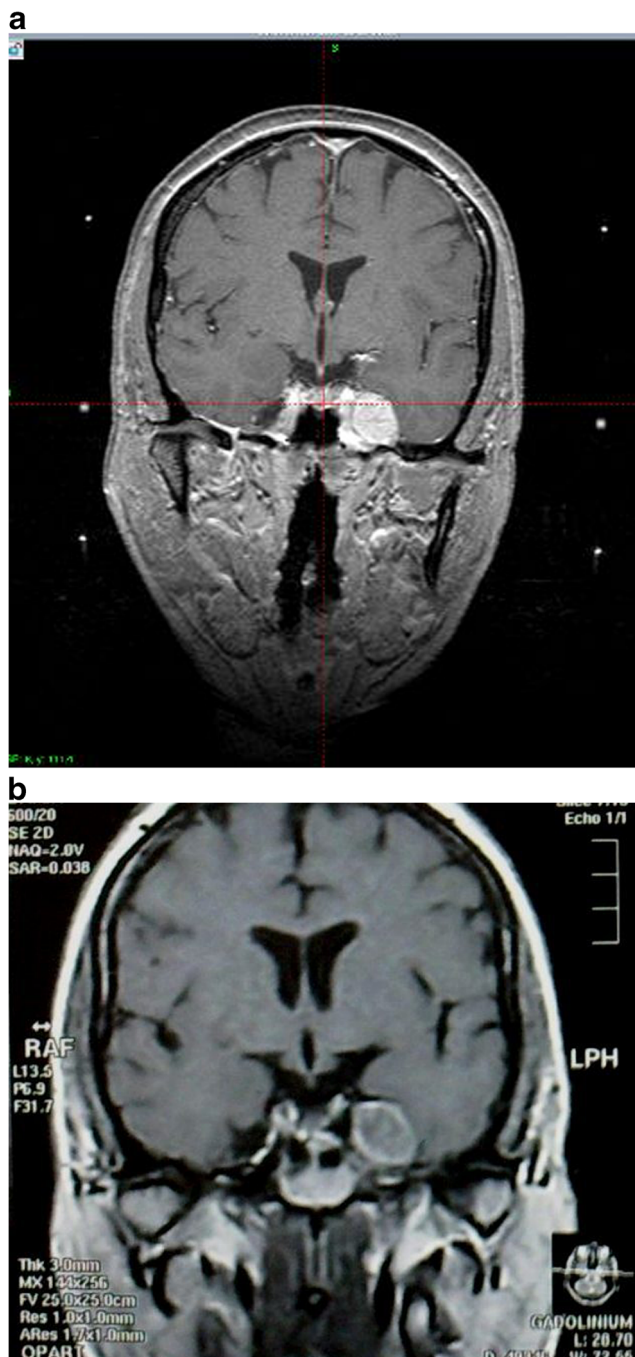


Fig. 2 T1-weighted enhanced MRI (a) illustrating a stereotactic MRI pre-GKS of left-side cavernous sinus meningioma in a 56-year-old woman with 3.2-cc tumor volume presenting with 6th nerve palsy and trigeminal pain treated with 15 Gy to 50 % isodose curve with 98 % tumor coverage. (b) Five-year post-GKS MRI showing local tumor control with decreased central enhancement. The patient showed a stable clinical condition

appeared 12 months after treatment. Two (3 %) of the 62 patients treated showed tumor progression in size at 12 and 18 months of follow-up post-GKS, respectively. One was retreated with GKS and the other who also had visual field deterioration was subjected to microsurgery.

Discussion

The optimal management of cavernous sinus meningioma still remains in debate. Based on the published literature, surgery-related morbidity for CSM was higher than that for stereotactic radiosurgery (SRS), including either gross total and subtotal resection. Patients receiving SRS experienced lower rates of tumor recurrence compared with patients who underwent surgery alone [4, 7]. Long-term studies of meningioma involving the cavernous sinus after surgery reported recurrence rates of 9.6 % after complete resection and 15.2 % after subtotal resection [6, 13].

Even when full coverage of the tumor target was not possible with GKS, good outcomes in the treatment cavernous sinus meningioma can be achieved. Kano et al. has shown progression-free survival rates of 94 % after 5 years and 86 % at 8 years, with a median follow-up of 62 months. The authors stressed that primarily intracavernous CSMs are ideal candidates for GKS as primary treatment and as adjuvant to postoperative residuals [14].

In our study, we reported the outcomes of 62 patients with symptomatic benign confined cavernous sinus meningioma < 3 cm in maximum diameters who underwent GKS at IMC Gamma Knife center in Cairo, Egypt, between 2005 and 2012 for either documented WHO grade I meningioma treated for postoperative residuals in 11 patients as adjuvant treatment or presumed cavernous sinus meningioma based on the imaging characteristics in 51 patients as primary treatment. The median follow-up period was 36 months (range, 24–96 months).

The mean tumor marginal GKS radiation dose in our study was 14.4 Gy. The mean isodose line was 38 % and the mean tumor coverage was 94.4 %. In all treated patients, the tumor's dural base was involved in the given radiation field, optic pathway received 8 Gy or less and brain stem received 10 Gy or less. Cranial nerve deficits were controlled (stable or improved) in 57 patients (92 %). Among the 37 patients presented pre-treatment with ocular movement deficit 14 were improved post GKS and 23 were stable, for the 13 patients with trigeminal neuralgia seven improved and six were stable, for the 11 patients with trigeminal hypoaesthesia, two improved and seven were stable. Among the nine patients who presented with minimal visual disturbances pre-GKS, two patients improved in visual field, six remained stable, and one developed additional visual deterioration with detectable tumor size progression toward the optic canal and was subjected to microsurgery. In total, at the most recent follow-up for the 62 treated patients, 57 (92 %) had stable or improved cranial nerve deficits, 38 % of those presented with ocular movement deficits improved and 54 % of those with trigeminal neuralgia improved.

In Roch et al.'s series, only a single sixth cranial nerve deficit deteriorated after the treatment, whereas 23 (43 %) of 54 ophthalmic paresis improved or recovered [12].

Leber et al. studied 50 middle fossa benign tumors, including 23 meningiomas. The third, fourth, and sixth cranial nerves were exposed to a mean dose of 14.2 Gy, and among the 28 nerves with impaired pretreatment function, six nerves (21 %) recovered markedly or even completely. Radiation-induced third and fourth cranial nerve neuropathies were observed at 7- and 8-month follow-up, respectively, in two patients in that series. They concluded that when the maximum radiation dose to the visual pathways was less than 10 Gy, no signs of radiation-induced optic neuropathy were observed. However, when the dose ranged from 10 to less than 15 Gy, the incidence of radiation-induced optic neuropathy was 26.7 % [15].

Pollk et al., in their series on 115 cavernous sinus meningiomas, used single-fraction SRS(GKS) to treat patients with tumors that contacting the optic nerves and chiasm but not causing visual loss, the majority of the tumor received a margin dose of 14–15 Gy, while the superior portion of the tumor (typically 2–5 % of the total tumor volume) received 11–12 Gy and with median follow-up of 89 months no tumor progression or visual deficits have been detected [3].

Tumor growth control in our study was achieved in 60 patients (96 %), as documented in the last follow-up imaging (stable in size in 48 and reduced in size in 12 patients) all of them had tumor volume of 10 cc or less. Two patients (3 %) showed progression of tumor volume post-GKS, one with CSM volume of 12.4 cc showed tumor progression toward optic canal with deterioration of affected visual field and this patient was subjected to microsurgery after 12 months of GKS. The other patient has CSM of 11.2 cc tumor volume and was retreated with Gamma Knife surgery tumor regrowth after 18 months post-first GKS. The tumor progression-free survival at 3 and 5 years in 40 patients who completed at least 5 years of follow-up in our study was 95 %.

Nicolato et al. published a retrospective series evaluating 122 benign cavernous sinus meningioma treated with GKS at a marginal dose of 14.6 Gy and after a median follow-up period of 48.9 months, disease-free progression over 5 years was 96.5 % [16].

Lee et al. examined 159 cases of cavernous sinus meningioma treated with GKS at a marginal dose of 13 Gy; in this series, 49 % of cases had undergone previous surgical treatment. In these patients, the control rate was 93.1 % over 10 years. In the patients who had GKS as the primary treatment, the 5-year local control rate was 96.9 % [8].

Five patients (8 %) in our study developed new or worsened cranial nerve deficits related to Gamma Knife radiation, including trigeminal hypoesthesia in two patients, trigeminal pain in one, additional diplopia in one, and deterioration of visual field in one patient. All of these deficits appeared with 8–12 months post-Gamma Knife surgery.

Pollk et al., in their series on 115 cavernous sinus meningiomas treated with Gamma Knife with median follow-up of

89 months, reported 14 patients (12 %) had permanent radiation-related complication at a median onset of 23 months. Eleven patients developed new or worsened cranial nerve deficits including trigeminal dysfunction in nine and diplopia in two patients. Two patients had ischemic strokes and one patient developed pituitary insufficiency [3].

GKS provides durable tumor control and a low risk of new cranial nerve deficits for patients with small-volume CSMs. Nevertheless, it remains a debate on how to best manage patients with large CSMs. One option is to perform initial non-radical surgery to reduce the tumor size to a volume more compatible with GKS. Other options for patients with large tumors include low-dose stereotactic radiosurgery, fractionated radiosurgery, or external beam radiation therapy [3, 9, 10, 17].

For larger extensive cavernous sinus meningioma with maximum diameters >3 cm, especially those with significant visual affection, we usually advised microsurgery first essentially to decompress the optic pathway and debulking the tumor followed by GKS for residual or fractionated radiotherapy depending on patient's age, the tumor's location, extension, and tumor size.

Study strengths and limitations

The strengths of our study include a relatively homogenous patient population and regular follow-up documentations. In our study, there are a number of limitations that must be considered. First, the limited number of treated patients, one must be careful about comparing our outcomes directly with outcomes at other centers. Secondly, the short follow-up period (median follow-up period was 36 months).

Conclusions

GKS is a safe and reliable technique for the management of symptomatic benign confined cavernous sinus meningioma patients and could be used as the sole treatment and/or complementary treatment in symptomatic benign confined cavernous sinus meningioma. GKS allows good local tumor control and stabilization or improvement of the neurological deficits with reduced complication rate. Additional long-term analysis is required to determine further the long-term tumor control rate and differentiation between in-field or out-of field recurrences.

Competing Interests The authors declare that they have no competing interests, and certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial

interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. We declare that this is an original article and it was never published whole or in part or submitted elsewhere for review.

Author's contributions Raef Farouk Ahmed Hafez conceived, prepared, and reviewed the manuscript.

Magad S. Morgan participated in the design of the study.

Osama M. Fahmy participated in the design of the study.

All authors read and approved the manuscript.

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