Short Term Outcomes of Gamma Knife Radiosurgery for Skull Base Meningiomas in Iran

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Abstract
Introduction: Skull base meningiomas constitute a large proportion of the meningiomas, which are the most common benign brain tumors. The treatment of skull base meningiomas is specially challenging and controversial due to the proximity of these tumors to the vital brain structures. Radiosurgery is now emerging as an efficient alternative treatment modality which involves the ablation of tumor and the supplying blood vessels by a conformal dose of colliding gamma rays from 201 cobalt-60 sources.
Methods: We here report the first 100 meningioma cases treated in Iran using Leksell Gamma knife model C system. Gamma knife treatment was performed by means of 18 grays at 50% isodose.
Results: Seventy percent of the total patients referred to the Gamma knife center were skull base meningiomas, 40% of patients were new cases of meningioma and the remainder had undergone one or more microsurgery procdeures. There was no mortrality associated with treatment. The most common complications were severe headache (10 patients) and peritumoral brain edema (9 patients). There was 95% tumor control rate as indicated by stable or reduced tumor volume.
Conclusion: There was better clinical improvement in new cases relative to those with previous microsurgery. Our study shows that gamma knife could be considered as primary or adjuvant therapy in all cases of meningioma specially the skull base meningiomas.

Key words: Meningiomas, Skull base meningiomas, Gamma Knife Radiosurgery

Received: 5, Mar., 2005
Accepted: 20, Apr., 2005

Introduction
Skull base meningiomas constitute 30-40% of total cases of brain meningiomas; meningiomas by themselves have an annual incidence of 2 per 100,000.These tumors have generally an indolent natural history and present with minimal, mild symptoms even when the tumor is large. This indolent course spares the tumor uninvestigated until late stages by which time the tumor has invaded the dura matter and bone, making complete resection impossible in many cases. In addition, the adjacency of these tumors to the vital structures of the brain complicates the microsurgery of these tumors. Two types of complications arise during the surgery of these tumors: 1- Morbidity mainly due to the injury to major cranial nerves. 2-Mortality due to periopertive events such as injury to the carotid arteries. At present microsurgery is the treatment of choice in the management of large skull base meningiomas even when total resection is not plausible. However for small to medium sized meningiomas, radiosurgery offers a non-invasive and promising approach. Radiosurgery is particularly suitable for treatment of meningiomas, because they are well encapsulated, usually do not invade the brain, and are well defined by computed tomography or magnetic resonance imaging (MRI). The blood supply of the meningioma arises from the dura, which can be included in the treatment volume and its ablation causes tumor infarction and necrosis. Gamma knife radiosurgery is shown to have excellent long-term results in several studies in the treatment of the brain meningiomas including the skull base meningiomas.[1-4] In this report, we present the short term results of first 100 patients treated by the gamma-knife radiosurgery in Iran.

Methods

Between Jan 2004 and Jan 2005, 100 (55 male, 45 female, mean age=65, range=35-70) patients were referred to the Iran Gamma Knife center for treatment of brain meningioma. Of these population, 60% had undergone one or more microsurgery procedures, for whom a tissue diagnosis was available (Group-1). The remainder of the patients were new cases of the meningioma for whom the diagnosis was made solely on the radiological criteria (Group-2). Table 1 describes the tumor location in different patients. All the patients were treated on an outpatient basis. On the day of treatment, a Leksell Model C stereotactic frame was fixed to the patient's head under local anesthesia. A stereotactic enhanced MR imaging was performed to determine the stereotactic coordinates of the treatment target. Computerized dose-planning was performed using GammaPlan work-station. In all patients, radiosurgery was performed using the 201-source cobalt-60 Leksell gamma knife Model C (Elekta Instruments, Sweden). Multi-isocentric treatment was used in all patients, with the average number of 12 isocenters (range 3-25). The reference peripheral isodose was the 50% isodose in the majority of cases (range: 40-60%). The mean dose delivered to the tumour margin was 13Gy (10–18 Gy), using previous publications in meningioma radiosurgery.[4,6,7] Parameters of the treatment, particularly selection of doses, were adjusted to the individual tumor volume and evidence of relationship to critical neural structures. Table 2 shows the summary of treatment data for two distinct groups of patients.

Follow-up imaging: After treatment, patients were instructed to return for clinical evaluation (obtained by the referring physician or the treating neurosurgeon) and serial imaging at 6-months, 1 and 2 years.

Table 1: Tumor location in different patients.

Location	Percentage
In the skull base	
Cavernous sinus & parasellar	45
C.P.Angle	14
Petroclival	13
Olfactory and tuberculum sellae	4
In the other sites	
Parasagitall and falx	22
convexity	2
Orbital sheath and cavity	4
Others	2

Table 2: summary of treatment data for two distinct groups of patients.

Group	F/M	Age	Tumor size (Mean)	Marginal dose	Isodose
I	41/25	59	10-54 (26.7)	10-18 Gy (18Gy)	40-65%
II	21/22	64	7-30 (20.5)	10-18 Gy(14Gy)	40-65%
Total	62/45	61.5	7-54(23.6)	10-18Gy (15Gy)	40-65%

Results

Radiological Follow-up: Follow-up MRI studies and clinical analyses of patients were performed in 6-month intervals, followed by 12-month intervals after one year. Mean follow-up of 8 months (ranging from 1 to 12 months) revealed a decrease of the maximum tumor diameter in 21 patients (20%). No change of tumor size was observed in 83 patients (77%), whereas in 3 patients (3%) the meningioma increased in size. The overall tumor control rate was 97%. Group I presented 96.7% tumor control rate and group II revealed 93.3% tumor control rate. There was no statistical difference of the tumor control rate of skull base meningiomas that were radiosurgically treated, directly after microsurgical removal as a planned procedure, and those that received GKRS because of tumor recurrence after prior surgery.

Treatment related complications: Most frequent treatment related complication was headache occurring in the first 24 hours post-treatment. Peri-tumoral treatment brain edema (PTBE) occurred in 10% of patients, which was symptomatic in two patients.

Neurological Follow-up: Neurological deficits were present in 69% of the patients in the frst treatment group, whereas only 25% of the patients in the second group had neurological deficits. Neurological follow-up examinations showed the neurological status being unchanged in 74%, ameliorated in 25% and worsened in 5% of the patients. Comparing the two treatment groups, remarkable neurological improvement after GKRS was observed in group II (20%), whereas in group I the amelioration of symptoms was less frequent (15%), but most of the symptoms remained stable.

Table 3: Comprison in the neurologic recovery and tumor control in first (previous microsurgery) and new-case group

Group	Percent	Decrease in N.S. &S.	Stable N.S &S.	Increase in N.S &S	Decrease in tumor diameter	Stable tumor diameter	Increase in tumor diameter
I	64(71%)	16	44	4	12	50	2
II	43(39%)	11	30	2	9	33	1
Total	107(100%)	27(25%)	74(70%)	6(5%)	21(20%)	83(77%)	3(3%)

Table 4: Post gamma knife complications in all patients

Complication	Number of cases
Severe headache	10
PTBE	9 (2=symptomatic)
Increased paresia	3
Other C.N.	3
New seizure	2
Visual field and acuity problems	2

Table 5: Incidence of neurologic deficits in new and re-surgery cases before gammaknife radiosurgery.

Group/Neurologic status	*With Deficit*	*N.N.D.*
Skull Base Meningioma (76)	55(72%)	21(28%)
Other (31)	10(33%)	21(77%)

Table 6: Incidence of neurologic deficits in new and re-surgery cases after gammaknife radiosurgery.

Group/Neurologic status	*With Deficit*	*N.N.D.*
Group I (48)	33(69%)	15(31%)
GroupII (28)	7(25%)	21(75%)

Discussion

Meningiomas are usually benign and slow growing neoplasms mainly affecting women over 40 years. It is widely agreed that the best chance of cure is total surgical removal of the tumor and its nidus of origin. Skull base meningiomas are often particularly challenging, because they frequently are incompletely resectable, and surgery may be associated with significant morbidity. In skull base meningiomas, surgeons have to choose between “aggressive" tumor resection, with a substantial risk of neurological sequelae, or partial tumor removal with lower morbidity and a higher percentage of tumor progression. Two aspects of such tumors thus plague the neurosurgeon: 1- the tumor is histologically benign and causes relatively mild neurological impairment with which the patient learns to live, and 2- major surgery is needed for complete removal, with considerable risk of worsening of symptoms after the surgery. Therefore, two goals should be followed in treating the patient: first, to obtain tumor control, and then to minimize patient short- and long-term morbidity. These goals are especially true for patients with meningiomas located in the cavernous sinus and petroclival regions.

Meanwhile, tumors growing at the base of the skull present a variety of technical dilemmas for the surgeon. In cases with cavernous sinus involvement, the major problem is damage to the cranial nerves with consequent extraocular movement palsy. Damage to these nerves can lead to temporary or permanent diplopia in 20 to 50% of patients; although considred as a minor consequence of such surgery, this can be very disabling for the patient. In this series, radical surgical resection from the cavernous sinus was used only when paralysis of the oculomotor nerves was already present and the tumor did not infiltrate critical structures such as cranial nerves and the carotid artery at exploration. In petroclival meningiomas, the relation to small perforating arteries, brain stem, and cranial nerves is crucial. Complete dissection in the absence of an arachnoid plane may result in brain stem microinfarction. In these cases the brain stem should only be decompressed by piecemeal removal of tumor from lateral to medial, if necessary leaving a few millimeter thick tumor layers.

Most studies report that complete resection is obtained in only 50 to 70% of patients. The incidence of new postoperative cranial neuropathies after surgery varies from 19 to 86%, and combined cerebrospinal fluid leakage, infection, and other surgical morbidity rates approach 31% of patients. Radical surgery even in expert hands has a morbidity as high as 30-40% because of the way in which these tumors surround or infiltrate cranial nerves or brain stem. Furthermore, after complete resection the probability of recurrence has been reported to be 7-10% at 5 years and 20-22% at 10 years . Incomplete removal is associated with a much higher rate of recurrence of 26-37% at 5 years

and 55-74% at 10 years. In a series of 42 patients with cavernous sinus tumors, Sekhar et al reported total excision" in as high as 29 (69%). Although no patient was reported to have a permanent postoperative oculomotor nerve deficit, 33% had persistent trigeminal nerve deficits. Extraocular muscle function was impaired permanently in 12% of patients; 31% suffered other surgical complications, including wound infection and cerebrospinal fluid leakage. Goldsmith and colleagues and Maroon and colleagues provide evidence that surgery short of total removal reduces morbidity. When followed by adjuvant radiation techniques such as in this study (64% of all patients had undergone previous surgery), subtotal surgical removal is one method to obtain tumor control while preserving neurological function.[5]

In previous studies, Al-Mefty et al. reported a 62% incidence of new or worsened neurologic deficits following surgical resection of petroclival meningiomas in 13 patients. In describing their 6 year experience with 41 patients, Sekhar et al reported 2% mortality and 7% incidence of permanent postoperative major neurological changes after resection of meningiomas involving the clivus. Fifteen percent of these patients developed recurrent tumor growth after a follow-up ranging from 3-76 months. Two patients required reoperation and 9 radiotherapy. In a follow-up report there was permanent postoperative dysfunction in 12 of 75 patients (16%). Couldwell et al. reporting on the largest series of petroclival meningiomas to date noted a complication rate of 35% and mortality rate of 4%.[6]

Two other options also exist for the treatment of meningiomas; Radiotherapy and radiosurgery. These two options differ considerably in the definition of outcomes: Local control after resection implies complete removal of the tumor without evidence of recurrence on follow-up evaluations. In contrast, local control after radiosurgery or radiotherapy implies stabilization of the tumor with no evidence of progression on follow-up evaluations.

Several recent series have reported that postoperative external beam radiation therapy improves long-term local control of subtotally resected or recurrent meningiomas. It has now been consistently shown that meningioma regrowth can be prevented in the majority of patients by the use of radiation therapy. An example is the report by Goldsmith et al. with excellent results using radiotherapy following partial tumor removal with recurrence rate of 29% compared with 74% if there was no radiotherapy.[6,7]

However, fractionated RT of meningiomas imposes risks of long-term side effects, such as loss of vision, pituitary dysfunction, delayed radiation-induced injury of the brain, and the development of secondary neoplasms after irradiation for benign CNS tumors .Benign tumors may regress partially, but they rarely disappear after successful irradiation.

Favorable results have also been shown with stereotactic single high-dose radiation therapy for intracranial meningiomas using either linear accelerator or gamma knife techniques. Duma et al. reported a 0% incidence of tumor progression and a 6% incidence of new or worsened cranial nerve deficits following gamma knife radiosurgery in 34 patients with cavernous sinus meningiomas. For a series of 36 skull base meningiomas with linear accelerator radiosurgery, Villavicencio et al. demonstrated a 95% actuarial freedom from progression rate after a median imaging follow-up of 26 months (range, 6-66 months). Five patients (9%) developed new or worsened neurological deficits during the clinical follow-up interval (median, 28 months). Kondziolka and colleagues previously reported a 3-year actuarial tumor control rate of 96% in 50 meningioma patients undergoing gamma knife radio-surgery. Alexander et al. performed stereotactic radiosurgery on ninety-nine patients with meningiomas. 91% of these lesions were located within the skull base. Three of five patients who were followed for more than 4 years after radiosurgery had a decrease in tumor size. Eleven patients were evaluated between 3 and 4 years after radiosurgery; six had tumor shrinkage and five had no change. Thirty patients were evaluated between 2 and 3 years after radiosurgery; 10 had tumor shrinkage and 20 had unchanged tumor sizes. A decrease in tumor size was visible in some patients as early as 3 months after radiosurgery. Lunsford and colleagues 37] reported a 4-year actuarial tumor control rate of 92%, defined as either growth cessation or tumor volume reduction, for 94 benign meningiomas.[5,8]

Comparing these studies, it can be deducted that GKRS is an excellent therapeutic option for the treatment of skull base meningiomas, and should be considered in suitable cases whenever possible. Simillar to the above statistics of other gamma knife centers, the referred patients to our center were mostly skull base tumors.

Three different factors were considered in selecting the cases for gamma knife treatment in our patients: 1-tumor size, 2-possibility of the surgical resectibility of the tumor and 3- adjacency to critical structures and the chance of preservation of the normal brain tissues. Using these criteria, we had a short-term tumor control rate of more than 95%, which was predictable due to the comparability of the treatment procedure and selection data to the international studies.

Previous studies have shown that complications after GKS for meningiomas would be found in 25% (29% in our study) of the treated cases.[9]. The complications are divided into peri-tumor imaging changes on follow up MRI and cranial nerve dysfunction. Peritumourous imaging changes includes newly developed imaging changes and aggravation of pre-existing imaging changes on follow up MRI after GKS. These imaging changes are probably explained by post-radiosurgical peri-tumoral edema. It is noteworthy to mention that patients with cerebral hemispheric meningiomas of convexity, parasagital region, or falx cerebri have a higher incidence of peri-tumor imaging changes after GKS than those with skull base meningiomas, so it is rational that these tumors undergo microsurgery unless strict indications for radiosurery are met.

Although ideally an excellent method, GKRS does have its own limitations. One is the size (tumor diameter should be less than 3 mm); the precise definition of the target may be another limitation, particularly with en-plaque clivus meningiomas, or tentorium and tentorial edge extensions of the tumor. Sometimes, the main bulk of the meningioma is compatible with radiosurgical treatment but pathological contrast enhancement along the free edge of the tentorium cannot be totally included in the target and hence limits long term tumor control. Brain stem mass effect and encasement of basilar perforators are also important considerations, with possible risk of brain stem injury as a result of microvascular ischemia.

In conclusion, GKS for intracranial meningiomas is a safe and effective form of primary or adjuvant treatment after incomplete surgical resection.

Figure 1: MRI imaging in a case of Meningioma before and six months after the surgery.

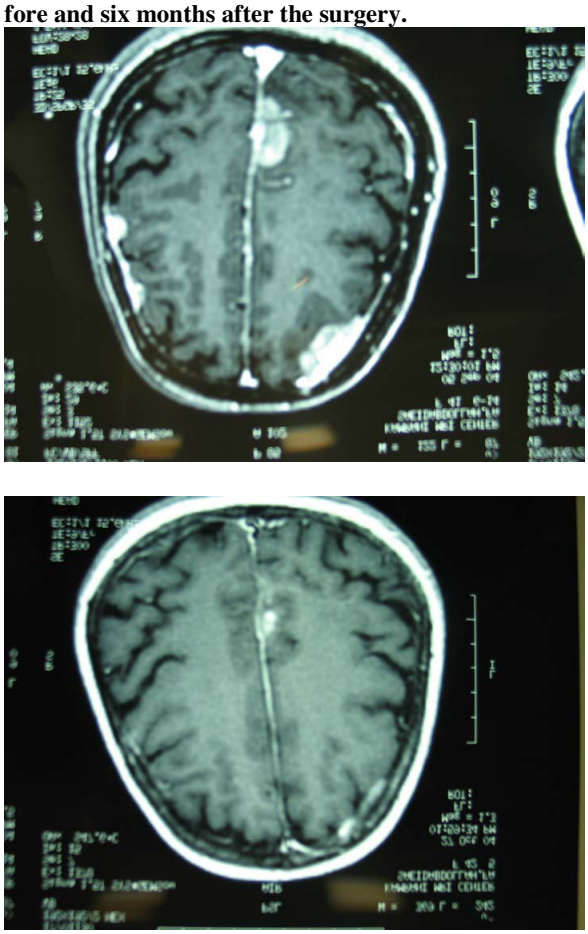
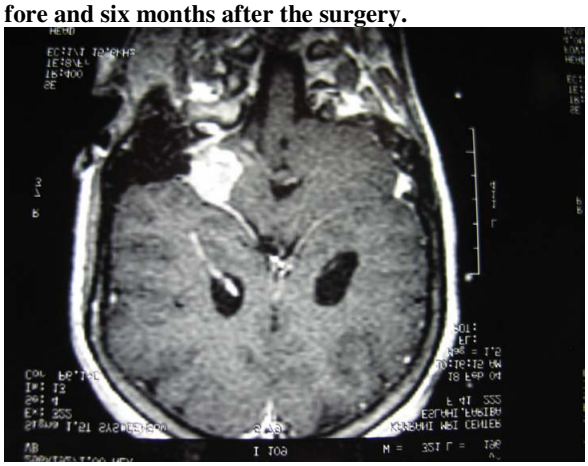
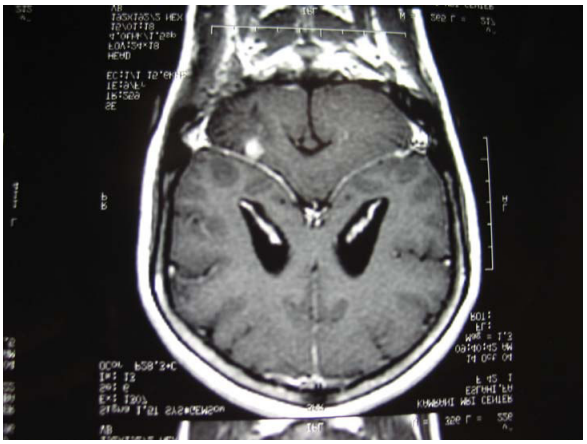


Figure 2: MRI imaging in a case of Meningioma before and six months after the surgery.





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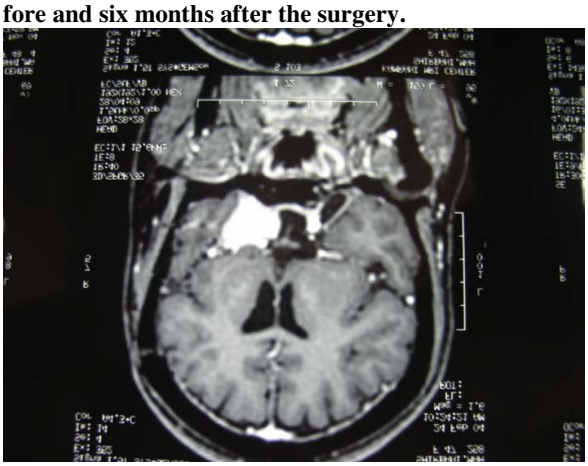

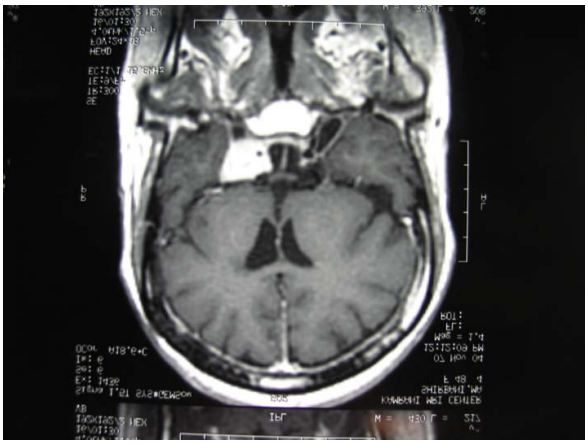

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