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CLINICAL STUDY/PATIENT STUDY

Cavernous sinus meningiomas: a large LINAC radiosurgery series

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Abstract One hundred and seventeen patients with cavernous sinus meningiomas had LINAC radiosurgery at our institution in the period 1993–2007. Six cases were lost and 9 had less than 1 year follow up. The remaining 102 patients were prospectively followed up at 1 y intervals with clinical, neuro-ophthalmological and MRI examinations. Patients' age ranged between 31 and 86 years (mean 57). Seventy percent were females. The mean tumor volume was 7 cc. Thirty-three patients had previous microsurgery. Tumors were defined with high resolution MRI obtained 1–2 days before treatment and fused to stereotactic CT. Treatment was mostly delivered through a minimultileaf collimator and multiple dynamic arcs. The minimal dose to the tumor margin was 12–17.5 Gy (mean 13.5) encompassed by the 80% isodose shell. Radiation dose to the optic apparatus was kept below 10 Gy. Follow up ranged from 12 to 180 months (mean 67 months). Tumor control (lack of growth) was 98% (58% of the tumors reduced their volumes). Sixty-four patients presented with cranial nerve deficit. Thirty-nine percent improved or resolved following radiosurgery. Cranial neuropathy had significantly higher resolution rates when radiosurgery was performed early (<1 year) after its appearance (53% as opposed to 26%) even in patients with deficits post surgery. Complications were seen in five patients (1 with deafferentation pain, 1 with facial hypesthesia, 1 with visual loss and 2 with partial VI neuropathy). Radiosurgery had a high control rate for meningiomas of the cavernous sinus with few and mild complications. Cranial neuropathy can be solved by treatment, particularly those of recent onset.

Keywords Cavernous sinus meningioma · LINAC radiosurgery · Cranial neuropathy · Radiation dose

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Introduction

Management of meningiomas of the cranial base involving the cavernous sinus has represented a formidable challenge. For decades the brisk bleeding from its venous channels prevented surgeons from attacking tumors in this space.

Owing to advances in microsurgical techniques and more precise knowledge of the cavernous sinus anatomy, technical reports and increasingly large surgical series appeared in the literature of the late 1980s and 1990s. Still, even in experienced hands results remained less than satisfactory.

Morbidity from injury to the carotid artery, or more frequently from damage to the nerves in the cavernous sinus space are reportedly high, ranging from 6 to 42% [2–4, 7, 11, 15]. Mortality rates are up to 10% [2–4, 12, 20].

Moreover, because of tumor infiltration of central structures, such as the carotid artery or nerves [15, 17], surgical resection of meningiomas in the cavernous space

is frequently incomplete [1, 3, 14, 20] resulting in a high incidence of recurrence [2, 3, 14]. Since these tumors are by and large histologically benign, a poor functional outcome after treatment results in a high cost to patient and community.

The impulse for microsurgery of the cavernous sinus was more or less concomitant with the appearance of radiosurgery as an increasingly available treatment technique in the late 1980s. Although radiosurgery had been in clinical use in a handful of places since the late 1960s, its transformation into a mainstream neurosurgical weapon had to await the introduction of two important technologies: three dimensional imaging of the brain (first Computed Tomography [CT] and later Magnetic Resonance Imaging [MRI]), and the microcomputer. These inventions fueled the rapid evolution of radiosurgery by enabling the direct visualization of intracranial tumors, and the execution of three-dimensional dosimetry with reasonable speed. The potential of radiosurgery for treating tumors in the cavernous sinus appeared obvious and we started offering this option early in our experience. In a previous report from 2002, we detailed our preliminary results in a cohort of 44 patients with a mean follow up of 3 years [23]. In the present communication a larger population of patients (117) with a mean follow up of close to 6 years, enlarges the database for analysis.

Patients and methods

From 1993 through 2007, 462 patients with meningiomas underwent LINAC radiosurgery at the Chaim Sheba Medical Center. Of those, 117 had tumors involving predominantly the cavernous sinus. At the time of this writing, 102 patients who had completed 12–180 months of follow up (mean 67 months) were available for analysis, and they represent the body of this series.

Patients' age ranged from 31 to 86 years (mean 57). Seventy-two (70%) were females. Thirty-five patients had histological proof of their diagnosis, from tissue obtained during previous attempts at surgical removal. The rest of the cohort was diagnosed by imaging alone. Patients without previous surgery were diagnosed as harboring meningiomas when their MRI scans revealed a lesion with sharp margins that was either iso or hypointense on T1-weighted images, iso or slightly hypertense in T2-weighted images, and showed homogeneous enhancement in post-contrast images. All patients had at least two MRI studies, compatible with a slow growing tumor, before treatment.

Presentation

Twenty-seven patients had no neurological deficit attributable to the cavernous sinus meningioma. However, only eight of them were completely asymptomatic and had their cavernous sinus tumor detected by cranial imaging done for unrelated complaints. Seventeen patients had moderate to severe chronic headaches, and two other had troublesome dizziness which prompted investigation. Headaches were a chief complaint in 18 other patients who had previous surgery (2), cranial nerve deficit (6), or both (7).

Sixty-four patients (62%) had functional deficit of cranial nerves 2 through 6 (sixth nerve in 39, third nerve in 17, fourth nerve in 7, facial hypesthesia in 11, orbital or facial pain in 9, and unilateral visual loss in 12). One patient presented with inappropriate antidiuretic hormone secretion, and three had unilateral proptosis. Of the 35 patients who had undergone previous surgery, 24 (69%) were left with a new neurological deficit.

Treatment parameters

Patients were admitted to the neurosurgical department on the morning of their treatment day. Under local anesthesia, a Brown–Roberts–Wells stereotactic base ring (Radionics Integra, Plainsboro, New Jersey) was applied bedside to the patient's head, and a stereotactic CT scan was obtained with fine axial cuts (1 mm) of the whole head. The imaging data were transferred to the treatment-planning computer. MRI-to-CT fusion software became available at our center in 1998, and since then, MRI has been obtained for all treated patients ($n = 68$) 1–2 days before treatment. MRI protocols were changed over the years in pace with evolutionary changes in MRI technology. Currently, our MRI protocol for cavernous sinus tumors includes T1 weighted, contrast enhanced, fat suppressed 1–2 mm-thick axial cuts with no gap, and a high resolution CISS (constructive interference in steady state) axial series, again with 1–2 mm cuts. These protocols provide exquisite definition of tumor boundaries within the cavernous sinus and orbit. The CISS images beautifully depict the cranial nerves (Fig. 1a, b). Treatment planning was performed with the goal of achieving a complete conformal coverage of the tumor at the highest possible isodose shell. Diverse optimization tools were used for this purpose, including differential arc weighting, arc span and spacing, and for the M3, optimized collimator rotation, and manual leaf stop-position planning. Forty-four patients were treated with multiple non-coplanar arcs using cylindrical collimators ranging from 10 to 25 mm in diameter and with 1 to 9 isocenters (mean, 3 isocenters). The last 58 patients were treated with a single conformal isocenter using a minimultileaf collimator (M3; BrainLab, Munich, Germany). Twenty-six of them with multiple [9–11] fixed conformal beams and the last 32 with the dynamic conformal rotation paradigm. Regardless of technique, all doses were normalized to 100%. The prescription dose was delivered to the 60–80% isodose line

(mean, 68%) in patients treated with cylindrical collimators, and to the 80% in those treated with a single conformal isocenter. Doses ranged between 12 and 17.5 Gy (mean, 13.5 Gy). Median tumor volume was 7.2 cm^3 (range 0.61–23 cm^3). The prescription dose was adjusted whenever necessary to limit the dose to the hypothalamus and functional anterior optic pathways to 10 Gy or less. All patients were discharged immediately after treatment.

Follow-up

All patients were followed up prospectively yearly with neurological examinations, contrast-enhanced MRI studies, neuro-ophthalmological assessment, and measurement of serum hormonal levels related to the hypothalamic–pituitary axis. Tumor size before and after radiosurgery was assessed by measuring the contrast-enhanced margins in the three standard MRI planes. Tumor size reduction was

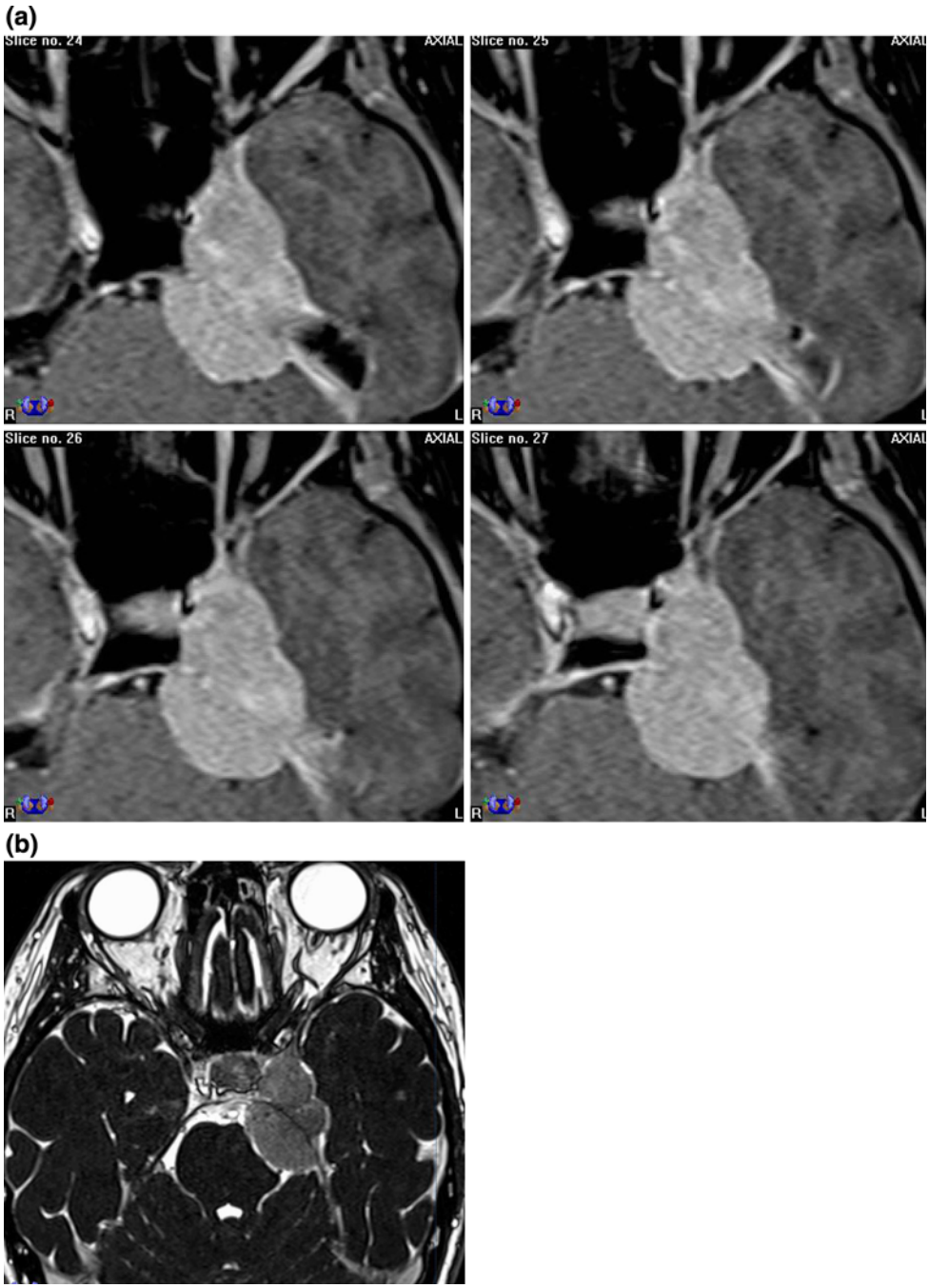

Fig. 1 **a** T1 weighted, gadolinium-enhanced axial images of a cavernous sinus meningioma obtained with a fat-suppression protocol. With the fat suppression protocol, the enhanced tumor shows clear boundaries against the normal contents of the cavernous sinus, which are displaced anteriorly and medially. **b** T2 weighted CISS axial images of the same tumor exquisitely define the tumor boundaries and the cranial nerves as they course the cavernous sinus

defined as a decrease of at least 10% in any dimension. Tumor enlargement of more than 10% in any dimension was defined as tumor progression. Tumors of decreased or unchanged size were defined as controlled.

Results

Tumor control rates

All patients were available for follow-up at 12–180 months after treatment (mean, 68 months; median, 60 months). The actuarial 5-year control rate was 98%. Fifty-nine patients (58%) had a volume reduction of 20–95%. Forty-one (40%) had stable tumor volumes at the end of follow-up. Two tumors grew. In one patient, tumor growth was seen on the MRI performed 36 months after treatment. The patient remained asymptomatic, and the tumor later stabilized until the patient's death, 54 months after treatment, from complications of acute renal failure. The second tumor growth was detected 84 months after treatment. This patient had bilateral cavernous sinus meningiomas with multiple resections on both sides and gamma knife surgery for the contralateral tumor. After his radiosurgical failure he has recently been retreated with fractionated stereotactic radiation without tissue sampling.

Sixty-three patients in this cohort had extended follow up of 60–180 months (mean 93 months). In this subpopulation, tumor volume reduction was seen in 65%. In patients with less than 5 years follow up (12–48 months, mean 31 months) the volume reduction rate was 43%. This difference was significant ($P < 0.05$ chi square test).

Acute side effects

A few patients complained of headaches persisting several days, and two had vomiting for up to 24 h. All the patients returned to their normal activities 2–3 days after radiosurgery.

Transient complications

One patient had persistent headaches lasting more than 2 years which subsided thereafter. Two patients had transient oculomotor neuropathies during the first year following radiosurgery. In both the deficit lasted for a few weeks and resolved spontaneously. One patient had transient facial hypesthesia.

Permanent complications

One patient developed facial hypesthesia. Two patients complained of new facial pain, one fully controlled with carbamazepine, and another, with deafferentiation features, is only partially controlled with medication. One patient had diplopia due to IVth nerve paresis. One patient developed a visual field defect (upper homonymous quadrantopsia) 18 months after radiosurgery.

Two patients developed communicating hydrocephalus (one at 6 months, and one at 2 years after radiosurgery) which required ventriculoperitoneal shunting. One patient with a partially exophytic tumor involving the temporal fossa, had symptomatic temporal lobe edema 1 year after radiosurgery and required partial resection of her tumor. When seen 6 years after radiosurgery, she had a normal neurological status. Her MRI scan showed a small intracavernous tumor and no residual temporal lobe pathology.

Overall, four patients had a new lasting neurological deficit (facial hypesthesia or pain in two, trochlear neuropathy in one, and visual defect in one), for an incidence of 4% in persistent neurological complications. No patient has developed a new pituitary insufficiency.

Outcome of existing cranial neuropathies

Sixty-four patients had cranial nerve deficits attributable to their cavernous sinus tumors. Several of them had multiple neuropathies.

Optic nerve: 12 patients had deficits at presentation, 5 of them had no light perception (all following surgery). Seven had moderate to severe visual loss (five of them following surgery). Of these, two improved (Fig. 2) and one deteriorated.

Third nerve: Deficits were present in 17 patients (partial in 8). Improvement or resolution was seen in 6 (35%).

Trochlear nerve: Seven patients had 4th cranial nerve palsy. In six of them it was a sequel of surgery. None of them improved. The only case unrelated to craniotomy resolved following radiosurgery.

Abducens nerve: This was the most frequent cranial neuropathy at presentation (39 patients). Resolution or improvement was seen in 11 (28%). In one patient a partial deficit deteriorated to full palsy.

Trigeminal nerve: Sensory deficit was present in 11 of which 4 (36%) improved after treatment; 9 patients had facial pain, improving in 3 of them (33%). Six patients had parenthesis, which cleared in 5 of them.

In summary: Of 101 cranial neuropathies, improvement or resolution was seen in 32 (32%). Deficits of early onset (less than 1 year before radiosurgery) had a significantly higher rate of resolution: in 43 cranial neuropathies of early onset, 21 improved or resolved (49%), whereas of 58 deficits lasting for more than 1 year, improvement was seen in only 11 (19%). This difference was statistically significant ($P < 0.03$ chi square test).

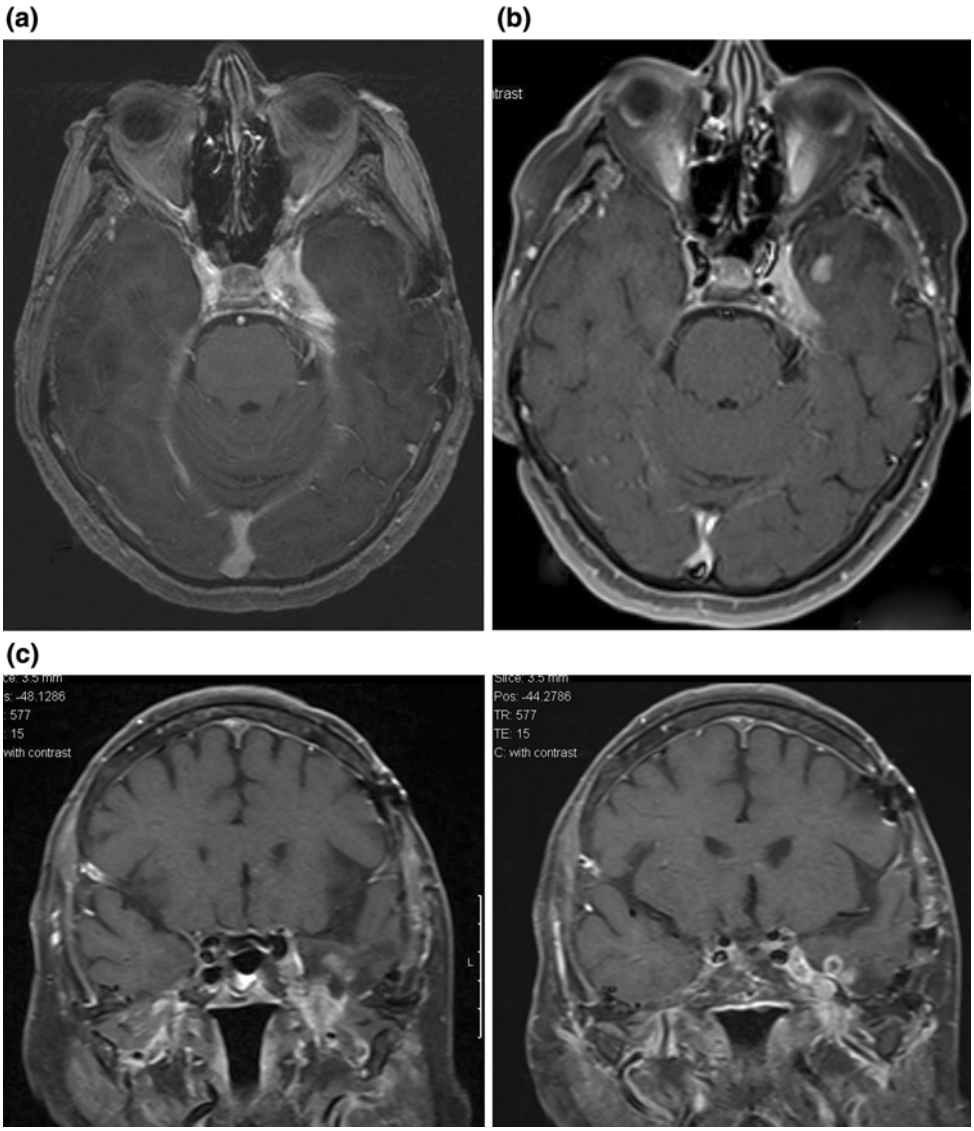

Fig. 2 **a** This cavernous sinus meningioma was treated with radiosurgery in 2003. **b** The same patient in 2008 with a slightly smaller tumor. An enhancing node is seen besides the cavernous sinus. **c** The coronal images show that the enhancing node stems from a previously undetected infratemporal extension of the original cavernous sinus meningioma. In the image on the *right* it is clear that the new paracavernous tumor does not extend from the lateral cavernous wall. The image on the *left* shows that the node is continuous with the infratemporal tumor

Previous surgery affected negatively the chance to recover from cranial nerve deficits: of 47 deficits in patients who had surgery, 9 improved (19%). Conversely, of 54 deficits in patients without surgery, 23 improved (43%, $P = 0.012$, chi-square test).

It could be argued that post surgery patients arrived to radiosurgery with greater delay due to the need to recover and get reassessment. Nonetheless, in 12 post-surgical deficits lasting for less than 1 year, improvement was seen in just 3 (25%). Of 35 post surgical deficits lasting for more than 1 year, improvement registered in 6 (17%). Conversely, in patients without surgery, deficits lasting less than 1 year improved in 58% (18 of 31), whereas deficits lasting for >1 year improved in 23% (5 of 22). Accordingly, for patients treated with radiosurgery within 1 year of onset of cranial nerve deficit, non-surgical patients fared better than surgical patients. This difference reached statistical significance ($P = 0.052$)

Discussion

Microsurgery of the cavernous sinus peaked in the late 1980s and early 1990s, following the seminal efforts by Dolenc [5, 6].

Early enthusiasm chilled when over time it became clear that complete removal of intrinsic cavernous sinus meningiomas is relatively rare, tumor re growth is the rule with incomplete resection, and that surgery takes a high toll in terms of cranial nerve deficits. Proof of this is the meager number of series on resection of cavernous sinus meningiomas published in the last years. Al-Mefty and co-workers [9] reported in 2003 on his personal series of 163 patients.

Total removal was achieved in 71 cases (44%). In the latter group, tumor recurrence was observed in 7%. In the cases with partial resection re-growth was registered in 57%. No information was given on their incidence of

neurological deficits, but the authors proclaim that "the majority of neuropathies in these patients exist at presentation, whereas a minority develop permanently after surgery, and many of those affect sensory function or can be treated with strabismus surgery". Strabismus surgery, however, does not correct oculomotor deficit. It can only improve in some cases its cosmetic effect. Facial sensory deficits are a minor deficit only when not complicated by deafferentation pain.

Sindou et al. [22] reported in 2007 on a series of 100 patients with cavernous sinus meningiomas with extrasinusal extension (supra, lateral, or posterior). Follow up ranged from 3 to 20 years (mean 8.3 years). The appearance or aggravation of disorders in vision, ocular motility, or trigeminal function occurred in 19, 29, and 24% of patients respectively, with a significantly higher rate of complications when resection was performed inside the cavernous sinus. Gross-total removal of both the extra and intracavernous portions was achieved in 12 patients, removal of the extracavernous portions with only a partial resection of the intracavernous portion in 28 patients, and removal only of the extracavernous portions was performed in 60 patients. Mortality was 5%. Interestingly, tumor regrowth was observed only in 11 of the 82 surviving patients with subtotal removal. The authors concluded that there is no oncological benefit to resection of intracavernous tumor components. It is of note that their low re-growth rate is in conflict with data from other surgical series.

The data presented in these contemporary series reaffirm the high cost in terms of mortality and morbidity of microsurgery of cavernous sinus meningiomas.

In a previous publication by our group [23] the excellent results afforded by radiosurgery of cavernous sinus meningiomas were documented in the short term (mean follow up of 36 months). We stressed the need for more extended follow up to assess the role of radiosurgery in the definitive control of these difficult tumors.

Our current series has a mean follow up of 67 months. In 59 patients, follow up has reached 5–15 years (mean 107 months). This cohort allows analysis of late results and it is certainly one of the series with the longest follow up so far reported.

Volume control

Early and late tumor control rate were 98%. Tumors shrank in 58% of the patients and remained stable in 40%. Control rates ranging from 87 to 98% have been reported by large gamma knife series [8, 18, 19].

As would be expected, with longer follow up, more tumors were seen to shrink. In the 36 patients with stable tumor size, mean follow up was 57 months. In those reduced ($n = 59$), follow up was at a mean of 74 months.

Two patients showed tumor growth detected at 36 and 84 months post treatment. The early growing tumor remained then stationary until the patient's demise from unrelated causes 2 years later. The late recurrence is a cautionary event. It occurred in a patient whose tumor, although histologically benign, had a very aggressive course. This male had a bilateral cavernous sinus meningioma. The left sided, larger tumor, was fist partially resected, then treated with gamma knife surgery, and upon massive relapse was completely exenterated with the whole contents of the cavernous sinus (with a concurrent supraclinoid carotid bypass). The right sided tumor treated by us, grew outside of the cavernous sinus into the temporal fossa and retroclival area. We have re-treated it with fractionated stereotactic radiotherapy recently.

After closing this series for analysis, we have observed two patients in whom tumors grew in the temporal fossa adjacent to the cavernous sinus, from untreated infra-temporal extensions of the original cavernous sinus meningioma. The new tumors apparently reentered the cranium from the pterigoid fossa. The infratemporal extensions were present in retrospect at the time of radiosurgery (Fig. 2).

Tumor growth outside of the treatment volume is frequently mentioned as a reason for failure of radiosurgery in other series [8].

It is of note that tumor control rates have remained unchanged over time in spite of changes in quality of imaging, and radiosurgical dose.

Tumor delineation of our first 34 cases relied on stereotactic CT imaging alone. Since 1998, when MRI to CT fusion became available, tumors have been outlined on MRI (83 cases). It may be argued that MRI has substantially improved our ability to define tumor boundaries within the cavernous sinus only in the last 3–4 years, when high resolution T2 weighted imaging (CISS) and T1 fat-suppression became available in our center. The main contribution of MRI has been to enable the definition of surrounding anatomy, and particularly the hypophysis, the stalk, the optic apparatus, and the hippocampus, structures to which we try to reduce radiation exposure.

The optic apparatus receives obviously the highest consideration. Since radiation damage to this structure results in irreversible visual loss, radiation exposure of the optic pathways is the main factor limiting the marginal dose to the tumor. The issue of how much irradiation may be safely applied in a single session to the optic nerves and chiasm is not fully settled.

The most widely cited paper dealing with dose limits for radiation-induced optic neuropathy is a joint publication by the Harvard and Pittsburgh groups, from 1993 [25]. In that retrospective analysis, the authors reviewed a total of 62 patients treated for lesions around the cavernous sinus with

both a gamma knife and a linear accelerator. They calculated the radiation exposure of the optic nerves and observed a 24% incidence of optic neuropathy in cases wherein the radiation dose exceeded 8 Gy, as compared to 0% when the dose to the optic apparatus was below 8 Gy. That 8 Gy golden number has hold. However it is to note that all the assessments regarding optic nerve exposure in that paper were done based on CT imaging alone, and consequently were subject to gross errors due to poor visualization of the optic nerves. We have always regarded 10 Gy as our maximal exposure limit to the optic nerves and chiasm. With this limit respected, optic neuropathy has occurred in two cases of pituitary tumors in our series (unpublished data). If we considered the whole cohort of patients with lesions in and around the cavernous sinus, the incidence of optic neuropathy is below 1% (2 cases in 234 patients at risk). Higher doses to the optic nerves (12 Gy) have been given routinely by other groups with reportedly no ill effect [10].

Over the years, in an attempt to improve the therapeutic index of radiosurgery, doses have been modified for most pathologies, Meningiomas have not been an exception, and in this series we started out with marginal doses as high as 17.5 Gy. In the last 5 years 13 Gy has become our standard dose regardless of the tumor mass. This relatively low marginal dose enables treatment of rather large tumors in the area while preserving the 10 Gy limit to the optic nerves.

Our group was an early adopter of the micro-multileaf collimator (M3, BrainLab, Munich, Germany) as the standard radiation delivery tool (since 1998). The introduction of the M3 profoundly transformed the practice of LINAC radiosurgery. Treatment planning and radiation delivery have been greatly simplified (single isocenter). This is usually accomplished with high reliability in execution, and tight conformality of the treatment dose to the tumor margins.

This apparatus also allows a more homogenous radiation distribution across the target (since in almost every situation the marginal (treatment) dose is the 80–90% of the maximum). Before the introduction of the M3, LINAC radiosurgery for cavernous sinus meningiomas consistently required the use of multiple isocenters with cylindrical collimation to conform the dose distribution to the irregular shape of these tumors. For dosimetric reasons, multiple isocenter treatment demands that the dose to the tumor margin be prescribed to lower isodose shells (typically 50–60%). The lower the marginal dose, the more dose inhomogeneity is created within the tumor. In gamma knife routine, treatment to the 50% isodose line is the rule, with zones of the tumor absorbing twice the marginal dose. In most tumors it is really not relevant how much more radiation is absorbed within the target, since our intention is to eliminate it. In the cavernous sinus however, as the tumor encases normal (functional) tissue (neural and vascular structures) which we want to preserve, radiation definitely has a safety limit. Attesting this, carotid artery occlusion following radiosurgery for cavernous sinus lesions has been documented by gamma knife groups.

A report from the Mayo Clinic [24] included 60 meningiomas involving the cavernous sinus. Two patients exhibited ischemic events 35 and 60 months after radiosurgery. One of them had a 50% internal carotid artery (ICA) stenosis, and the other had a complete occlusion of the intracavernous ICA. Both patients developed permanent cerebroischemic neurological deficits. Radiation doses were higher than in our series (median tumor marginal dose 16 Gy; median maximal tumor dose, 32 Gy). The authors noted that in both patients, the radiation dose to the carotid vessels exceeded 25 Gy. One case of carotid occlusion was observed by Regis and associates, in a series from 2000 [21].

Because ICA stenosis or occlusion can stem from tumor invading the carotid wall, the causal relationship between radiosurgical irradiation and ICA occlusion remains unproven. Nevertheless, it should be noted that external carotid stenosis is not uncommon after high dose fractionated radiotherapy, and its clinical presentation may be delayed [16].

Functional results

Radiosurgery stands strong as the only treatment modality that consistently improves functional deficits produced by cavernous sinus meningiomas. As detailed above, cranial neuropathies improved in roughly a third of the patients. When radiosurgery was given early after the onset of the deficit (<1 year) and when surgery was not performed, close to 60% of the deficits improved or resolved. Improvement appeared early after treatment, in some cases in the first few weeks, which cannot be related to changes in the volume of the tumor. Similar functional outcomes have been reported recently by the University of Florida LINAC radiosurgery group [13].

Conclusions

This series of Linear Accelerator radiosurgery in more than 100 patients with cavernous sinus meningiomas is the largest in the literature to date. Our data strongly support the notion that early radiosurgery greatly increases the chance of improving cranial nerve deficits that are not surgically induced.

Our experience confirms that in the short and long term, radiosurgery affords excellent control for these difficult

tumors, a very low incidence of complications, and a high rate of improvement in pre-treatment cranial nerve impairment.

Radiosurgery can thus be regarded as the treatment of choice for cavernous sinus meningiomas.

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