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Chapter XXII

Optimally Invasive Skull Base Surgery for Large Benign Tumors

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ABSTRACT

Introduction: The management of large benign skull base lesions, such as vestibular schwanommas, meningiomas or pituitary adenomas remains challenging, with microsurgery seen as the main treatment option and complete resection as the primary goal. While previous studies have shown the value of complete resection for good long-term tumor outcome, the postoperative neurological results remain suboptimal. The concept of a "combined approach", as defined below, was developed with a view of preservation or amelioration of neurological outcome as the primary goal while maintaining optimal long-term tumor control. This chapter analyses our series with a review of the treatment outcomes from literature for these tumors.

Material: Between 2010 and 2012, we treated 33 patients, male/female 11/22, with ages between 12.73 and 73.41 years (mean 53.98). There were 11 patients with vestibular schwanommas, 14 with meningiomas (5 petroclival and 9 clinoidal) and 8 with pituitary adenomas. We analyzed the clinical presentation of these patients, as well as audiograms, ophthalmological and endocrinological tests, as indicated. In this context, treatment planning is performed prior to surgery with a combination of techniques namely transcranial microsurgical or endoscopic trans-nasal approach or both, with a view of performing a subtotal tumor resection. The residual part of the tumor, which is frequently

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adherent to cranial nerves, brainstem or vascular structures, is then treated with Gamma knife radiosurgery. The postoperative outcome with respect to neurological/ endocrinological function and tumor control was analyzed.

Results: Patients with vestibular schwanomma underwent subtotal surgery with facial nerve monitoring through a retrosigmoid approach. There were no post-operative facial nerve deficits. Of the 3 patients whom had useful hearing pre-operatively, this improved in 2 and remained stable in 1. After a period of 3 to 6 months, the residual tumor attached to the facial and cochlear nerves was treated with RS. Nine patients with clinoidal meningiomas underwent subtotal resection of the tumor, and one patient also underwent a staged endonasal resection. The cavernous sinus component of the tumor was later treated with RS. The visual status normalized in four and improved in 3. Of the five patients who underwent petroclival meningioma surgery, 3 had House-Brackmann (HB) grade 2 facial function that recovered completely while one continues to have HB grade 4 facial deficit following surgery. Of the 8 patients with pituitary macroadenoma, 2 had GH secreting tumors while the others were non-functional. Seven patients underwent endoscope assisted trans-sphenoidal microsurgery, while one patient had a staged trans-cranial and trans-sphenoidal surgery. While visual status improved/normalized in 4 patients, no patient had worsening of visual or occulomotor function. Two patients had transient diabetes insipidus following surgery. No additional neural dysfunction or tumor progression was noted at latest follow up following RS.

Conclusion: Our data suggest that combined approaches have an excellent clinical outcome with respect to preservation or improvement of neurological function. Microsurgery (transcranial and/or endoscopic transnasal) and radiosurgery are complementary treatment modalities. As long-term results emerge, this multimodal treatment paradigm could become the standard of care for the "optimally invasive" management of difficult skull-base benign tumors.

Introduction

Surgery for large benign skull-base tumors has evolved greatly in the last three decades. Initially deemed inoperable, the description of novel skull-base approaches led many surgeons to attempt a complete resection of these tumors. The use of image guidance, intraoperative electrophysiological monitoring and better techniques of skull-base repair have made these surgeries safer. Despite the large experience accumulated over several decades, the neurological morbidity associated with these aggressive approaches still remains significant and considered inevitable. On the other hand, several large series of radiosurgery for the treatment of small benign skull-base lesions have demonstrated adequate tumor control along with markedly diminished neurological morbidity and improved preservation of functions. In the last decade, endoscopic skull-base surgery has also emerged as an alternate surgical approach for many of these lesions. This chapter deals with our approach towards these lesions, wherein we prefer to combine skull-base microsurgical techniques with endoscopic surgery and radiosurgery in a tailored fashion based on patient and tumor characteristics, with a view to optimize the preservation of neurological functions. This series of patients include only those cases where this multimodal therapy was utilized in a manner where the precise strategy was decided prior to surgery with respect to the combination of techniques used. This chapter deals specifically with the use of this strategy for the treatment of four groups of tumors for which its application has gained interest predominantly, namely

vestibular schwannomas, petroclival meningiomas, clinoidal meningiomas, and pituitary adenomas.

The Principle of Combined Approaches

Combined approaches are mostly relevantated to the management of large benign skull-base lesions. In these particularly challenging cases, surgery alone cannot be radical without a high risk for neurological functions, and radiosurgery cannot be used safely as a first line of treatment because the risks of radiation-induced complications are high. Indeed, radiosurgery bears 2 intrinsic risks that are related to the size of the lesion, which in turn and that, limits the treatment of lesions that are "too large". One is related to the fall-off of dose outside of the target area.; W when the volume of the lesion increases, the quality of the dose gradient decreases, and the dose fall-off becomes worse.; T this will increase the so-called area of penumbra around the target, thus increasing the dose outside of the target, and therefore resulting in radiation-induced side-effects. The second is related to the temporary swelling of the tumor that may be generated by radiosurgery in the weeks or months following the treatment. I; in larger lesions, this may have clinical consequences due to an increase in the mass effect. Thus, in large lesions presenting with mass effect, especially when they interface or impinge with critical structures such as the brainstem, or even in small lesions in contact with radiosensitive structures such as the optic apparatus, radiosurgery cannot be used as a primary treatment and combined approaches will be offered, if radical surgery bears too high functional risks.

The surgical techniques used in combined approaches vary with patients and tumor characteristics, and are described below for each of the tumor groups. In our center, radiosurgery is performed with the Gamma Knife. The principle of Gamma Knife surgery (GKS), as it is used as part of combined approaches, is described below. There is some specificity related to the location, anatomy, and characteristics of the skull-base lesions. T; these are emphasized separately for each of the tumor groups addressed in this chapter.

Principle of Gamma Knife Radiosurgery as Part of Combined Approaches

Radiosurgery was invented by the Swedish neurosurgeon Lars Leksell at the beginning of the 1950s and defined as the "delivery of a single, high dose of ionizing radiation to a small and critically located intracranial volume through the intact skull" [1]. Originally, Leksell conceived radiosurgery as a primary tool for functional disorders [1, 2]. In the 1960s, Leksell created the Gamma Knife, a tool for radiosurgery using multiple focusing cobalt-60 sources [2]. Linear accelerators (focused X-rays, as in adapted Linac, dedicated Linac, or robotic devices such as Cyberknife®) and synchrocyclotrons (charged particles) are also used for radiosurgery [3]. Whatever the technique used in radiosurgery, two conditions are mandatory: the first is highest precision and best possible fit between the irradiated volume (called prescription isodose volume, PIV) and the target-volume (TV), in what is called high conformity (% coverage, PIV/TV); the second is minimal irradiation of the normal surrounding tissue, thanks to a steepest dose gradient, in what is called high selectivity [3].

The key limiting factor remains the volume of the target, as a large volume is increasesing the dose delivered outside the target and also the risk of complications, depending on the location and the nature of the lesion.

GKS, as used in our center, is a dedicated neurosurgical stereotactic procedure, combining image guidance with high-precision convergence of multiple gamma rays emitted by 192 sources of Cobalt-60 (Leksell Gamma Knife Perfexion®, Elekta Instruments, AB, Sweden) [3, 4]. In practice, GKS represents a succession of steps closely connected one to each other: stereotactic frame attachment under local anesthesia, acquisition of stereotactic images, target determination and treatment planning, stereotactic irradiation, and clinical and neuroradiological follow-up. The procedure is performed on an ambulatory basis.

Currently, the clinical applications of GKS include benign (pituitary adenomas, meningiomas, vestibular schwannomas, etc …) and malignant (mostly metastases) tumors of the brain and skull-base, vascular malformations (arterio-venous malformations, dural arterio-venous fistulas, cavernomas) and functional disorders (trigeminal neuralgia, epilepsies, movement disorders). The mechanisms of action differ according to the treated condition and the targeting strategy. In the case of tumors, apoptosis may be the major mechanism of cell death [5-7]; in vascular malformations, it induces vessels obliteration by thrombotic endothelial proliferation [8-10]; in functional disorders, GKS is used either to target a specific anatomical point in an anatomical structure (e.g. thalamus [11], anterior limb of the internal capsule [12], trigeminal nerve [13-15] or to target a larger zone, such as an epileptic focus [16], and the mechanism of action may differ [17].

Leksell Gamma Knife Perfexion®, which appeared in 2006, represents a clear technical advance in radiosurgery for the treatment of brain pathologies, allowing very sophisticated dose planning [18]. The advantages consist especially in the possibilities of shaping of the isodoses in very complex manners. It can also treat multiple targets, located close or far from each other, lesions in eloquent areas and lesions with , of with complicated forms. It also saves time in addition to radiation protection which is much improved compared to the previous models and other radiosurgery devices [18]. The technical possibilities of Leksell Gamma Knife Perfexion® are particularly applicable for the post-operative treatment of residual skull-base lesions, which often present with complex shapes and are located very close to highly functional neural structures.

Vestibular Schwanommas

General Considerations

Vestibular schwannomas (VS) are benign tumors that arise from the vestibular branches of the vestibulo-cochlear nerves. These tumors originate from the distal sheath at/or close to the neuroglial–neurilemmal junction that occurs 1 cm away from the pons, commonly at or close to the internal auditory canal (IAC). They are often lobular, well-encapsulated solid tumors, though cystic variants are also seen. The vestibulo-cochlear and facial nerves are flattened and stretched over the tumor surface by progressive tumor growth. Other nerves of the cerebellopontine angle (CPA) like the trigeminal, glossopharyngeal and vagal nerves, along with blood vessels like the anterior inferior and posterior inferior cerebellar arteries

may also be apposed or adherent to the tumor capsule, based on the tumor size. The tumor growth proceeds through several stages and thereby represents the different clinical symptoms associated with this tumor. The intracanalicular stage presents with otological symptoms like high-frequency sensori-neural hearing loss, tinnitus, vertigo, and disequilibrium. The extracanalicular stage starts as tumor grows out of the porus acoustics, which causes worsening of the auditory symptoms and the onset of headache and facial hypoesthesia. The cerebellopontine cistern stage is characterized by filling of the CPA with compression of the brainstem and the lower cranial nerves. The last stage is represented bywith hydrocephalus caused by shift and compression of the fourth ventricle [19-22].

Hearing loss is the most frequent clinical symptom of VS, which affects 91% of patients suffering from these tumors. The other common symptoms are related to the vestibular (61%), trigeminal (9%), facial (6%), lower cranial nerves (2.7%), and abducens nerve (1.8%). Patients are classified regarding tumor extension as follows: T1, purely intrameatal; T2, intra- and extrameatal; T3a, filling the cerebellopontine cistern; T3b, reaching the brainstem; T4a, compressing the brainstem; and T4b, severely dislocating the brainstem and compressing the fourth ventricle [23]. The House-Brackmann scale is used to assess facial function: grade I (normal symmetrical function), grade II (slight weakness noticeable only on close inspection, complete eye closure with minimal effort, slight asymmetry of smile with maximal effort, synkinesis barely noticeable, contracture, or spasm absent), grade III (obvious weakness, but not disfiguring, may not be able to lift eyebrow, complete eye closure and strong but asymmetrical mouth movement, obvious, but not disfiguring synkinesis, mass movement or spasm), grade IV (obvious disfiguring weakness, inability to lift brow, incomplete eye closure and asymmetry of mouth with maximal effort, severe synkinesis, mass movement, spasm), grade V (motion barely perceptible, incomplete eye closure, slight movement corner mouth, synkinesis, contracture, and spasm usually absent), grade VI (no movement, loss of tone, no synkinesis, contracture, or spasm) [24]. The auditory function is analyzed by using the Gardner Robertson (GR) classification, as follows: grade I (good-excellent), with pure tone audiogram, 0-30 dB and speech discrimination 70-100 (%); grade II (serviceable), with pure tone audiogram 31-50 dB and speech discrimination 50-69 %; grade III (non-serviceable) with pure tone audiogram 51-90 dB and speech discrimination 5-49 %; grade IV (poor), with pure tone audiogram 91-max dB and speech discrimination 1-4 %; grade V (none), with pure tone audiogram not testable, and speech discrimination 0% ; if PTA and speech do not correlate, a lower class has to be used [25].

Retrosigmoid Approach for VS

The various surgical approaches for these tumors include the retrosigmoid, trans-labyrinthine and middle fossa approaches. We prefer to use the retrosigmoid approach with the patient in the lateral decubitus position. Electrophysiological monitoring is routinely performed with somatosensory evoqued potentials (SSEPs) and electrical stimulation of cranial nerves V, VII, IX and X along with continuous VIIth nerve EMG. The head is fixed with a 3-point Mayfield clamp with the head in minimal flexion without obstructing venous return. The hair is shaved to simplify the identification of the surface anatomy. A linear slightly curved skin incision is drawn 2 cm behind the pinna, passing through the asterion and terminating 1 cm medial to the mastoid tip. The skin flap is elevated with the periosteum

elevator and the neck muscles are divided in line with the skin incision. The burr hole is placed at the asterion and then a sub-occipital craniotomy or craniectomy is carried out. The borders of the lateral part of the transverse sinus and medial border of the sigmoid sinus are exposed with a high-speed drill. Bone wax is used to pack the mastoid air cells and the emissary vein. The dura is opened with a linear incision 5-8 mm from the sigmoid sinus border and curved to the transverse sigmoid junction. Additional oblique incisions at the angles of the primary incision increase surgical view. Several tack-up sutures are placed on the dural edge to increase surgical view and to reduce cerebellar retraction. Cerebrospinal fluid (CSF) is withdrawn from the lateral cerebello-medullary cistern to relax the cerebellum. The tumor is then identified at the IAM and the arachnoidal planes around the poles of the tumor are opened. Stimulation of the posterior capsule of the tumor is performed to assure that the neural elements on the posterior and superior surfaces do not contain an aberrant facial nerve course. The posterior part of the capsule containing the vestibular nerves is incised. Internal debulking is performed with the cavitatory ultrasonic surgical aspirator (CUSA). The posterior lip of the IAM is drilled after opening the petrous dura. This allows the nerves at the IAM to be decompressed. The facial and cochlear nerves are most vulnerable at the lip of the IAM and therefore a thin layer of tumor is left behind on the nerves. The facial nerve is identified anterior to the tumor by stimulation and its course is mapped out. The tumor is progressively decompressed and the capsule is removed except for the portions covering the entire facial nerve. Stimulation of Direct the facial nerve on the anterior capsule with currents (as low as stimulation of 0.1 mA) during its entire course from the brainstem to the IAM is maintained. Stimulation of the nerve through a thin layer of tissue at a level of 1 mA ensures that the thickness of the residual tumor left behind is approximately 5 mm. If cochlear nerve is also to be preserved, a larger tumor residue is intentionally left in place covering the cochlearis nerve.

Alternation of stimulation of the facial nerve directly and through the tumor ensures preservation of facial nerve function while ensuring that the tumor remnant is not too large. Hemostasis is secured, and the drilled petrous bone is sealed with bone wax and covered with a piece of fascia secured with fibrin glue. The dura is closed in a watertight fashion. The mastoid cells are covered with muscle and fibrin glue. Cranioplasty is performed with methyl-methacrylate. The pericranium, muscles, fascia, subcutaneous fat and skin are closed in separate layers. A compressive bandage is used after the skin closure [23, 26-29].

Case Series

Eleven patients (6 males and 5 females) with VS had been treated using this combined approach (Ffigure 1). Mean age in this series was 50.3 years (range 24.1- 73.4). These patients presented with hearing loss (7 patients), trigeminal nerve symptoms (4 patients), gait problems (1 patient) and incidentally in three cases. Two patients (18.2%) had a stereotactic fractionated radiotherapy before the surgical intervention, which had failed to ensure tumor control. The lesions were solid in 9 cases (81.8%), and mixed (solid and cystic) in 2 patients (18.2%). Presurgical tumor volume was of a mean of 18.5 cm^3 (range 9.7- 34.9). All patients were operated though a retrosigmoid approach in the lateral decubitus position.

The timing of the GKS was decided on the basis of the residual tumor shape following surgery. This was evaluated on an MRI performed at 3 months after surgery. If the tumor

capsule had not closed on itself, an additional 3 months were given before evaluating suitability for GKS. The mean duration between surgery and GKS in this series was 10.5 months (range 4- 22.8 m). The mean tumor volume at GKS treatment was 4.9 cc (range 0.5-12.8). A mean number of 20.7 isocenters was used (range 8-31). Nine patients were treated with 12 Gy and 2 patients with 11 Gy as the dose prescription at the periphery of the tumor. A lower maximal dose was related to a higher tumor volume in cases where cochlear nerve function was also preserved. Dosimetry was made in the sense of the principles of radiosurgery stated above, with improving both conformity and selectivity. In patients with preserved hearing after surgery, special care was made to improve the gradient dose towards the cochlea, as several studies have shown the importance of the dose received by this structure, with a cut-off dose of approximately 4 Gy, so as to offer statistically significant chances of preserving functional hearing).

We did not have any major complications in our series. Two patients needed a second surgical intervention for postoperative meningocele. Two patients needed re-intervention before GKS, because the remnant tumor volume was too large to ensure optimal GKS treatment. This has been done 6.8 and 15 months after the first surgical intervention, respectively.

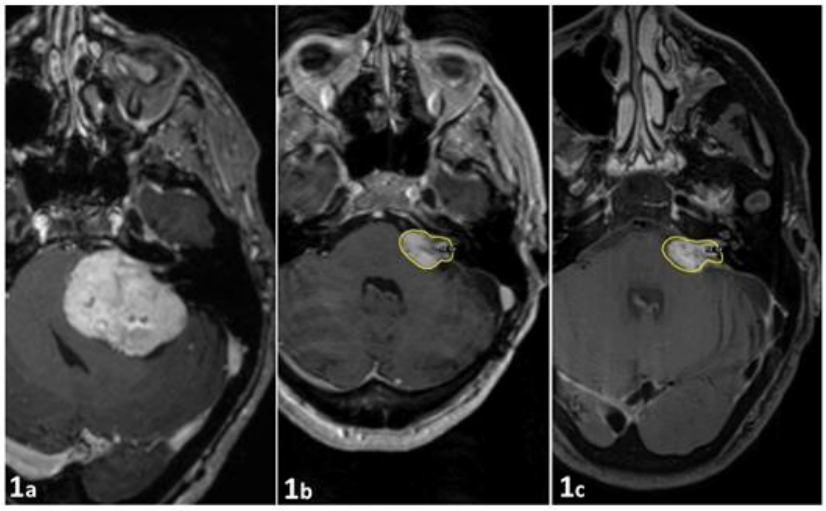

Figure 1. Example of a large vestibular schwannoma treated with combined approach. This 66 year-old female patient presented with hearing loss, tinnitus and gait instability; the MRI showed a large vestibular schwannoma (1a). The tumor was subtotally removed through a retrosigmoid approach. She had normal facial function following surgery. Three months after surgery, she underwent GKS for the residual tumor. The tumor volume before surgery was 24 cc while the target volume at the time of radiosurgery was 2.4 cc. GKS was performed with a dose of 12 Gy at the 50% isodose (1b). The MRI performed 6 months following GKS show slight shrinkage of the tumor, as illustrated by the co-registration and projection of the GKS prescription isodose on the 6-month follow-up MRI (1c).

Postoperative status showed no facial nerve deficits (0%). Four patients with useful pre-operative hearing underwent surgery with the aim to preserve cochlear nerve function. Of these patients, the patient who had GR class I before surgery, remained in GR class 1. Two patients improved hearing after surgery, one from GR 5 to GR 3 and the other one with slight improvement, remaining in the same GR 3 class as preoperatively. Mean follow-up after surgery was 15.4 months (range 4- 31.2). One patient, who presented with secondary

trigeminal neuralgia before surgery, had transienttory facial hypoesthesia following surgery. No other neurological deficits were encountered. Following GKS, the patients had a mean follow-up of 5.33 months (range 1-13). No new neurological deficits were encountered and hearing remained stable in all patients with preost-surgery preserved hearing.

Discussion

Vestibular schwannomas are known to have a small annual rate of growth [22]. Despite this, recurrences may occur between 7 to 11% when surgical resection is considered to be total [23, 30], and between 7 to 53% is resection is subtotal [31-34]. Following total microsurgical resection of large VSs, facial nerve function preservation (HB I or II) has been achieved in 27 to 58% [23, 30, 35-38] while subtotal resection achieves better preservation rates between 82 to 88% [39, 40]. From recent GKS series data, it is evident that GKS is considered to have an long-term efficacy in controlling tumor growth, of as much as 97-98%, with a very low risk of facial nerve dysfunction, of less than 1% in most of the series [20, 41-44]. Hearing preservation following microsurgical resection in large vestibular schwannomas varies between 0 to 29% (37, 45-50), and in GKS from 38 to 94% [46, 51-53].

Several studies have compared radiosurgery to microsurgery for treating smaller VS. In a retrospective review by Myrseth et al. in 2005 with median follow up of 5.9 years, local control rates between microsurgery and gamma knife were not statistically different (89.2% versus 94.2%) [54]. Facial nerve function and quality of life were both significantly worse in the surgery group versus the GKS group. GKS achieved a facial nerve preservation rate of 94.2% while surgery achieved only 79.8% HB grade I-II [54]. To give further strength to Myrseth's study, Pollock et al. in 2006 performed a prospective study comparing surgery versus radioand knifesurgery in 82 patients with tumors <3cm in size. Median follow up was 42 months and local control rates were not significantly different between the groups (96% versus 100%). Despite these findings, facial nerve function and hearing preservation were both significantly worse in patients treated with surgery versus those treated with Ggamma knife (75% and 5% versus 96% and 3%) [55].

If the "attractive combination" [56] of microsurgery and GKS is used, preservation of facial nerve function occurs between 85.7 to 95% of the cases [40, 57-60]. Regarding combined approaches, Yang et al. [60] reported up to 50% of maintaining serviceable hearing in those patients having preoperative hearing. Our results with 100 % facial nerve preservation (whole series) along with preservation of hearing for all patientsthose with useful pre-operative hearing pre-operatively, confirms the view that combined approaches for large VS achieves much better results than microsurgery used as stand-alone treatment.

Petroclival Meningiomas

General Considerations

Petroclival meningiomas (PCM) account for approximately 3 to 10% of the meningiomas of the posterior fossa [61-63]. Radical removal of these tumors remains challenging, primarily

due to the fact that they usually involve multiple regions with significant adherence or invasion of the brainstem, encasement of the basilar artery and its perforators, as well as involvement of cranial nerves V, VII, VIII, IX, X, XI [62, 64]. PCM are typically described as those meningiomas attached to the lateral dura, along the petroclival borderline where the sphenoid, petrous and occipital bones meet [65-67].

Retrosigmoid Approach for PCM

Several skull-base approaches have been described in the literature to resect PCM, namely the trans-labyrinthine, trans-cochlear, total petrosal, retrosigmoid and subtemporal approaches. We prefer to use the standard retrosigmoid approach. The main advantage of this approach is the familiarity with this approach and the fact that when compared to the other approaches it represents a minimally invasive microsurgical strategy that can adequately ensure a planned subtotal resection while preserving neurological function. The retrosigmoid approach has been described in the section on vestibular schwanomma. For the intraoperative electrophysiological monitoring, the occulomotor cranial nerves are also monitored in addition to evoked potentials and monitoring of VII-IX cranial nerves. After dural opening, the tumor is frequently seen anterior to the vestibulo-cochlear and facial nerves. The tumor is accessed through windows between the V,- VII-VIII and the IX-X-XI nerves complex. The tumor is disconnected from its attachment to the petrous bone and tentorium based on its location. Internal decompression of the tumor is performed with CUSA making sure that the nerves are not damaged by manipulation. The continuous EMG and intermittent electrical stimulation of the nerves posterior adjacent to the tumor proves to be invaluable in preserving neural function. The extent of tumor removal depends on the amount of the clival component, invasion of the cavernous sinus and adherence to the brainstem pia and basilar artery and its branches. The parts of the tumor that are deemed risky to remove are left behind for later treatment with GKS. Specific issues related to GKS treatment are definition of the target in "en-plaque" lesions, extension to the tentorial edge and involvement of occulomotor cranial nerves, potential cavernous sinus invasion and persistent brainstem mass effect.

Case Series

We treated four patients who presented with PCM (Ffigure 2). Three were females and one was male. Mean age in this series was 60.27 years (range 42- 73.3). Mean follow-up was 7.6 months (range 5.1- 13.2). All the lesions were located on the left side. They presented with hearing loss (3 patients), hemiparesis (one patient), VIth cranial nerve paresis (one patient); one was an incidental finding. The mean tumor volume before surgery was of 17.1 cc (range 11.2-24.2). The histology was WHO I meningotheliomatous meningioma in all patients. Postoperative clinical examination showed a House-Brackmann grade 2 facial function in 3 cases, which completely recovered. One patient continues to have a grade 4 facial weakness. This patient also had a transient VIth nerve paresis (that completely recovered) and trigeminal hypoesthesia in the V1 distribution. No other complications were encountered. In one case, surgical re-intervention was attempted due to a large residual tumor volume, which was not favorable for GKS; this second surgery did not achieve a significant

debulking due to severe adherences to the brainstem and the lower cranial nerves. The patient was later treated with staged GKS. The mean duration time between surgery and GKS was 5.6 months (range 4.3-7). The mean tumor volume at the moment of GKS was 9.9 cc (range 5.1- 14.2). A mean number of 26 isocenters was used (range 21-29). Three patients (75%) were treated with 12 Gy and only one (25%) with 14 Gy at the periphery, at the 50% isodose. The 12 Gy peripheral dose is preferred, especially when there is a contact between the residual tumor and the brainstem.

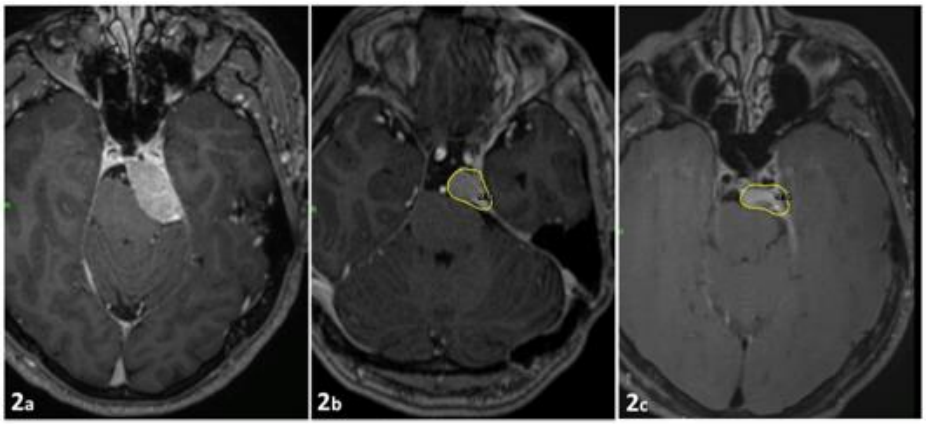

Figure 2. Example of a petro-clival meningioma treated with combined approach. This 42 year-old male patient presented with an incidentally discovered petroclival meningioma. A "wait-and-see" approach was first adopted. Subsequent imaging showed tumor growth and surgery was performed at this stage (2a). He underwent subtotal excision of the tumor. In the immediate postoperative period, the patient had a House-Brackmann grade III facial function along with V1 hypoesthesia. Subsequent clinical follow-up showed an improvement of the facial function to House-Brackmann II. The residual part of the tumor was treated with GKS. The tumor volume before surgery was 11.2 cc; the target volume at the time of radiosurgery was 5.1 cc; the GKS was performed with a dose of 12 Gy at the 50% isodose (2b). Subsequent shrinkage of the residual tumor is illustrated by the co-registration and projection of the GKS prescription isodose on the 6-month follow-up MRI (2c).

Special care was than given to optimize the dose gradient at the interface between the tumor and this neural structures. Two patients had staged GKS. In one case, the remnant tumor volume after surgery was 13.6 cc; an important progression has been confirmed at the moment of GKS into the ethmoidal sinus; the delay between surgery and GKS in this case was of 5.1 months; in the first stage, we treated the evolutive part, along with the invasion into the cavernous sinus and the temporal fossa; a second stage was planned 6 months later, to the posterior part of the tumor, at the interface with the brainstem. No complications have been noted following GKS.

Discussion

Cushing was the first to describe PCM as "the most challenging and formidable meningiomas to treat" [68]. For a long period of time, they were often regarded as "inoperable". A first successful total removal case was reported by Mayberg et al. [69]; before the 1970s, the risk of mortality could be as high as 50% [70-72]. Despite advances in

microsurgery, neuroimaging (especially high-quality MRI) and electrophysiological monitoring, they are still associated with high morbidity and mortality [61-65, 67, 73, 74]. Selection of the optimal strategy for these tumors still remain a matter of debate in the current literature [85], and depends on several factors like natural history, patient's age, tumor size, symptoms, quality of life and also the possibility of using radiosurgery as first intention treatment. For large to giant PCMs, microsurgery is generally considered as the primary treatment [75]. When dealing with small to medium lesions, several studies have shown the value of subtotal resection followed by adjuvant therapies, or first intention radiosurgery [63, 75, 76]. GKS has gained increasing acceptance as a therapy in the armamentarium for PCM, in newly diagnosed, subtotally resected or recurrent tumors. Radiosurgery achieves good tumor control in 80% to 100% of the skull-base meningiomas, with low morbidity [75-79]. There have also been few studies reporting results of radiosurgery as a complementary treatment after initial surgical tumor debulking [80, 81]. Surgical mortality in PCM has been reported to range between 0 to 10% in previous series [62, 64-66, 70, 82-85]. Major morbidity varies between 8 to 45%, with cranial nerve deficits between 20 to 70% [62, 64-66, 70, 82-85]. A recent study by Flannery et al. (86) on a large series of 168 patients treated with GKS reported a tumor control of 91% at 5 years and 86% at 10 years (90% after excluding the higher grades). Our series of combined treatment of PCM had no mortality or major morbidity, and the cranial nerve function preservation rates compare favorably with those other series from literature.

Clinoidal Meningiomas

General Considerations

The clinoidal meningiomas (CM) are a subcategory of the sphenoid wing meningiomas that develop at the junction of the anterior and middle cranial fossae. The incidence of CM ranges between 34 to 43.9% of all meningiomas [87-89]. The surgical treatment of the CM needs to deal with the preservation of the carotid artery and its branches, preservation or recovery of visual function, limiting occulomotor cranial nerve palsy and achieving a total resection or adequate tumor control. Visual involvement usually occurs either in relation to direct compression of the optic nerve or in relation to ischemia or demyelination of the optic nerve [90]. These tumors may grow towards the midline and involve the jugum sphenoidale, the diaphragm sellae, the pituitary gland stalk (and infundibulum) and the clivus. They can extend to the cavernous sinus [91] or invade the optic foramen or orbital cavity. They can infiltrate the bone or be associated with cause hyperostosis [89, 91-93].

One of the still confounding issues today is related to their classification, which may differ from one study to another. In 1938, they were classified by Cushing and Eisenhardt [94] into outer (pterional), middle (alar) and inner (deep, clinoidal). Al-Mefty [87, 88, 95] proposed a classification that takes into account not only the point of origin of the meningioma, but also its relationship with the internal carotid artery (ICA), as follows: group I, with implantation on the lower part of the clinoid and that develop in the carotid cistern and incase ICA; group II, originating from the superior or lateral aspect of the anterior clinoid process and as they grow, may enter in contact with ICA; group III, that originating from the

optic foramen in which the arachnoid membrane is present between the vessels and the tumor, but may be lacking between tumor and optic nerve. The presence of the arachnoid membrane is of high importance, as it offers a cleavage plane and allows the vessels to be totally freed from the tumor. Finally, Risi et al. [93] proposed a classification regarding the direction of tumor development, into pure clinoid, clinoid with lateral extension and clinoid with cavernous sinus extension.

From a surgical perspective, 2 challenges arise when ensuring optimal strategies of these lesions: the surgical approach and the management of the intracavernous extension of the tumor, which is reported to be as high as 44.1% in several series [87, 93, 96, 97]. The advances in skull-base surgery, like the orbito-zygomatic osteotomy, the epidural approach to the clinoid, and access to the cavernous sinus, have contributed to a large extent to make surgery for these tumors feasible while substantially reducing the risk of vascular injury or neurological deficits.

Pterional Approach for CM

Either a fronto-lateral or a pterional approach is performed, with an orbito-zygomatic osteotomy in addition if necessary, based on tumor location. In the fronto-lateral approach, a burr-hole is placed just posterior to the anterior temporal line. This approach provides a more medial view of the clinoid and suprasellar region, which allows early identification of the optic nerve. For the pterional approach, the single burr-hole is placed at the same location, but the craniotomy is performed more posteriorly, exposing the sphenoid ridge, sylvian fissure and the frontal and temporal lobes. The lesser wing of the sphenoid is drilled-off up to the superior orbital fissure. The superior orbital fissure is unroofed to expose the periorbital fascia, which is opened in cases of tumour infiltration of the optic foramen or intraorbital structures. For cases where there hyperostosis around the optic canal, a partial clinoidectomy is performed prior to extradural unroofing of the optic canal. The dura of the region of the tuberculum sellae and chiasmatic sulcus is inspected for evidence of meningeal tumor infiltration and to identify the optic nerve intradurally. The falciform ligament, around the optic nerve is opened for a short distance towards the orbital apex in cases of tumor in this region. While dealing with clinoidal meningiomas, great care needs to be taken because the carotid and middle cerebral arteries may be embedded in the tumor and in some cases there can be involvement of the vessel wall by the tumor. The tumor is then visualized in the intradural compartment after opening the sylvian fissure and separating the frontal and temporal lobe. The tumor capsule is opened and it is internally decompressed with bipolar coagulation, micro-scissors, and ultrasonic aspiration. After the tumor has been dissected off the vessels, the optic nerve, chiasm or the pituitary stalk, the capsule is removed in pieces. In case of vasospasm following dissection along cerebral arteries, local administration of nimodipine or papaverine sponges can be done to prevent cerebral ischemia. After resection of the tumor, the dural attachment is resected, including the hyperostotic bone of the lesser sphenoid wing or the anterior clinoidal process, if this is possible without endangering nerves or vessels. The portion of the tumor invading the cavernous sinus is not aggressively removed. In these cases a small fat graft is interposed between the optic nerve, chiasm, pituitary stalk and the residual cavernous sinus component of the tumor. This form of “chiasmopexy” or “hypophysopexy” allows for optimal dose treatment with GKS. The dura is

closed primarily and for the parts of the skull-base dural defects, these are reconstructed with fascial grafts and fibrin glue. This ensures that there remains no communication with the ethmoidal or sphenoidal sinuses. Bone flaps are repositioned and the muscle and skin flaps are closed in layers over a drain.

From a radiosurgical point of view, a safe optimal distance between the tumor and the optic nerve is mandatory, in order to deliver an optimal radiation dose and to avoid toxicity due to irradiation close to the optic pathways. A good conformity and selectivity of the tumor with respect to the optic pathways is crucial to achieve a marginal maximal dose between 12 and 14 Gy to the tumor, with a an optimal dose gradient in the direction of the optic pathway. This achieves a high-rate of tumor control, with very low risk of optic nerve toxicity. In general, the optic pathway is considered to tolerate up to 8 Gy without risk (maximum of 10 Gy in selected situations for very small volumes) [81, 98-100].

Extended Endoscopic Endonasal Approach to Parasellar Regions

A complete preoperative evaluation is performed with high-resolution brain computed tomography (CT) scans in bone window, CT-angiography and magnetic resonance imaging. Converse to endoscopic endonasal approach to pituitary tumors, this extended approach often uses a bi-nostril approach in order to improve the anatomical exposure, the endoscope being placed in the nostril contralateral to the lesion and surgical tools being placed within both nostrils [101]. The whole endoscopic procedure until the sellar floor opening is performed with a hand-held short 0°, 30° or 45° endoscope (diameter: 4mm; length: 18 cm). The superior and middle turbinates ipsilateral to the lesion are resected. The middle turbinectomy allows both enlarging the nasal corridor to facilitate access to surgical tools and facilitating the identification of major anatomical structures: the vidian nerve and the sphenopalatine artery. Anatomical landmarks are confirmed with the neuronavigation system with CT scan / MRI fusion and Doppler. The contralateral middle turbinate is out fractured. These turbinectomies allow constructing a nasoseptal flap pedicled on the sphenopalatine artery and its nasal branches. The middle turbinate is kept intact until the closure time. Both the flap and this middle turbinate will be used for the cranial base defect reconstruction at the closure time. The nasoseptal flap is elevated with its intact blood supply and placed within the nasopharynx for protection. Opening the maxillary sinus and the posterior ethmoidal cells ipsilateral to the lesion consists in a far lateral approach to the sphenoid recess. The nasal corridor is completed by the realization of posterior nasal septectomy and large bilateral sphenoidotomies. Then, a wide opening of the sphenoid sinus is required to have access to the anterior skull base to the sphenoid floor and beyond to the ispsilateral sphenoid recess consisting in a transpterygoid approach. To be noted, after the opening of the sphenoid sinus, a transcavernous sinus approach, consisting in the exposure of the pituitary dura by removing bone over the sella turcica, may be performed allowing an exposure of the cavernous sinus more directly than the traditional approach to the pituitary. This approach requires the use of Doppler technology to identify the internal carotid artery (ICA). However, we prefer to be not so aggressive and would leave intracavernous tumor in place for later treatment with GKS.

The endonasal route to more lateral lesions is performed through a transmaxillary corridor, which give access to pterygopalatine and infratempral fossa and Meckel's cave. The transpterygoidal approach often combined with transethmoidal and transsphenoidal

approaches depending of the targuet to be treated (from optic nerve, orbital apex, cavernous sinus, to infratemporal and pterygopalatien fossa. A large antrostomy allows exposuree and removal of e the entire posterior wall of the maxillary sinus. The first step is to clip the sphenopalatine or maxillary arteries in the pterygomaxillary fossa, to prevent local bleeding. The anatomical landsmarks are the floor of the sphenoid sinus in which run the vidian nerf the maxillary nerve (V2) which is identifiedy aton the floor of the orbit.al floor.. The vidian foramen located in the floor of the sphenoide sinus is a major anatomical landmark allowing identificationying of the petrous internal carotid artery (ICA) and the V2 reaching to the Meckel's cave. Drilling the vidian canal is realized to isolate the ICA and bone removal is realized in order to achieve proximal and distal ICA control. The V2 is followed through the foramen rotundum into the middle cranial fossa. To reach the Meckel's cave lesion, the opening of the dura mater is realized within the space between the distal ICA medially, the V2 laterally, the proximal petrous ICA inferiorly and the abducens nerve superiorly. In case of huge tumors, the anterior temporal fossa is also opened using the anteromedial (between V1 and V2) and anterolateral (between V2 and V3) middle fossa triangles landmarks. To reach lesions located in the petrous apex region, it is necessary to drill medially the bone and along a vertical plane parallel to the ICA. When the bone is thin enough, small pieces are removed and the lesion can then be reached.

The tumor removal step is the same as in microsurgical procedure. The closure time consists ofin plugging with fat the region that communicates with the intradural space. intradurally protecting neurovascular strucures. Extradurally, a resorbable dural substitute is used along with an overlay of a as well as nasoseptal flap and/ theor the middle turbinate, reinforced with fibrin with glue. Plugging of the sphenoid sinus is made with fat.

Case Series

Nine patients (all females) presented with a CM (figures 3 and 4). The mean age in this series was 56 years (range 35- 71 years). Tumors were located on the right side in 2 patients and on the left side in 7 patients. The mean tumor volume before surgery was 20.2 cc (range 4.4- 55.1). Visual loss was the most common symptom (8 cases) of which 2 patients had complete unilateral blindness at the time of surgery. All underwent a transcranial surgery through a frontolateral/ pterional approach, while in one patient an additional endoscopic endonasal tumor resection was also performed. Eight tumors were WHO I meningioma and one tumor was an atypical grade II meningioma. The visual status normalized in four cases (44.4%) and improved in 3 (33.3%). One patient had visual deterioration following surgery, which was clearly related to the chiasmopexy and, following of reduction in size of the fat graft at a second surgery, the visual function completely recovered. One case each of transient IIIrd and VIth nerve palsy were noted. No other worsening of pre operative neural dysfunction was seen. No major complications were thus encountered in this series. There were no wound problems or CSF dural leaks.

Five patients have already been treated with GKS while four await for GKS as part of the combined approach. The mean duration between microsurgery and GKS was 5.2 months (range 3.2- 8.4). The mean tumor volume at the moment of GKS was 4.4 cc (range 0.386- 11.1).

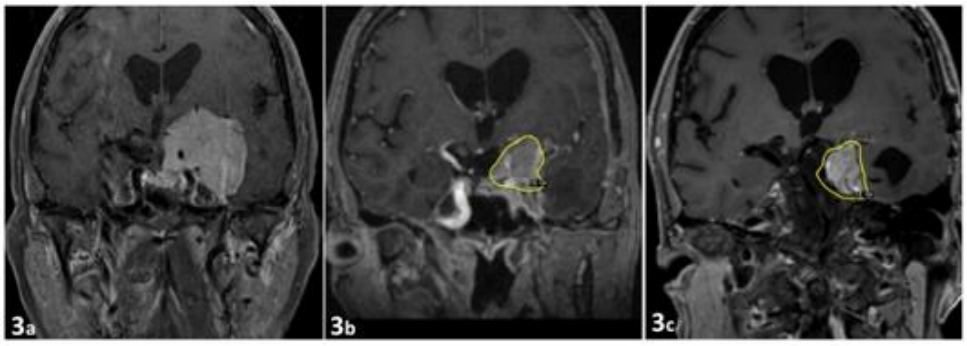

Figure 3. Example of a large clinoidal meningioma treated with combined approach. This 71 year-old female patient presented with markedly reduced visual acuity on the left side and with VIth nerve palsy. The preoperative MRI scan shows a large clinoidal tumor with encasement of the supraclinoid and cavernous sinus carotid artery (3a). She underwent a resection of the tumor though a pterional craniotomy and the part of the tumor encasing the carotid was left behind for GKS. Postoperatively, she completely regained her vision and had no diplopia. The tumor volume before surgery was 39 cc and the target volume for GKS was 7.5 cc. GKS was performed with a dose of 12 Gy at the 50% isodose (3b). Subsequent shrinkage of the residual tumor is illustrated by the co-registration and projection of the GKS prescription isodose on the 6-month follow-up MRI (2c).

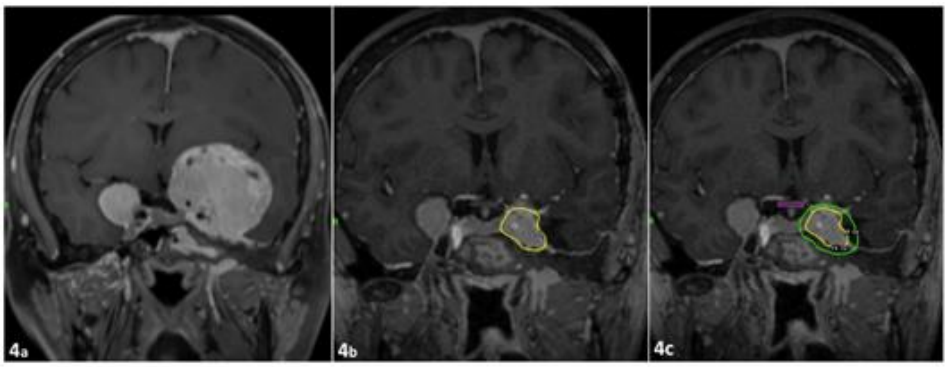

Figure 4. Example of a large clinoidal meningioma treated with combined approach, in a patient with bilateral clinoidal meningiomas. This 47 year-old female patient presented with visual loss on the left side. MR images showed bilateral anterior clinoid meningiomas (4a). On the left side, there was a large clinoidal meningioma markedly displacing the optic nerve and the chiasm and encasing the intradural carotid artery. There was also a component of the tumor in the cavernous sinus and in the sphenoid sinus extending laterally around the orbital apex. The intracranial part of the tumor was approached through a pterional craniotomy. The entire intradural part of the tumor was completely removed including the part encasing the carotid artery and its bifurcation. Following surgery, she completely recovered the vision on the left side. AAt a second stage surgery was performed 3 months aiming at the extracranial part of the tumor, which was removed through an endoscopic endonasal approach. GKS for the cavernous sinus component was performed 6 months later. The tumor volume before surgery was 55.1 cc and the target volume at the time of radiosurgery was 1 cc. GKS was performed with a dose of 14 Gy at the 50% isodose (4b). The maximal dose to the optic chiasm and the left optic nerve was 3.6 Gy and 7.6 Gy respectively. Fig 3c shows the 8 Gy isodose line (as reference for the maximal dose allowed to the optic pathways) in green while the optic chiasm is delineated in pink showing its distance from the treated volume. The smaller tumor on the right side was completely excised through a suprabrow mini-craniotomy 3 months later.

A mean number of 21.8 isocenters was used (range 17-28). Four patients were treated with a marginal dose of 12 Gy and one patient (11.1%) with 14 Gy at the periphery. Four patients await GKS treatment. In our experience, with the current GKS technique and the use

of Perfexion®, a minimal marginal dose of 12 Gy is almost always achievable, provided that there is a small distance (even as low as 1-2 mm) between the tumor and the optic pathway. One patient had transitory IVth nerve palsy accompanied by decreased visual acuity and left trigeminal neuralgia (V1 and V2 distribution), 6 weeks after the GKS. This was clearly related to tumor size increase/swelling related to GKS. She was treated with steroids and within 6 weeks all neurological symptoms had completely recovered. In fact, subsequent imaging showed a marked reduction in tumor size with the intracavernous ICA becoming more visible. The mean interval between surgery and GKS was intentionally reduced because of the close proximity of the residual tumor to the optic apparatus. The mean follow-up was 8.1 months (range 1.8-17.5).

Discussion

Complete resection of these types of tumors remains challenging, especially in large or giant cases [102]. In the current literature, the clinical status has been reported to be stable or improved following treatment in 50 to 78% of the cases [88, 92, 93, 103]. In our series, the visual status normalized or improved in 7 of the 9 patients. This has to be seen in the light of the postoperative worsening that has been published in literature, reported to range between 10.7% and 29% [88, 92, 93, 102, 103]. For occulomotor cranial nerve function, we had no long-lasting deficits in any patient, though trans-cavernous surgery is particularly known to produce these deficits in up to 50% based on reports from literature (104, 105). Major morbidity is a well-recognized concern following radical resection of these tumors. Hemiparesis or hemiplegia has been reported to be as high as 13.6% in giant clinoid meningiomas [88, 92, 93, 102, 103]. Mortality has been reported as a complication in 5.9%, but as high as 42.8% in some reports [88, 91-93, 102, 103]. We have had no mortality or major morbidity in our series. Following surgery alone, rates of tumor recurrence occur in up to 17.6% in subtotal resection [88, 89, 92, 102, 103] after macroscopically complete tumor removal to vary between 0 to 26% in several recent series [91, 96, 103, 106, 107]. As the size of the tumor has an important impact on surgical outcome, combined approaches are of huge value in diminishing morbidity and mortality related to surgery, while offering the possibility for GKS to be made in optimal conditions. Gamma Knife surgery has already documented its safety-efficacy in several studies regarding good control of the meningiomas within the cavernous sinus [79, 81, 98, 100, 108-111]. In this context, combined approaches with planned subtotal resection and GKS on the remnant tumor are crucial in obtaining tumor control while achieving a good neurological outcome.

Pituitary Adenomas

General Considerations

Pituitary adenomas (PA) arise from the anterior pituitary gland and are classified based on their size into microadenoma (< 1 cm) or macroadenomas [112]. They represent approximately 10% of intracranial tumors and are most common in the 3rd and 4th decades of

life, affecting equally both sexes. Pituitary tumors usually present either due to endocrinological disturbance, or due to mass effect. A small number presents with pituitary apoplexy. Classically, pituitary tumors are divided into two groups: functional (or secreting), and non-functional (non-secretory or else secreting products such as gonadotropin that do not cause endocrinological symptoms). The latter usually do not present until of sufficient size to cause neurologic deficits by mass effect, whereas the former frequently present earlier with symptoms caused by physiologic effects of excess hormones like prolactin, growth hormone (acromegaly) or ACTH (Cushing's disease) [112-116]. Panhypopituitarism may be caused by large tumors of either variety (usually the non-functional type) as a result of compression of the pituitary gland. Except for prolactinomas [117-123], the primary treatment for all other symptomatic PA is surgery [112-116, 124-128]. The endocrinological and oncological outcome following surgery primarily depends on the extensions of the tumor. The majority of the sellar and suprasellar tumors can be treated with surgery only. When they invade the parasellar structures or involve multiple compartments, like subfrontal or temporal fossa extensions, additional surgery, medical therapy or radiosurgery are necessary to achieve tumor control and/or endocrinological remission. This is especially true for secreting PA where even a small residue in the cavernous sinus will preclude remission. The combined approach is therefore specifically indicated in this subgroup of patients.

Endoscopic Endonasal Transsphenoidal Approach for Pituitary Adenomas

Generally the right nostril is chosen for the approach. All necessary instruments are inserted through the chosen nasal cavity parallel to the endoscope. Exceptionally, in case of large tumors, both nasal cavities can be used along with a four-hand technique. The whole endoscopic procedure until the sellar floor opening is performed with a hand-held short 0° (or 30°) angled endoscope (diameter: 4mm; length; 18 cm) allowing panoramic visualization of the anterior wall of the sella turcica as well as the optic and carotid protuberances. When this endoscope is introduced in the nasal cavity, it is necessary to identify the superior and middle turbinates to push them laterally aside. Sometimes, in cases of turbinate hypertrophy such as in acromegalic patients, it will be necessary to remove the middle turbinate in order to allow the endoscope clearing. Then the coagulation and the opening of the mucosa from the sphenoidal ostium to the choana at the base of the vomer is performed. A large sphenoidotomy is performed and the vomer is pushed away until the apparition of the contralateral ostium allowing a better anatomical visualization. The dura mater is opened after the realization of a small bone flap from one cavernous sinus to the other and from the anterior skull base to the clivus. The sellar dura is opened in rectangular shape and the tumor is visualized using a long 0° endoscope (diameter: 4 mm, length: 30 cm). The tumor is resected piecemeal and the pituitary gland is visualized and kept intact along with the arachnoid pouches. At the end of the procedure, the sellar and suprasellar regions are explored using 30° or 45° endoscopes pushed up through the sella turcica to detect potential residue within suprasellar and lateral regions. In order to detect potential cerebrospinal fluid leakage, the anesthesiologist raises the pCo2 to increase the intracranial pressure. The closure is performed by filling the tumor cavity and the durotomy defect with a fat graft. This achieves dural closure as well as serves as a means of distancing the chiasm and pituitary gland from a residual cavernous sinus portion of the tumor [129-133]. This allows the use of

high doses of GKS especially for the treatment of secreting PA in the cavernous sinus. Nasal packing is only rarely used.

Case Series

Eight patients (3 males and 5 females) were treated with PA utilizing the combined approach (figure 5). The mean age in this series was 52.3 (range 13-72 years). The presenting symptom was visual deficit in 7 of 8 patients, and one patient presented with symptoms of acromegaly. All patients underwent endoscope-assisted trans-sphenoidal microsurgery, while one patient had a staged trans-cranial resection of tumor in addition. The mean tumor volume before surgery was 16.2 cc (range 5.2-27.1 cc).

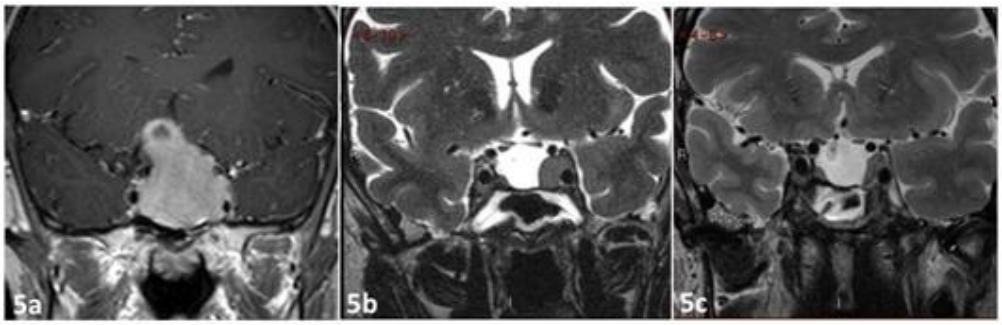

Figure 5. Example of a large pituitary adenoma treated with combined approach. This 13 year-old female patient presented with marked reduction of visual acuity especially on the right side and with a homonymous hemianopia. Endocrine evaluation revealed a non-functional tumor with partial anterior pituitary dysfunction. MRI with gadolinium enhancement showed a large pituitary adenoma, Hardy's grade D, Knosp IV, with bilateral invasion of the cavernous sinus (5a). She underwent a staged trans-nasal trans-sphenoidal endoscopic resection of the tumor. The vision on the left side partly improved while the visual field deficit of the right eye completely recovered. She needed hormonal substitution for the hypopituitarism. A residual tumor located bilaterally in the cavernous sinus was visible on T2-weighted coronal MRI (5b). The tumor volume before surgery was 20.3 cc while the target volume at the time of radiosurgery was 1.1 cc. GKS was performed with a dose of 12 Gy at the 50% isodose for both right and left targets, while the maximal dose to the optic pathway was 8.5 Gy. Six months following GKS, there is a marked reduction of the residual tumor (5c).

Postoperatively, visual status improved/ normalized in all patients while no patient had worsening of visual or occulomotor function. Two patients had transient diabetes insipidus following surgery. Three patients had postoperative anterior pituitary hormone insufficiency, which subsequently improved.

GKS was performed at a mean duration of 7 months (range 2.8-12.5) following surgery. The mean tumor volume at GKS planning was 2.8 cc (range 0.9- 6.4 cc). The residual tumor was located in the right cavernous sinus (4 patients), the left cavernous sinus as well as in the right infrachiasmatic sella (one patient), bilaterally in the right and left cavernous sinus (one patient), in right cavernous sinus with a posterior part in contact with the brainstem and a lateral extension in the temporal fosa (one patient). A mean number of 16.9 isocenters was used (range 4-25). The mean peripheral dose at the 50% isodose, was 24 Gy (range 18-30) in secreting and 13 Gy (range 12-14) in non-secreting PA, respectively. The maximal dose received by the optic pathways was 7.9 Gy (range 5.5-11.7). Current literature admits a

maximal dose between 8 and 10 Gy. Only one patient overpassed the maximal limit of 10 Gy, but the dose received by the 1 mm^3 and $10mm^3$ of the optic apparatus was 9.4 and 8 Gy, respectively.

Two patients (50%) had staged radiosurgery. One of them had a bilateral residual tumor located in the cavernous sinus. Thus, we decided to perform a staged radiosurgery, so as to avoid the overlap of dose at the level of the chiasm but also pituitary gland and stalk. The other patient had a tumor which was extending in the right cavernous sinus and also at the level of the petro-clival junction; this patient had lost vision on the right side so the main objective was to avoid toxicity for the chiasm and the left optic nerve; thus, we avoided any dose overlap that could endanger the vision of the left eye. No additional deficit after GKS was encountered. The mean follow-up period for this group was 18.7 months (range 5.8-30.7).

Discussion

Surgical approaches to pituitary lesions was initially transcranial until the transsphenoidal approach became the gold standard with the introduction of operative microscopey and fluoroscopy by Guiot et al. (134) and Hardy [135]. Current classification of PA divides it into secreting (or functioning) PA and non-secreting (or non-functioning) PA based on endocrinological presentation, immunohistochemistry and electron microscopy. Surgery is required for the great majority of secreting PA except for prolactinomas, where medical treatment is efficacious in the majority of patients. For non- secreting PA, surgery is required when there are visual and/or endocrinological impairments. This surgery is performed either by a microscopic or endoscopic approach. The main advantage of the endoscopic approach is improved visualization of the sellar and suprasellar anatomy, improved gross total removal [136, 137], reduction of nasal swelling, avoidance of the use of fluoroscopy (138) and shorter hospital stay [139]. Its major disadvantages are the lack of binocular vision and the narrow nasal corridor.

With regards to postoperative results, gross total removal is achieved for non-secreting PA in 35.5 % to 74 % [137, 140, 141] in microscopic series versus in 56% to 93% [133, 137, 142] in endoscopic series. For secreting PA, remission is obtained with surgery alone in 75% to 85% of non-invasive adenomas (143). For ACTH-secreting adenomas and GH-secreting adenomas, remission is respectively obtained in 81 % and 85% with endoscopic approach versus 78% and 67% with microscopic approach [144]. Long term recurrence rates of hormonal hypersecretion vary from 7 to 25% [144]. Visual dysfunction may be present at the time of surgical management. With both microscopic and endoscopic approach, all patients with preoperative visual impairment recover enough vision to resume a normal life, unless a long preoperative evolution has already caused an optic atrophy. The visual outcome reported in literature show more than 92 % of normalization or improvement with no experience of worsening across several large series [137, 144-146].

Nasal morbidities are reported in 0.7% to 7% of cases and are either major bleedings secondary to sphenopalatine artery lesion or minor epistaxis [133, 144, 145, 147]. Sphenoid sinus complications occur in about 2% and 9% in endoscopic and microsurgical series respectively. Other rare complications like fracture of the sphenoid bone, injury of the optic nerves or lesions of the carotid artery have also been reported [148]. The most common

complication of transsphenoidal surgery is obviously the occurrence of CSF leaks reported in 1.2% to 6% of endoscopic series and 0.9% to 3 % of microsurgical series [133, 144, 145, 147]. This risk is increased in cases of suprasellar and/or parasellar extensions. Meningitis has a comparable risk to intracranial open skull base surgery with a rate of about 1.8%, increasing with persistence of CSF leaks and postoperative external ventricular or lumbar drains. [149]

Transsphenoidal procedures are at risk of endocrinological impairment such as transient or permanent diabetes insipidus and hypopituitarism. Permanent diabetes insipidus is reported in 1% to 5% and 0.9% to 7.6% in endoscopic and microscopic series respectively [133, 144, 145, 147, 150, 151]. Postoperative hypopituitarism may be avoided by careful tumor resection but occurs in around 14% of cases [133].

Particular attention needs to be given for PA that invades the cavernous sinus, existing in around 10% of cases [152]. Indeed, injury to the internal carotid artery typically occurs during aggressive surgery of macroadenomas extending in the cavernous sinus. These injuries are rare (0% to 0.68%) but may be responsible for mortality [153]. Intracranial hemorrhage is very rare and results from internal carotid lesion, carotid-cavernous fistulas or pseudo-aneurysm, all as a result of aggressive surgery within the cavernous sinus. The overall mortality rate following pituitary adenoma surgery is reported to be between 0% to 0.68% and 0% to 0.9% in endoscopic and microsurgical series respectively [133, 144, 145, 147]. Delayed vascular complications following such surgery can also occur several weeks or even years after such procedure [154]. Trans-cavernous surgery also has a high risk of cranial nerve morbidity [104, 155, 156]. It is mainly these major complications that can be largely avoided following the combined approach where the cavernous sinus portion (in our series) is treated with radiosurgery.

Regarding GKS, tThe two major risks of complications in PA are pituitary insufficiency and visual loss. In non-secreting PA, pituitary insufficiency varies between 0 to 25% and visual complications between 0 to 4.8% [157-162]. In secreting PA, pituitary insufficiency varies between 0 to 19% in acromegaly [163-166], between 0 to 16% in Cushing disease [167-169] and between 0 to 49% in prolactinomas [164, 170, 171]. The most important predictors are the treatment maximal dose and the target volume. Recent papers have shown the importance of the dose received by the pituitary stalk (cut-off at 4.1 Gy) [172] and by the pituitary gland (cut-off at 15 Gy) [173] as predictors of pituitary insufficiency. This is the most frequent complication, usually appearing within 12 months, but it can also appear as a late side-efffeect (up to 100 months) [174]; andit is more frequent after previous radiation therapy. Visual complications can be avoided when using a dose of no more than 8 Gy to the optic apparatus.

As the optic pathway is the most sensitive intracranial structure, the risk increases in cases of previous radiation therapy. A safety distance is necessary to ensure optimal GKS planning. In our unit this is achieved by the use of peroperative spacer (fat or muscle tissue) and is of valuable help to avoid such type of complications. Still used in some centers and also in specific cases, conventional radiation therapy caries a risk of endocrine dysfunction of around 50%, with also a risk of vascular complications (less than 5%), optic neuropathies (1 to 2%), secondary malignancy (1-3%), neuropsychological deficit (less than 1%) and radiation necrosis (less than 1%) [161, 163, 165, 175-177].

Conclusion

Early results from our series of patients who underwent combined treatment for large benign skull base tumors show that there is an excellent clinical outcome with respect to preservation/improvement of neurological functions. Microsurgery (trans-cranial and/or endoscopic trans-nasal) and GKS are to be viewed as complementary treatment modalities. For achieving optimal results, there needs to be a perfect collaboration between the microsurgeon and the GKS surgeon. Preoperative planning of the strategy is crucial to assign parts of the tumor to individual treatment modalities. The inherent philosophy of this treatment along with its safety-efficacy evaluation depends largely on a good understanding of both therapeutic steps and modalities, each of which is of high importance. While the microsurgeon can avoid operating on the part of the tumor that is at highest risk, the GKS surgeon needs to appreciate that surgery will modify local conditions and thereby make GKS treatment planning more difficult. Under these conditions, the contact between the two neurosurgeons is crucial for both the pre-operative strategy and the GKS planning. As long-term results emerge, this multimodal treatment paradigm could become the standard of care for the management of difficult benign skull-base tumors.

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