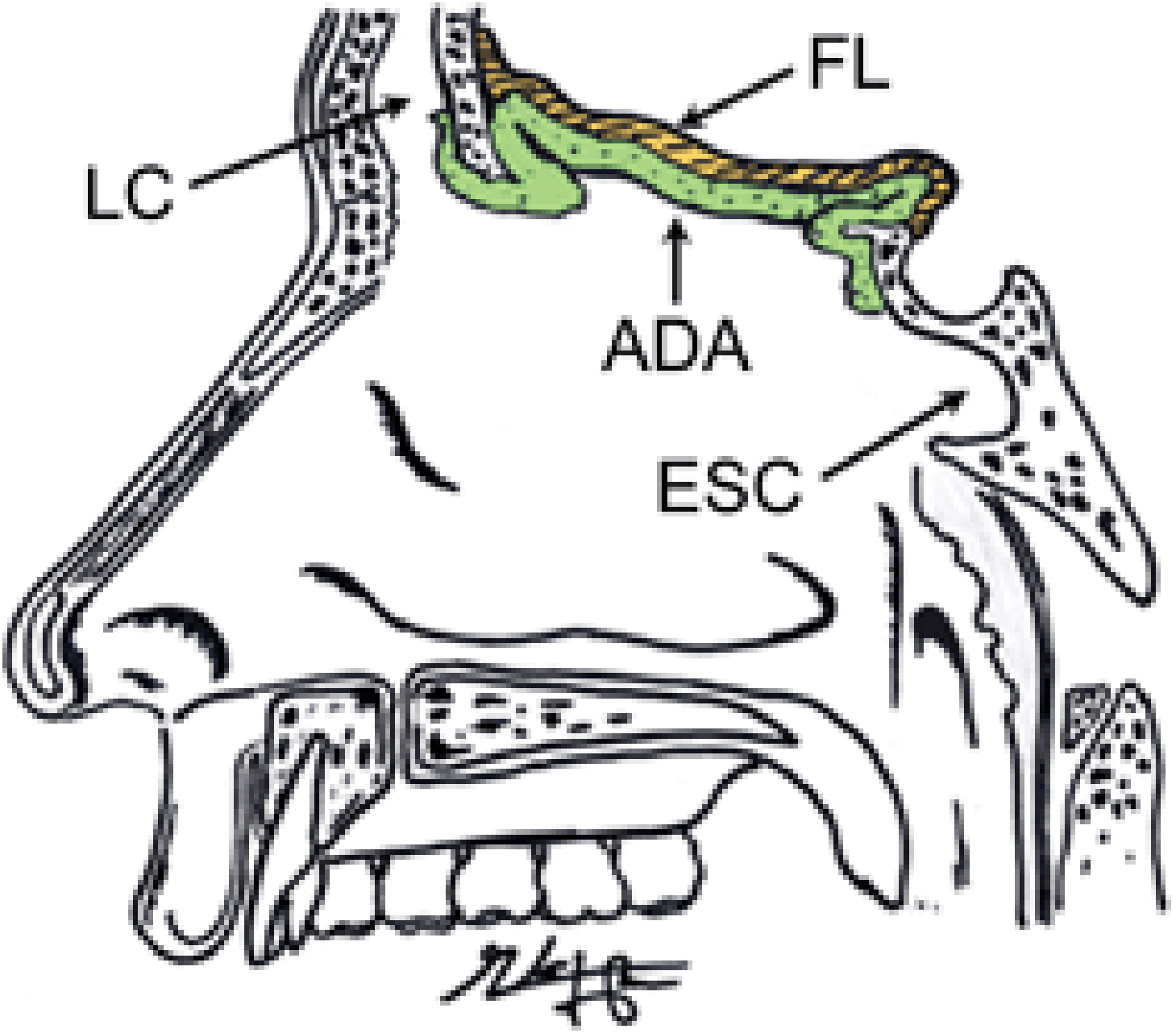
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Introduction

Skull base meningiomas

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Skull base meningiomas represent some of the most complex problems facing neurosurgeons. Often indolent in their presentation with minimal symptoms, they may be formidable lesions to remove, with a correspondingly high morbidity rate due to vascular or nerve compromise.

In this issue of *Neurosurgical Focus*, we have compiled a series of papers covering many facets of the surgical management and evolving medical management of skull base meningiomas. Topics include radiological evaluation of characteristic sinus changes adjacent to skull base meningiomas (Gibbons et al.), and the novel use of protoporphyrin to detect resection limits and margins in meningioma surgery (Roberts et al.). There are several papers that provide timely reviews of the state of the art in techniques and the limitations of endoscopic resection of anterior skull base and parasellar meningiomas (Liu et al., Van Gompel et al., and Couldwell et al.). Important selection case criteria are discussed by the authors for the use of these approaches. The authors of additional papers on surgical technique discuss the graded level of craniofacial approaches (Baskaya et al.), management of meningioma within the optic canal (Al-Mefty et al.), posterior fossa meningiomas (Roche et al.), and management and outcome of aggressive hemangiopericytomas (Schirmer et al.).

Finally, the issue includes 2 wonderful overviews of our current understanding of molecular genetics (Pham et al. and Yang et al.), which identify several potential avenues of targeted therapy for those meningiomas that defy surgical cure. In this regard, Shulz et al. provide a current overview of their interesting experience with somatostatin analog for unresected meningiomas. Postoperative hydrocephalus occurs following some cases of meningioma resection, and the risk factors for this occurrence are reviewed in a large series of patients presented by Burkhardt.

Taken together, the issue covers a wide range of topics that will be of very practical importance to any neurosurgeon (and other clinicians) who provide treatment for these challenging patients. We thank all the authors and *Neurosurgical Focus* administrative staff for helping put together this comprehensive issue. *(DOI: 10.3171/2011.3.FOCUS1185)*

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Surgical decision-making strategies in tuberculum sellae meningioma resection

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Object. Although the transcranial route (TCR) has been the traditional approach for removing tuberculum sellae meningiomas (TSMs), the use of the microscopic and/or more recently the endoscopic transsphenoidal approach (ETSA) has gained acceptance for selected cases. In this study, the authors present their experience with the ETSA and the TCR and examine the criteria most important for deciding the optimal approach in a particular case.

Methods. The authors retrospectively reviewed recent cases of TSMs treated surgically by the senior author via either the TCR or the ETSA or both. Demographic information, clinical presentation, and clinical and radiological outcomes of the patients were evaluated.

Results. Twenty-seven patients underwent removal of a TSM during a recent period. Gross-total or near-total resection was achieved in 20 (91%) of 22 patients who underwent resection via the TCR and in 3 (60%) of 5 patients who underwent the ETSA. Among the patients in whom gross- or near-total resection was achieved, recurrence was observed in only 1 patient, whose tumor was removed via the ETSA.

Conclusions. In the majority of patients, the TCR provided complete resection of the tumor without compromising the safety of the procedure. In select cases of tumors with a reasonable size and location (midline and/or extending into the sphenoid sinus) as well as no involvement of inaccessible neurovascular and bony elements via this approach, the ETSA could also be a viable option. *(DOI: 10.3171/2011.2.FOCUS1115)*

Key Words • **tuberculum sellae meningioma** • **transcranial route** • **endoscopic transsphenoidal surgery**

Tuberculum sellae meningiomas constitute 5%–10% of all intracranial meningiomas.[5] Visual loss and headaches are the most common presenting symptoms.[14] These tumors occupy a unique space in that they take a subchiasmal position by pushing the optic chiasm superiorly and laterally.[5] Resection of a TSM is surgically challenging because of the proximity of vital neurovascular structures including the carotid artery and optic nerves/chiasm.[10] Resection is further complicated by the fact that TSMs usually have a firm, rubbery consistency and often require sharp dissection rather than simple suctioning for their removal.[14] Various approaches to the tuberculum sellae region have been used for resection.[11] Traditionally, a variety of craniotomies (pterional, unilateral subfrontal, bilateral subfrontal, and so forth) have been used in an attempt to find the most direct route to this region with the fewest potential complications or anatomical limitations.[5]

While transsphenoidal surgery for pituitary adenomas has been practiced successfully for more than 50 years, in the past 25 years there have been many different innovative strategies for extending the transsphenoidal approach to other areas of the cranial base.[4,6,7] Since the first description of the ETSA,[15] there has been steady interest in using the transnasal approach to remove tumors of the parasellar area and anterior skull base.[5–7,12,14] Recently, the ETSA has been used to treat TSMs, and studies have shown that tumors can be removed effectively and safely from the tuberculum sellae region via this route.[5,6,11,13,14] However, there has been much discussion and controversy over when to use the ETSA and when to approach a TSM via the traditional TCR.

In this report, we present a series of 27 consecutive patients with TSMs surgically treated via the TCR or the ETSA, including case descriptions of the ETSA procedures. We describe our experience and compare the advantages and disadvantages of approaching TSMs via the TCR and ETSA. We specifically evaluated pre- and postoperative images from patients who underwent resection via the ETSA as well as, intraoperatively, what tumor characteristics affected TSM resectability with this approach.

Methods

The OpCoder operative database at the University of Utah was queried to identify patients who had surgery for TSM between January 2002 and December 2010. Patients

Abbreviations used in this paper: ETSA = endoscopic transsphenoidal approach; GTR = gross-total resection; NTR = near-total resection; TCR = transcranial route; TSM = tuberculum sellae meningioma.

with meningiomas arising from the clinoid processes, olfactory groove, or diaphragma sellae were excluded. The hospital charts of included patients were then reviewed to determine patient demographics, surgical approaches used, and patient outcome. This retrospective review was approved by the University of Utah Institutional Review Board. All chart reviews and data acquisition were in compliance with the regulations determined by the University of Utah Institutional Review Board and with the Health Insurance Portability and Accountability Act of 1996. The pre- and postoperative clinical evaluations included a detailed neurological examination with formal visual field and acuity tests (Goldmann perimetry and Snellen chart, respectively). Neuroimaging was also evaluated in considering which approach would be used. Computed tomography and MR imaging were utilized for the initial diagnosis as well as the assessment of postoperative outcome.

Clinical and endocrinological outcomes were evaluated at 3–4 weeks postoperatively. Patients underwent clinical and neuroradiological (MR imaging with and without Gd unless otherwise contraindicated) evaluations at 4–5 months after surgery and annually thereafter.

Transcranial Approach

A standard pterional approach was used preferentially by the senior author (W.T.C.) in all cases. This approach involves a wide pericranial flap preparation and satisfactory removal of the sphenoid ridge as far down as the superior orbital fissure. The dura mater is opened in a curvilinear fashion on the floor of the frontal fossa. Slight frontal retraction is applied, and the tumor is exposed in its entirety on the tuberculum sellae. The tumor is first devascularized, working toward an inferomedial direction on the tuberculum sellae with bipolar coagulation. This step is followed by debulking of the tumor either by piecemeal cutting with microscissors or by ultrasonic surgical aspiration. Then an arachnoidal dissection plane between the tumor and optic nerve is followed, and the tumor is gently dissected away from the optic nerve medially. The remaining portion of the tumor is again cut out in a piecemeal fashion using microscissors. Dura over the anterior clinoid is cut, dissected, and removed. Anterior clinoid is drilled away, and the optic canal is unroofed, which can be performed bilaterally if indicated by tumor extension. All hyperostotic bone is then removed with a high-speed drill. Tumor within the canal is resected away with gentle microdissection. Dural attachment of the tumor is resected and coagulated. The periosteal flap and fat graft are then laid over the tuberculum sellae and planum sphenoidale in case of opening the sphenoid sinus.

Endoscopic Transsphenoidal Approach

In purely endoscopic cases, we do not place an endonasal retractor but instead work through both nares. The rostrum of the sphenoid sinus is identified, and the sphenoid ostia is located. The rostrum of the sphenoid is removed together with the adjoining perpendicular plate of the ethmoid and the posterior cartilaginous septum. The interior of the sphenoid sinus is then exposed in the usual fashion, and all mucosa is exenterated. Specialized microinstruments, such as curved and angled alligator microscissors, a long monopolar coagulator with a malleable tip, and malleable-tip microring curettes, facilitate resection at the lateral extremes of the exposure. In addition, long, narrow bipolar forceps with up- or down-angled fine tips are used. Access to the anterior cranial base is facilitated by slight extension of the patient's head and direct viewing more superiorly. The bone of the tuberculum sellae is removed by first extracting a small amount of bone over the anterior sellar wall to expose the anterior circular sinus and then by extending this bony removal rostrally with microrongeurs. If the bone is hyperostotic, the use of a high-speed drill may be necessary. Bony removal in this location also yields additional exposure of the suprasellar region. The surgeon must remain cognizant of the position of the circular sinus, which demarcates the anterior extension of the sella, the anterior communicating artery complex superiorly, the ethmoid sinuses anteriorly, and the optic nerves superolaterally. The optic canals are identified and drilled in their most proximal extent to remove tumor in the inferior and medial canal if necessary. After tumor removal, the dural defect must be carefully repaired. We prefer to use abdominal fascia or fascia lata and fat for this purpose. The sella and sphenoid regions are closed as previously described.[3]

Results

Twenty-seven patients were treated by the senior author for specifically located TSMs during the study period (Table 1). Twenty-two of the patients (81.5%) were women, and the ages of all the patients ranged from 23 to 77 years (mean 54 years). The main presenting symptom was vision loss, which occurred in 85.2% of the patients. Of the patients without visual symptoms, 1 presented with a headache, 1 had an incidental TSM, and 1 had cognitive difficulties. Tumor sizes ranged from 1.3 to 5.4 cm.

The ETSA was initially applied in 5 patients (18.5%), and the TCR was used in the remaining 22 (81.5%). Three patients (Cases 13, 17, and 27) who initially underwent the ETSA required a subsequent surgery for treatment of the TSMs. In 1 of these patients (Case 17), the ETSA was converted to a TCR after the TSM was found to be extremely hard and not amenable to resection via the ETSA. Another patient (Case 13) had an NTR except for a tiny portion of tumor capsule along the internal carotid artery; a recurrence of the TSM developed 2 years later. She required a TCR for the recurrent TSM from the NTR performed earlier. The last patient (Case 27) underwent a planned staged procedure with biopsy and debulking of the ethmoidal/sphenoidal sinuses via the ETSA and a subsequent TCR for most of the remaining tumor. The TSM in this case was unusual because it had extension into the cavernous sinus with extensive involvement precluding a GTR by either surgical approach.

The early postoperative outcome was GTR or NTR in 81.5% of the patients (22 of 27) who initially underwent the TCR and in 60% of the patients (3 of 5) who initially underwent the ETSA. These outcomes were confirmed with MR imaging performed 4–5 months after surgery.

A postoperative CSF leak requiring subsequent sur-

TABLE 1: Summary of characteristics and outcomes in 27 patients with TSMs*

Case No.	Age (yrs), Sex	Tumor Size (mm)	Presentation	Previous Treatment	Approach	Outcome	Complication
1	51, F	24 × 55 × 56	bilat blindness	none	TCR	GTR	none
2	23, F	17 × 18 × 18	lt eye visual loss	none	TCR	GTR	none
3	39, F	25 × 20 × 20	incidental finding, optic nerve compression	none	TCR	GTR	none
4	65, M	20 × 15 × 10	lt eye visual loss	none	TCR	GTR	none
5	46, F	20 × 27 × 37	HA, rt eye visual loss & field cut	none	TCR	GTR	none
6	46, F	15 × 18 × 18	lt eye visual loss & field cut	TCR	TCR	GTR	none
7	41, M	27 × 25 × 22	HAs	none	translabial ETSA w/ fat & fascia graft	GTR	CSF leak 1 wk postop after episode of nausea/vomiting; CSF leak resolved after repacking op
8	48, F	NA	HA, mild lt field cut	none	TCR	GTR	none
9	65, F	NA	bitemporal visual field cuts & decreased rt acuity	none	TCR	GTR	none
10	65, F	15 × 18 × 18	lt visual loss	none	TCR	GTR	none
11	72, M	NA	lt eye blindness	none	TCR	GTR	none
12	50, F	18 × 28 × 25	bilat vision loss rt>lt	none	TCR	GTR	none
13	65, F	15 × 17 × 15	bilat vision loss & bitemporal hemianopia	none	ETSA; TCR resection of recurrent meningioma	NTR w/ tiny piece left attached to ICA; tumor recurred & NTR achieved	none; tumor recurred along lt optic nerve 3 yrs later
14	52, F	13 × 24 × 18	lt eye visual loss	none	TCR	GTR	none
15	67, M	45 × 44 × 35	bilat severe vision loss for several yrs (blind in rt eye & only light perception in lt eye), HA	none	TCR	GTR	steroid & thyroid supplementation & DDAVP as needed
16	36, M	24 × 15 × 20	bitemporal hemianopia	previous cranial biopsy & stereotactic radiosurgery	TCR	GTR	none
17	39, F	20 × 20 × 21	lt eye vision loss	none	aborted ETSA w/ fat graft; TCR	aborted; GTR	none
18	77, F	25 × 21 × 17	rt eye complete vision loss & severe vision loss in lt eye	none	ETSA & fat/fascia	GTR	none
19	38, F	NA	bilat vision loss & bitemporal hemianopia	none	TCR	GTR	none
20	69, F	NA	bilat vision loss (lt>rt)	outside hospital craniotomy 3 mos earlier	TCR	GTR	none
21	65, F	5.4 × 4.9 × 4.5	cognitive difficulties	none	TCR	GTR	none
22	66, F	5.0 × 4.0 × 4.0	bilat visual loss (lt>rt)	none	TCR	partial resection	meningioma stable for 6 yrs since op

(continued)

TABLE 1: Summary of characteristics and outcomes in 27 patients with TSMs* ***(continued)***

Case No.	Age (yrs), Sex	Tumor Size (mm)	Presentation	Previous Treatment	Approach	Outcome	Complication
23	38, F	15 × 20 × 17	lt eye visual loss	none	TCR	STR	meningioma stable for 7 yrs since op
24	51, F	NA	rt eye visual loss	none	TCR	GTR	none
25	68, F	NA	lt eye visual loss (already blind in rt eye)	3 previous craniotomies & radiation	TCR	GTR	subsequent wound infections requiring free flap by plastic surgery for repair
26	48, F	15 × 20 × 25	rt eye visual loss	none	TCR	GTR	none
27	68, F	35 × 19 × 30	progressive rt facial numbness	previous transnasal biopsy at outside hospital	ETSA; TCR	biopsy & ethmoid/sphenoid sinus debulking; STR	none; residual tumor in cavernous sinus stable for 3 yrs

* DDAVP = desmopressin acetate; HA = headache; ICA = internal carotid artery; NA = no preoperative imaging available; STR = subtotal resection.

gical sphenoid repacking developed in 1 patient (Case 7). Another patient (Case 15) required steroid and thyroid supplementation in addition to occasional desmopressin acetate doses for transient diabetes insipidus after the removal of a massive TSM. The only other complication was multiple wound infections in 1 patient (Case 27) that required plastic surgery to aid in closure of the wound with a flap procedure. However, this patient had already undergone 3 previous craniotomies and radiation therapy before being referred to us for treatment. Of note, no patients had worsening of their preoperative visual symptoms.

Illustrative Cases

Case 7. This 41-year-old man presented with progressive headaches that worsened in frequency and intensity. Magnetic resonance imaging demonstrated a large TSM with inferior sellar extension (Fig. 1A and B). Because of the midline location and inferior sellar extension of the TSM, an ETSA was performed. The tumor was soft and descended easily, and we were able to resect the tumor inferiorly in the sella while preserving the normal pituitary gland. By using the endoscope at the end of the case, we found and removed a tiny spot of tumor that was difficult to see with just the microscope. A GTR was achieved (Fig. 1C and D), and the patient fared very well despite having to return to the operating room 1 week later to have a CSF leak repaired with repacking of a fat and fascia graft. He has not had any other complications in the 69 months since his surgery.

Case 13. This 65-year-old woman presented with bilateral loss of visual acuity and bitemporal hemianopia. Magnetic resonance imaging showed a very small TSM (Fig. 2A and B), which was amenable to resection via the ETSA. The resection was judged to be near total because there was a question of a tiny tumor capsule along the internal carotid artery seen with the endoscope at the end of the operation (Fig. 2C and D). The patient had a recurrence of her tumor 26 months later, with tumor lateral to the carotid artery and above the optic nerve in the region of the anterior clinoid process as well as left optic nerve compression (Fig. 2E). Resection via TCR was necessary to remove the tumor, and this procedure was complicated by extensive scarring in and around the optic nerve. Therefore, another NTR was performed. The patient has not had any complications since the TCR 13 months ago.

Case 17. This 39-year-old woman presented with a several-month history of left eye visual loss and headaches. Her workup included MR imaging of the brain, which demonstrated a small TSM centered midline without lateral extension beyond the internal carotid arteries (Fig. 3A and B). Because the tumor size and location were amenable to the approach, an ETSA was begun, but the tumor was found to be extremely hard in consistency and could not be mobilized. Given the difficulty in removing the lesion

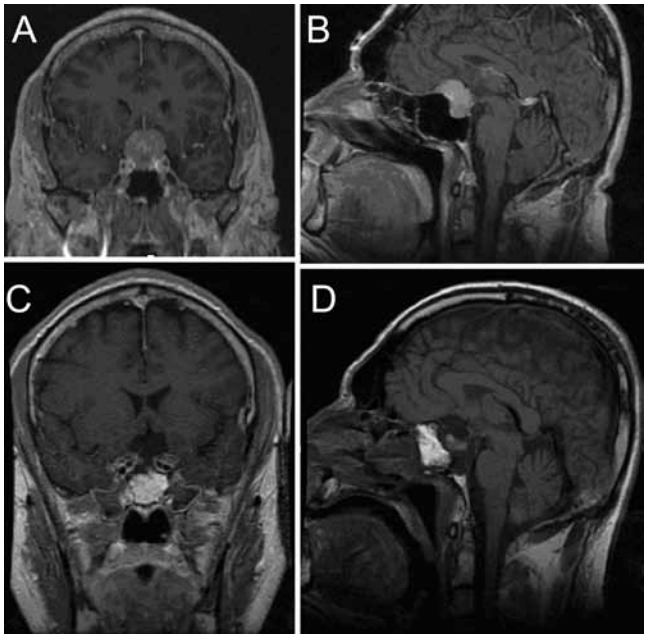

Fig. 1. Case 7. Preoperative coronal **(A)** and sagittal **(B)** contrast-enhanced T1-weighted MR images showing a large TSM with inferior sellar extension. Postoperative coronal **(C)** and sagittal **(D)** contrast-enhanced T1-weighted MR images showing GTR of the TSM.

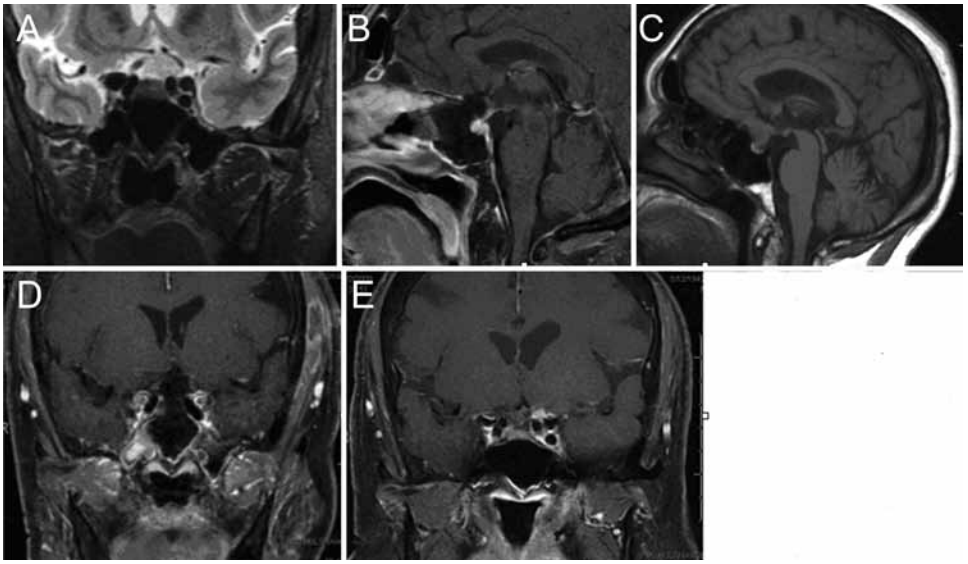

Fig. 2. Case 13. Preoperative coronal T2-weighted **(A)** and sagittal contrast-enhanced T1-weighted **(B)** MR images showing a TSM attached to the tuberculum sellae and compressing the optic nerves and chiasm. After an NTR via ETSA, sagittal **(C)** and coronal **(D)** fat-suppressed, contrast-enhanced T1-weighted MR images were obtained, demonstrating no evidence of residual tumor, although a small tumor capsule was seen on the carotid artery intraoperatively. Three years after TSM removal, the patient presented again with recurrent visual loss in the left eye. Coronal fat-suppressed, contrast-enhanced T1-weighted MR image **(E)** showing tumor above and lateral to the optic nerve. The patient underwent TCR with NTR of the TSM.

via this approach, we aborted the ETSA and instead performed a right pterional craniotomy, approaching the optic nerve using a subfrontal approach. We achieved GTR after a long piecemeal removal of this very hard tumor (Fig. 3C and D). The patient has done well without any complications since her surgery 9 months ago.

Case 18. This 77-year-old woman presented with a 3-year history of complete visual loss in her right eye and severe visual loss in her left eye. She was aphasic after a large left middle cerebral artery stroke 5 years earlier, and her aphasia led to a delay in diagnosis resulting in severe bilateral visual loss preoperatively. A TSM was determined to be midline and not large (Fig. 4A and B), and the decision was made to use the ETSA for resection. Intraoperatively, the tumor was found to be very soft and easily dissectible; GTR was achieved (Fig. 4C and D). The patient had no complications from the procedure and was doing well 8 months after surgery.

Discussion

In this review, we have focused on the choice of approach (transfacial compared with transcranial) to tumors specifically located at the tuberculum sellae. We have not included tumors of the planum sphenoidale or olfactory groove, in which endonasal approaches may be performed more simply;[3] neither have we included clinoidal lesions or tumors of the diaphragma sellae, for which the senior author would definitely choose a transcranial approach.

Advantages and Disadvantages of TCR and ETSA

The ETSA offers several advantages and desirable qualities as compared with the TCR (Table 2). The approach is the most direct to the tuberculum sellae, and the extraarachnoidal plane found in TSMs can be used to aid in tumor removal.[9] For patients with tumors in the midline, the approach does not require any brain retraction for tumor exposure. Thus, the olfactory nerve(s) is exposed to less risk of stretch injury than during the TCR, which is important given that olfactory nerve injury and anosmia

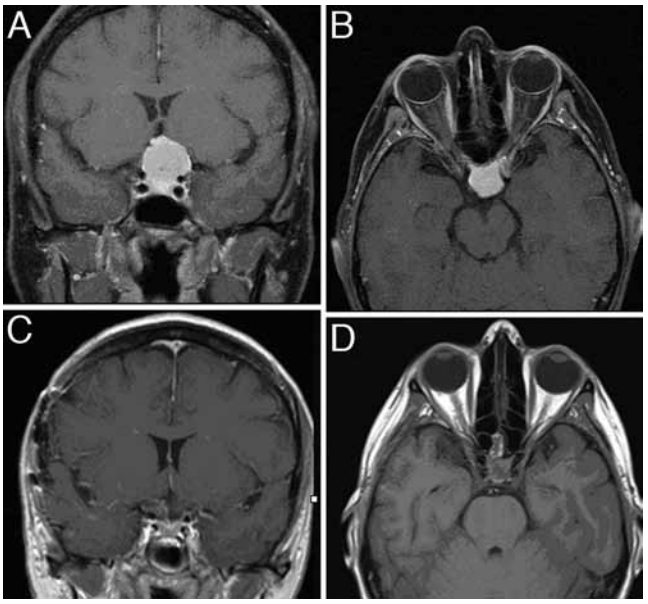

Fig. 3. Case 17. Preoperative coronal T1-weighted MR image with contrast enhancement **(A)** and axial contrast-enhanced, fat-suppressed T1-weighted MR image **(B)** demonstrating an avidly homogeneously enhancing TSM compressing the optic chiasm, with significant compression of the left optic nerve. Postoperative coronal **(C)** and axial **(D)** contrast-enhanced, fat-suppressed T1-weighted MR images showing that GTR was achieved via a TCR after the mass was found to be extremely hard and not amenable resection via the ETSA.

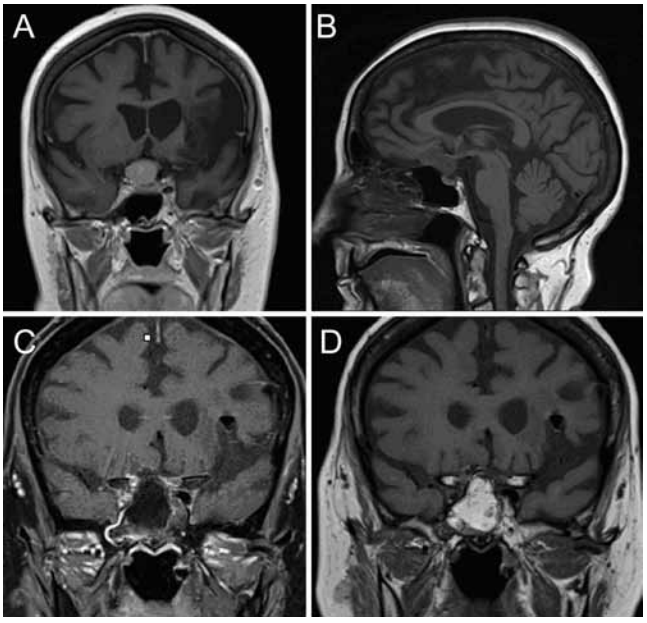

Fig. 4. Case 18. Preoperative coronal T1-weighted MR image with Gd enhancement **(A)** and sagittal T1-weighted MR image without contrast enhancement **(B)** showing a homogeneously enhancing TSM. The mass is centered at the tuberculum sellae and is right of midline. There is mass effect on the optic nerves and optic chiasm. Postoperative coronal T1-weighted MR images with **(C)** and without **(D)** contrast enhancement showing the GTR and hyperintense fat graft.

have recently been reported to be as high as 30% with some TCR operations.[10] The entire region medial to the carotid artery and optic nerve is visible, in contrast to the exposure in a unilateral TCR; however, the ETSA allows for little or no manipulation of the neural structures.[4] Another advantage is that a tumor extending down into the sella can be easily removed via the ETSA (as in Case 7). Furthermore, endoscopic visualization offers the ability to look laterally around corners with appropriately angled endoscopes. It has been our experience that a view through the endoscope after initial tumor removal using the microscope allows us to find tumor remnants that are not clearly visible with the microscope. Although the TCR for TSM resection has yielded high rates of NTR and GTR, the route has led to worsened vision in up to 20% of patients;[11] this worsened vision usually does not improve. The optic apparatus is thought to be especially vulnerable because of chronic compression, and the TCR often makes it difficult to visualize critical subchiasmatic perforators that can be preserved with the ETSA.[11] One recent study showed visual improvement in 11 of 12 patients who underwent the ETSA for TSM resection.[14] In another study, the authors performed 12 TCR cases consecutively followed by 16 consecutive ETSA cases and found that ETSA significantly improved visual acuity, although visual field defects were unchanged.[12] Furthermore, a recent meta-analysis showed that approximately 60% of patients who underwent TCR had improved visual function, whereas 74% of patients had improvement in visual function after an ETSA.[5] Presumably, the lack of retraction on the delicate optic apparatus and preservation of its critical vascular supply explain improved visual outcomes.[9,11,14] Furthermore, injury to the brain parenchyma with subsequent seizures and hemorrhage in TCR has been shown to occur less frequently with the ETSA.[5] Finally, the ETSA is an attractive option in elderly patients or those who are otherwise not good surgical candidates because the approach is less invasive and can be easier to tolerate given that it has been shown to cause less blood loss.[4,12] In these patients, even if a GTR is not achieved, meningiomas are usually highly responsive to stereotactic radiosurgery with low associated complication rates, and adjuvant stereotactic radiosurgery can be performed if necessary.[1,7]

Despite the many advantages offered by the ETSA, the drawbacks are also numerous and significant. Perhaps the most well-known drawback is the chance of CSF leakage, which can occur with the removal of bone and dura underlying the tumor. Bone removal anterior to the tuberculum sellae, as in the ETSA, is associated with a significantly higher risk of CSF fistulas than a standard transsphenoidal approach to the sella.[2,4,6] In a series of 4 patients who underwent ETSA, we noted 1 CSF leak (25%); and a recent meta-analysis of transsphenoidal approaches for TSM resection revealed a similar 20% rate of CSF leakage.[5] In contrast, CSF leaks from a TCR are rare. The other main disadvantage of the ETSA is the difficulty in removing tumor or its dural attachment from over the optic nerve in the canal or above and lateral to the anterior clinoid process. For this reason we recommend the ETSA for smaller TSMs, that is, those smaller than 3 cm. As TSMs enlarge, they tend to grow beyond the narrow visual corridor that the ETSA provides.[4] It is also important to make sure that these lesions do not have vascular encasement or that they have not extended laterally on either side of the internal carotid arteries or optic nerves. One must also verify that the brain is free of edema, which suggests that the subdural arachnoidal plane may not be intact.[10] It is also important to note that ETSA has a steep learning curve because of its unique anatomical view, and this is an important point for those deciding whether to use the ETSA.

Choice of Surgical Approach

Our small series of patients who underwent the ETSA for TSM removal demonstrates some important teaching points. Tuberculum sellae meningiomas are vascular lesions that usually receive their blood supply from dural vessels, ethmoidal arteries, and sometimes other branches.[14] The patient in Case 7 had multiple feeding vessels that were easily coagulated and cut, which allowed for devascularization of the tumor at the first step. This early devascularization created a less bloody tumor resection for the rest of the case and demonstrates how the ETSA can offer advantages over the TCR by providing improved visualization during tumor resection.[9] A recent retrospective study showed that surgical blood loss is reduced with the ETSA as compared with the TCR.[12]

Tuberculum sellae meningioma consistency seems to substantially influence resectability via the ETSA. Two (Cases 7 and 18) of our 3 patients in whom gross-total or near-total TSM resections through the ETSA had tumors that were very soft, whereas in the patient (Case 17) in whom the ETSA procedure was aborted, the tumor was incredibly hard. We preoperatively counsel all of our pa-

TABLE 2: Advantages and disadvantages of TCR and ETSA for resection of TSM

Op Approach	Advantages	Disadvantages
TCR	familiarity	easily visible scar
	allows direct visualization of microneurosurgical dissection of tumor from vessels/nerves	frontal lobe retraction
	critical vessel & nerve anatomy identified early	basal approach required for early devascularization of tumor from tuberculum
	easy removal of anterior clinoid & any tumor superior or lateral to optic nerve	increased potential blood loss
		tumor medial to ipsilateral carotid artery/optic nerve difficult to resect
ETSA	easy surgical approach	CSF leak/fistulae more likely the more anteriorly the ETSA is extended
	cosmetically pleasing (no scars)	difficulty removing tumor over the optic nerve or above/lateral to anterior clinoid process
	more direct access to tumor & bony attachments	larger tumors are much more difficult to resect
	no brain retraction required	
	early indirect decompression achieved w/ initial tumor removal	
	less chance for olfactory nerve injury	
	hyperostotic bone removed	
	no blind spots from carotid to carotid	
	if sellar extension of tumor, then easy removal	
	preserved arachnoidal plane allows for protected dissection	
	potentially shorter recovery time	
	may be better in older patients who are poorer surgical candidates (less blood loss)	

tients that the ETSA procedure can be aborted for a TCR if the intraoperative meningioma consistency will not allow a safe resection. New technologies are being used to resect TSMs of a hard consistency, but we recommend switching to a TCR if this situation is encountered intraoperatively.[8] The disadvantage of using the ETSA for such hard tumors is that there is no opportunity to remove the tumor under direct bimanual endoscopic control if the tumor is so hard or calcified that it does not allow deformation during the dissection process. In the senior author's opinion, proceeding with the ETSA in such circumstances increases the risk for cranial nerve deficit.

The ETSA can be offered to patients who refuse to have a TCR or who may not be as good surgical candidates since blood loss has been shown to be less with the ETSA and there is no brain retraction.[5] In these patients, even if a GTR or NTR is not achieved, stereotactic radiosurgery has been well proven to provide good control of typical meningiomas, with one recent paper demonstrating 87% control for skull base meningiomas.[1]

Evaluating lateral extension of the TSM is critical in selecting the correct approach.[10] The tumor recurrence in the patient in Case 13 illustrates the importance of selecting tumors for ETSA that remain medial to the supraclinoid internal carotid arteries and optic nerves.[7] When tumors extend into the carotid arteries or optic nerves, the ETSA resection is much more difficult as visualization is significantly compromised (Fig. 5). In the patient in Case 13, there appeared to be a tiny tumor capsule along the carotid artery that could not be comfortably accessed via the ETSA. Our suspicions of residual tumor capsule were confirmed when the tumor recurred after 3 years. The subsequent TCR was much more difficult because of the extensive scarring in the region, and an NTR was achieved. Conversely, when a TSM is located inferiorly or between the optic nerves, it can be very difficult to resect via a TCR, and the ETSA is a much better approach.

There are also occasions, such as with the patient in Case 27 in our series, in which a planned 2-stage procedure is performed because each approach can reach areas that the other approach cannot. The patient had extensive sphenoidal/ethmoidal extension of a TSM that could not be reached via the TCR but also had extreme lateral extension of the meningioma into the cavernous sinus that could not be reached through the ETSA. This case exemplifies the special situations in which each approach may be jointly implemented to achieve their respective goals to provide the patient with the best resection possible.

Conclusions

Because each approach has unique advantages and

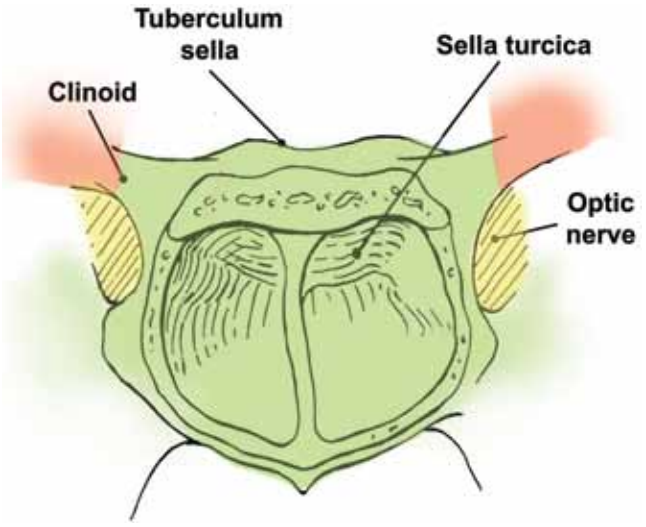

Fig. 5. Illustration showing the zones of access of the ETSA. *Green* indicates the region accessible via this approach; *yellow,* the optic nerve; and *red,* inaccessible zones. Figure modified with permission from Hardy J, McCutcheon IE: Pituitary microadenomas, in Apuzzo M (ed): **Brain Surgery: Complication Avoidance and Management.** New York: Churchill Livingstone, 1993, pp 276–295.

disadvantages, the choice to use an ETSA or a TCR for TSM resection must be made based on the specific characteristics of each case. Based on our experience and a review of the literature, we suggest several factors that should be considered when evaluating the surgical options. The ETSA is a safe and effective means of removing a TSM when it is smaller than 3 cm, is located medial to the internal carotid arteries, has dural attachments that are inferior to the optic nerve in the optic canal and do not extend beyond the clinoid processes, or extends inferiorly into the sella. The ETSA can also be an effective strategy in elderly patients with multiple comorbidities who may not be able to tolerate a prolonged craniotomy, as there is less blood loss with the ETSA.[12] However, it is the opinion of the senior author that while the ETSA approach may be suitable for many lesions of the anterior skull base,[3] these cases must be chosen carefully. More anteriorly located lesions of the planum sphenoidale or olfactory groove lend themselves to removal by this technique frequently. However, tumors of the tuberculum sellae must be well chosen, and the approach must not limit the ability to perform a complete Simpson Grade 1 removal.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Couldwell. Acquisition of data: Bowers, Altay. Analysis and interpretation of data: Bowers, Altay. Drafting the article: Bowers, Altay. Critically revising the article: Couldwell. Reviewed final version of the manuscript and approved it for submission: Couldwell.

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Surgical nuances for removal of tuberculum sellae meningiomas with optic canal involvement using the endoscopic endonasal extended transsphenoidal transplanum transtuberculum approach

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Tuberculum sellae meningiomas frequently extend into the optic canals. Radical tumor resection including the involved dural attachment, underlying hyperostotic bone, and intracanalicular tumor in the optic canal offers the best chance of a Simpson Grade I resection to minimize recurrence. Decompression of the optic canal with removal of the intracanalicular tumor also improves visual outcome since this portion of the tumor is usually the cause of asymmetrical visual loss.

The purely endoscopic endonasal extended transsphenoidal approach offers a direct midline trajectory and immediate access to tuberculum sellae meningiomas without brain retraction and manipulation of neurovascular structures. Although the endoscopic approach has been previously criticized for its inability to remove tumor within the optic canals, complete Simpson Grade I tumor removal including intracanalicular tumor, dural attachment, and involved hyperostotic bone can be achieved in properly selected patients. Excellent visualization of the suprasellar region and the inferomedial aspects of both optic canals allows for extracapsular, extraarachnoid dissection of the tumor from the critical structures using bimanual microsurgical dissection.

In this report, the authors describe the operative nuances for removal of tuberculum sellae meningiomas with optic canal involvement using a purely endoscopic endonasal extended transsphenoidal (transplanum transtuberculum) approach. They specifically highlight the technique for endonasal bilateral optic nerve decompression and removal of intracanalicular tumor to improve postoperative visual function, as demonstrated in 2 illustrative cases. Special attention is also given to cranial base reconstruction to prevent CSF leakage using the vascularized pedicled nasoseptal flap. *(DOI: 10.3171/2011.3.FOCUS115)*

Key Words • endoscopic endonasal approach • skull base • extended transsphenoidal approach • transplanum transtuberculum • tuberculum sellae meningioma • optic canal involvement

Tuberculum sellae meningiomas are surgically formidable tumors of the cranial base because of their anatomical location and proximity to critical neurovascular structures. They represent approximately 4%–10% of all intracranial meningiomas and typically arise from the region of the tuberculum sellae, chiasmatic sulcus, limbus sphenoidale, and diaphragma sellae.[9,27,47] These tumors are typically situated in a suprasellar midline position, displacing the optic chiasm posteriorly and slightly superiorly, and the optic nerves laterally.[9] Thus, they can occupy either a prechiasmatic and/or an infrachiasmatic location.[27,37] The most common clinical manifestation is progressive visual loss, thereby prompting decompressive surgical treatment with the goal of visual preservation or improvement. Total surgical removal of the tumor, associated dural attachment, and involved hyperostotic bone with preservation of visual function, neurovascular structures, and endocrine function is the ideal treatment.

Extension of tuberculum sellae meningiomas into the optic canals can be seen in approximately 67%–77% of cases,[43,55] and patients usually present with marked asymmetrical visual symptoms (Figs. 1 and 2).[52] Some have reported improved postoperative visual function when the optic canal is decompressed early during the operation.[46,49] Bony decompression with dural opening of the optic canal has been recommended by some to resect the intra-

Abbreviation used in this paper: OCR = opticocarotid recess.

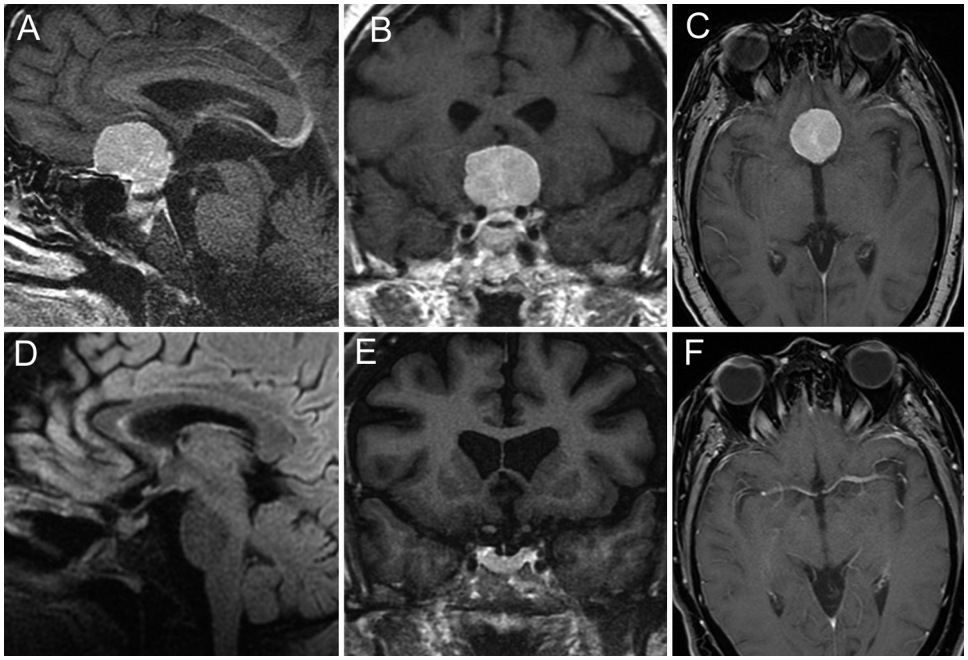

Fig. 1. Case 1. **A–C:** Preoperative T1-weighted post-Gd sagittal **(A)**, coronal **(B)**, and axial **(C)** MR images demonstrating a tuberculum sellae meningioma with optic compression. Complete Simpson Grade I removal including underlying hyperostotic bone was achieved using the endoscopic endonasal extended transsphenoidal approach. **D–F:** Postoperative sagittal **(D)**, coronal **(E)**, and axial **(F)** MR images showing gross-total resection of the tumor with decompression of the optic nerves and preservation of the pituitary stalk and gland.

canalicular portion of the tumor.[43,44,46,49,55] This maneuver has been reported to improve vision in 78%–80% of patients because it provides immediate decompression for rapid relief and alleviation of ischemia to the compromised nerve.[43,55] Access to the optic canals is critical not only for visual outcome, but also for extent of resection, as unaddressed residual tumor in the optic canal can be a source of recurrence or failure of visual improvement.[56]

Various transcranial surgical approaches to remove tuberculum sellae meningiomas include unilateral or bilateral subfrontal, bifrontal interhemispheric, supraorbital, eyebrow keyhole supraorbital, frontolateral, frontotemporal/pterional, orbitopterional, and orbitozygomatic approaches.[3,5,11,23,24,29,36,43,46–50,55] More recently, there has been interest in endonasal extended transsphenoidal approaches (microscopic, microscopic with endoscopic assistance, and purely endoscopic) to remove tuberculum sellae meningiomas.[7,8,12,13,15,16,21,25,31,32,35,37,58,59] The purely endoscopic endonasal extended transsphenoidal route via a transplanum transtuberculum corridor offers direct and immediate exposure to the tumor without having to apply brain retraction and manipulation of neurovascular structures. Because the dural origin is adjacent to the paranasal sinuses, early devascularization of the tumor and subsequent radical resection of the involved hyperostotic bone, dural attachment, and optic canal involvement can be achieved. Excellent dynamic close-up and panoramic visualization of the suprasellar region, including the superior hypophysial perforators to the undersurface of the optic apparatus and the inferomedial aspect of the optic canals, can be achieved without compromise of illumination. Extracapsular, extraarachnoid dissection of the tumor from the surrounding optic apparatus and anterior communicating artery complex using conventional bimanual microsurgical techniques can be performed with preservation of the arachnoid planes. However, the ability to perform optic nerve decompression and remove intracanalicular tumor associated with tuberculum sellae meningiomas using the endoscopic endonasal approach has not been well emphasized in the literature. In addition, several proponents of transcranial approaches have criticized the endonasal approach as being limited by its inability to decompress and remove tumor from the optic canals.[43,49,55]

In this report, we review the surgical technique and describe our operative nuances for removal of tuberculum sellae meningiomas with optic canal involvement using a purely endoscopic endonasal extended transsphenoidal (transplanum transtuberculum) approach. We specifically highlight the technique for endonasal optic nerve decompression and removal of intracanalicular tumor to improve postoperative visual function, as demonstrated in 2 illustrative cases. Special attention is also given to cranial base reconstruction to prevent CSF leakage using the vascularized pedicled nasoseptal flap.

Surgical Technique

Patient Positioning

The patient undergoes general anesthesia with the endotracheal tube secured to the patient's left side so that it is out of the way of the operating surgeon, who stands on the patient's right side. Although some surgeons may prefer to place a lumbar drain prior to final positioning for postoperative temporary CSF diversion, we no longer use postoperative lumbar drainage because of potential complications arising from intracranial hypotension (see

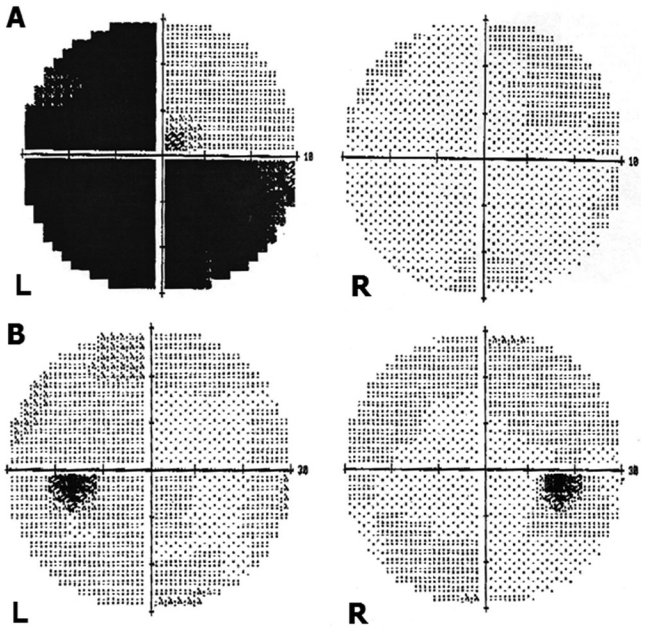

Fig. 2. Case 1. **A:** Preoperative visual field assessment demonstrating significant temporal and inferior nasal field loss in the left eye (L). The patient was only able to count fingers in the left eye. The right eye (R) was 20/20 with normal visual fields. Tumor extending into the left optic canal was removed along with the suprasellar component. **B:** Postoperative visual field assessment at 1 month after surgery demonstrating restoration of vision to 20/20 acuity in both eyes with normal visual fields. This presentation of asymmetrical visual loss is highly suggestive of optic canal involvement from tuberculum sellae meningiomas.

Case 2 below). The patient is positioned supine with the bed reflexed so that the head is slightly above the heart to allow good venous return. After the head is stabilized in a 3-point Mayfield head frame, the head is flexed gently toward the left shoulder, slightly rotated toward the right shoulder, and slightly extended. This head positioning optimizes the operating surgeon's comfort in accessing the nose from the patient's right side and facilitates access to the anterior skull base. Frameless stereotactic navigation is used to guide the extent of bone resection from the planum sphenoidale to provide adequate exposure and trajectory to the tumor. The nose and nares are prepared with Betadine solution followed by packing with Afrin-soaked pledgets. A thigh incision is also prepared for harvesting autologous fascia lata for dural repair and reconstruction. Intravenous antibiotics (preferably ampicillin/sulbactam) and 10 mg of dexamethasone are given at the start of the operation. Unless the patient has preexisting seizures, we do not routinely administer anticonvulsants for endonasal removal of meningiomas since the tumor removal is performed in an extraarachnoid fashion without brain retraction.

Endoscopic Endonasal Transsphenoidal Approach

For endoscopic endonasal approaches to the skull base, we use a multidisciplinary team approach comprised of a skull base neurosurgeon (J.K.L.) working simultaneously with an otolaryngologist specializing in endoscopic sinus and skull base surgery (J.A.E.). Using a binostril (binarial) technique without the nasal speculum, both surgeons can work simultaneously with 3–4 instruments in the field at a time (the so-called "3- to 4-handed binostril technique").[26] The otolaryngologist performs the initial endonasal exposure to the sphenoid sinus using a 4-mm-diameter, 18-cm-long, 30° endoscope (Karl Storz). Although most authors report using a 0° endoscope for the exposure and resection,[7,8,15–17,26,37] we prefer to use a 30° endoscope because of its versatility in providing the same degree of surgical exposure as with a 0° endoscope, but with the benefits of additional angled viewing capabilities around corners, without having to repeatedly exchange the 2 endoscopes. After injecting the nasal septum and the tail and anterosuperior attachment of the middle turbinates with 1% lidocaine with epinephrine (1:100,000 dilution), both middle and inferior turbinates are lateralized using a Goldman elevator. If necessary, the right middle turbinate can be removed to accommodate more instruments in the right nostril. After identifying both sphenoid ostia, a wide sphenoidotomy, posterior ethmoidectomy, and posterior septectomy are performed with a microdebrider and rongeurs. This creates an adequate working space for multiple endoscopic instruments to be inserted into both nostrils, which are triangulated at the deep surgical target. In some cases during the posterior ethmoidectomy, one may encounter an Onodi cell, a posterior ethmoid cell that is positioned superolateral to the sphenoid sinus. This is important to recognize because the optic nerve and carotid artery may often course through the lateral aspect of that cell.

We prefer to harvest a pedicled vascularized nasoseptal flap for later skull base dural repair at this juncture so that further exposure of the skull base can be safely performed while preserving the integrity of the vascular pedicle to the flap. The flap is harvested in a similar manner as described by Hadad et al.[28] and rotated inferiorly into the nasopharynx. Exposure of the sella, tuberculum sellae, and planum sphenoidale is achieved by maximizing the sphenoidotomy, posterior ethmoidectomy, and posterior septectomy with care to protect the vascular pedicle to the nasoseptal flap. Injury to the pedicle can compromise the integrity and effectiveness of the flap. It is important to ensure that there is no overhang of bone or soft tissue obstructing the line of sight to the planum sphenoidale target or inhibiting the surgical freedom of instrument maneuverability. Approximately 1.5–2 cm of the posterior septum is removed to allow triangulation of surgical instruments through both nostrils so that bimanual microsurgical dissection can be performed.

Transplanum Transtuberculum Exposure (Extended Transsphenoidal)

For the remainder of the operation at this juncture, the neurosurgeon works simultaneously with the otolaryngologist using a 2-surgeon, 3- to 4-handed binostril technique. While the otolaryngologist provides dynamic endoscopic visualization of the surgical target, the neurosurgeon can perform continuous bimanual microsurgical dissection with a suction primarily in the left hand inserted into the right nostril, and a drill, dissector, scissors, bipolar forceps, or tissue aspirator in the right hand inserted into the left nostril. Because the 30° endoscope

provides a direct "looking-up" view toward the tuberculum sellae and planum sphenoidale, we recommend placing the endoscope at the 6 o'clock position with the suction placed in the 12 o'clock position in the right nostril. The neurosurgeon is therefore working "above" the position of the scope while maintaining optimal surgical visualization. Alternatively, if a 0° endoscope is used, the scope is placed at the 12 o'clock position and the suction instrument at the 6 o'clock position.

The endonasal removal of bone at the skull base includes the sella, planum sphenoidale, tuberculum sellae, and both medial OCRs to unroof the optic canals. This is achieved using a high-speed curved endonasal diamond drill (Medtronic Xomed) with copious irrigation. We prefer to use a double-barrel suction-irrigating instrument that allows continuous self-irrigation to keep the surgical field clear of bone dust while cooling the drill tip from overheating near important neurovascular structures. The bone over the sella is initially removed followed by the bone of the planum sphenoidale. In some cases, the planum can be hyperostotic, as is expected with some meningiomas. We prefer to perform a wide opening of the planum so that there is no bony hindrance to the surgical freedom of dissecting instruments during intradural tumor removal. It is important to remove the planum anteriorly to the posterior cribriform so that there is an adequate anterosuperior trajectory to come anterior and superior over the top of the tumor during intradural extracapsular dissection.

The remaining tuberculum strut along with both medial OCRs are removed so that bilateral optic nerve decompression is achieved. The medial OCR is a critical landmark in locating the optic nerve canal as it joins the middle clinoid process. From the endonasal perspective, the medial OCR appears as an indentation in the bone that is formed at the medial junction of the parasellar carotid canal and the optic canal. It represents the pneumatization of the middle clinoid process and the lateral aspects of the tuberculum sellae.[26,33] The lateral OCR represents the pneumatization of the anterior clinoid process and is located at the lateral junction of the parasellar carotid canal and the optic canal. The tuberculum strut along with both medial OCRs are carefully drilled down to eggshell thickness. An up-angled 5-0 curette is then used to remove the remaining egg-shelled tuberculum strut. Removal of the medial OCRs unroofs the medial aspect of the optic canals, and facilitates exposure of the optic nerves and paraclinoid carotid arteries in the opticocarotid cistern.[33] Venous bleeding from the cavernous sinus and the superior intercavernous sinus can be readily controlled with Gelfoam or Surgiflo (Ethicon, Inc.) followed by gentle pressure with cottonoid pledgets. Drilling can be continued anteriorly to join the medial orbital wall, if necessary. Bony decompression of the extradural optic nerve sheath will provide access to open up the dural sheath into the posterior orbit to remove tumor within the optic canal. This maneuver is analogous to dividing the falciform ligament into the posterior orbit after an anterior clinoidectomy from a transcranial approach to decompress the optic canal.[49,55] The inferomedial and superomedial aspects of the optic canal can be readily accessed and decompressed using angled endoscopes and angled instrumentation. However, the superior and superolateral portions of the optic canal become more inaccessible from the endonasal approach.

Prior to opening the dura, the extent of skull base bone removal is inspected to ensure that the tumor and both optic canals can be adequately accessed without any obstruction to the line of sight or hindrance to the surgical maneuverability of instruments. The dura over the planum is coagulated with a pistol-grip endoscopic bipolar forceps to devascularize the meningioma. Adequate hemostasis and final confirmation with stereotactic navigation are achieved before proceeding with intradural exposure.

Intradural Exposure and Tumor Resection

We prefer to open the dura in a transdiaphragmatic fashion similar to the technique described by Weiss.[60] Using a No. 15 blade, a cruciate incision is made over the sellar dura followed by a second horizontal incision in the planum dura anterior to the superior intercavernous sinus. The superior intercavernous sinus is then coagulated with a pistol-grip endoscopic bipolar forceps and subsequently divided across the diaphragma sella with scissors to obtain direct access to the supradiaphragmatic suprasellar cistern. Care is taken to preserve the pituitary gland and stalk, so as to avoid traction on the stalk.

Initial intracapsular tumor debulking is performed using an extended tip endonasal ultrasonic aspirator. In fibrous meningiomas that do not respond to ultrasonic aspiration, we prefer to use a Gyrus Diego microdebrider (Olympus) that removes tissue by using rotating blades with integrated suction (Fig. 3). To reach tumor located deeper in the suprasellar space, an angled tip microdebrider can be used. Care is taken to ensure that the microdebrider tip remains intracapsular, so as not to breach the tumor capsule. Once adequate tumor debulking is achieved, collapse of the tumor capsule and extracapsular dissection of the tumor away from the neurovascular structures can be performed using bimanual microsurgical dissection techniques. Care is taken not to prematurely amputate the tumor capsule, so as not to "lose the handle" that serves to provide countertraction for extracapsular dissection.

Although meningiomas are histologically arachnoid-derived tumors, they are anatomically dural-based, and thus, displace the arachnoid ahead of them as they grow.[11] As such, these tumors are extraarachnoid structures with an arachnoid barrier that separates the tumor capsule from the neurovascular structures (anterior communicating artery complex and perforators, optic nerves and chiasm, and pituitary stalk).[11,23] It is important to identify the double arachnoid layer and to differentiate the tumor arachnoid from the cisternal arachnoid. In larger tumors, this may appear as a single layer of arachnoid. Extracapsular tumor dissection under direct vision is best carried out between the tumor capsule and the tumor arachnoid, not the cisternal arachnoid. Preservation of this arachnoid barrier provides protective coverage over the critical neurovascular structures, and thus, minimizes the risk of vascular injury and ischemia to the optic apparatus that

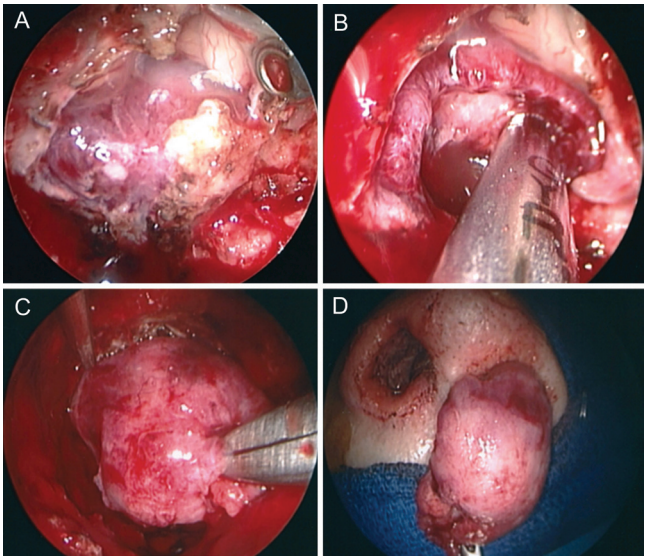

Fig. 3. Case 1. Intraoperative photographs demonstrating tumor removal with a 30° endoscope. **A:** The dural base has been cauterized to devascularize the tumor, which is visualized in the suprasellar space. **B:** Intracapsular debulking of the fibrous tumor is performed with a microdebrider to facilitate collapse of the tumor capsule for subsequent extraarachnoid extracapsular dissection from the critical structures. **C and D:** Once the tumor capsule has been dissected free from all the surrounding neurovascular structures, the tumor can be safely delivered through the nose. Bimanual microsurgical dissection principles and techniques are maintained during endoscopic tumor removal.

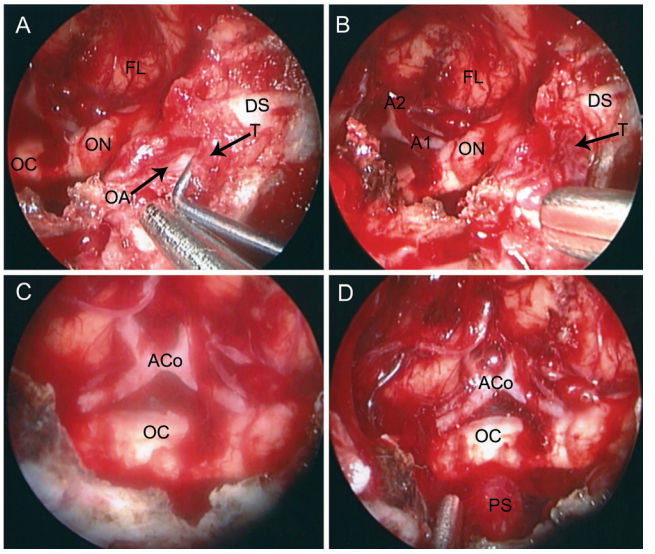

Fig. 4. Case 1. Intraoperative photographs. **A and B:** A 30° angled endoscope directed toward the left side demonstrating tumor extension (T) into the left inferomedial aspect of the optic canal. The A_1 and A_2 segments of the anterior cerebral artery are identified as well as the left frontal lobe (FL), optic nerve (ON), and optic chiasm (OC). The dural sheath (DS) is opened up with an angled blade, and a blunt hook is used to dissect the intracanalicular tumor off of the optic nerve. Care is taken to preserve the ophthalmic artery (OA) during intracanalicular tumor removal. This maneuver is analogous to opening the falciform ligament and dural sheath via a transcranial approach. **C and D:** Final inspection of the suprasellar structures using the underwater hydroscopy (diving) technique **(C)** and standard open-air interface **(D)** with an upviewing 30° endoscope. Complete tumor removal was achieved with decompression of the optic chiasm and preservation of the anterior communicating artery complex (ACo) and pituitary stalk (PS).

can potentially result in postoperative visual worsening.[12,23,34,43] Small perforators that supply the undersurface of the optic chiasm and nerves reside within the arachnoid and need to be preserved to avoid postoperative visual loss. The use of bipolar cautery in the subchiasmatic region should be minimized or avoided to preserve the blood supply to the optic apparatus. The key to preserving visual function is to minimize direct manipulation or trauma to the optic nerves and to avoid injury to the blood supply of the optic apparatus.[5,23,27,29,34]

It is important to avoid blind pulling of the tumor capsule, as this may increase the risk of arterial avulsion or optic nerve traction if the tumor has not been adequately dissected free from the critical neurovascular structures. Gentle countertraction of the tumor capsule can be applied with the suction to identify the arachnoid plane to carry out sharp dissection from the critical structures. Once the tumor capsule is completely dissected free from both optic nerves, optic chiasm, and the anterior communicating artery complex, the remaining tumor capsule can be delivered through the nose (Fig. 3). If the tumor is strictly adherent to any critical structure, such as the optic nerves, anterior cerebral artery, internal carotid artery, or perforators, a small remnant should be left behind, so as to avoid a major neurovascular complication. Complete tumor resection should not be achieved at the cost of increased rates of morbidity or mortality.

At this point, both optic canals are inspected with a 30° endoscope. The medial aspect of the optic dural sheath is opened with an angled hook to expose the optic nerve as it traverses the optic canal (Fig. 4). This maneuver is analogous to dividing the falciform ligament and opening the optic dural sheath to decompress the optic nerve in a transcranial approach. Tumor that has extended into the optic canal can be readily removed to optimize visual function and minimize recurrence. Care is taken to identify and preserve the ophthalmic artery when working in the optic canal. Final inspection of the surgical cavity is performed to look for any residual tumor. We often use the suction-irrigator tool to deliver continuous irrigation so that underwater hydroscopy can be performed (so-called endoscopic diving technique), as described by Locatelli et al.[42] This technique can optimize visualization with a dynamic fluid film lens, wash out any small residual tumor in the suprasellar cistern, and exert hydrodynamic pressure to facilitate hemostasis (Fig. 4).

Closure and Skull Base Reconstruction

Successful reconstruction of the skull base dural defect is paramount to preventing a postoperative CSF leak. An autologous fascia lata graft is harvested from the thigh and placed as an inlay graft with the edges of the graft tucked underneath the dural edges. Stamp-size pieces of Surgicel are placed over the bony defect to temporarily hold the fascia graft in place. Although some have described placing a fat graft intradurally in the resection cavity to obliterate dead space,[37] we prefer not to have any substance in contact with the optic apparatus to avoid potential swelling of the

fat graft and mass effect resulting in postoperative visual loss.[12] The key component to the closure is coverage by the vascularized nasoseptal flap, which is rotated superiorly to cover the dural closure and bony skull base defect. It is important to confirm that the edges of the nasoseptal flap are in contact with demucosalized bone to ensure flap adherence.[26,28,33] A thin layer of tissue sealant, Duraseal (Covidien) or Tisseel (Baxter Healthcare Corp.) fibrin glue, is administered over the nasoseptal flap followed by Gentamicin-soaked Gelfoam pledgets to buttress the flap repair. Sealant should not be placed in between the dural closure and the nasoseptal flap, as this may prevent flap adherence. A Merocel (Medtronic Xomed) nasal pack is then placed in the nasal cavity to bolster the Gelfoam layer and is left in place for about 10 days. The patient is maintained on antibiotics until the packs are removed. Because the patient is already in a CSF hypovolemic state at the end of surgery, we now prefer not to use postoperative lumbar drainage to avoid complications of CSF hypotension (see Case 2 below). Absence of a lumbar drain allows the patient to recover quicker and mobilize sooner, thus minimizing the risk of thromboembolic and pulmonary complications. Since the nasoseptal flap is robust and well-vascularized tissue, we believe that additional lumbar drainage is not necessary as long as meticulous preparation of the flap and reconstruction is performed as described above. We have not experienced any CSF leakage using this protocol in 14 cases of endoscopic endonasal resection of anterior skull base and suprasellar lesions including craniopharyngiomas, meningiomas, giant pituitary adenomas, and sinonasal malignancies.

Illustrative Cases

Case 1

History and Examination. This 62-year-old woman presented with visual loss in the left eye that progressed over the past 12 months. Magnetic resonance imaging demonstrated a 3-cm tuberculum sellae meningioma with mass effect on the optic chiasm and displacement of the anterior communicating artery (Fig. 1). Preoperative visual examination demonstrated visual acuity of 20/20 in the right eye with normal fields, but only finger counting in the left eye via a superior nasal quadrant (Fig. 2).

Operation. A transplanum transtuberculum, endoscopic endonasal extended transsphenoidal approach was used to remove the tumor. Hyperostotic bone at the tuberculum sellae was removed, and bilateral extradural decompression of both optic nerve canals was performed endonasally. The tumor was quite fibrous and required use of a rotation-suction microdebrider to debulk the tumor. Bimanual extracapsular dissection was performed to dissect the tumor from both optic nerves and anterior communicating artery complex (Fig. 3). The optic sheaths were opened bilaterally and intracanalicular tumor was removed from the left optic canal (Fig. 4). Suprasellar hydroscopy using the endoscopic diving technique, as described by Locatelli et al.,[42] was performed to facilitate hemostasis and inspection of the field (Fig. 4C). Complete Simpson Grade I removal was confirmed after inspection was performed using a 30° endoscope. The anterior skull base dural defect was repaired with an autologous fascia lata inlay graft followed by a vascularized pedicled nasoseptal flap. No lumbar drainage was used after surgery.

Postoperative Course. Postoperatively, the patient was neurologically intact with immediate improvement in her vision (20/20 in the right eye, 20/40 in the left eye, improved visual fields with only small superior temporal quadrant defect in the left eye). Postoperative MR imaging demonstrated gross-total resection of the tumor without any evidence of residual tumor (Fig. 1). Three-dimensional reconstruction of the postoperative CT angiogram demonstrated removal of the planum sphenoidale, tuberculum sellae, and middle clinoid processes, as well as bilateral medial optic canal unroofing (Fig. 5). At the 1-month follow-up, her vision returned to 20/20 bilaterally without any visual field deficit. At 3 months' follow-up, she remained neurologically stable with a well-mucosalized skull base defect. There was no postoperative CSF leakage.

Case 2

History and Examination. This 38-year-old woman presented with a 3-year history of headaches and progressive visual loss in the right eye. Her visual acuity was 20/20 in the left and 20/400 in the right eye via a small superior nasal field only. Magnetic resonance imaging demonstrated a 2.7-cm enhancing tuberculum sellae meningioma with enhancement in the right intracanalicular and orbital apex optic nerve sheath consistent with optic canal invasion (Fig. 6).

Operation. A transplanum transtuberculum, endoscopic endonasal extended transsphenoidal approach was used to remove the tumor. Hyperostotic bone at the tuberculum sellae was removed. Early extradural decompression of both optic nerve canals was performed endonasally prior to dural opening. After internal debulking of the tumor, bimanual extracapsular dissection was performed to dissect the tumor from both optic nerves and anterior communicating artery complex (Fig. 7). Opening the optic sheaths bilaterally allowed removal of intracanalicular tumor that had invaded both optic canals (Fig. 7C). Complete Simpson Grade I removal was confirmed after inspection was performed with the aid of a 30° endoscope. The anterior skull base dural defect was repaired with an autologous fascia lata graft followed by a vascularized pedicled nasoseptal flap (Fig. 8). Lumbar drainage at 5 ml per hour was instituted after surgery.

Postoperative Course. Postoperatively, the patient was neurologically intact with an improved visual examination. On the 3rd postoperative day, the patient developed increased confusion and transient visual worsening bilaterally, which was attributed to intracranial hypotension and CSF hypovolemia from postoperative lumbar drainage. The postoperative MR image demonstrated gross-total removal of the tumor without any evidence of residual tumor. However, there were radiographic signs of intracranial hypotension including increased enlargement of the pituitary

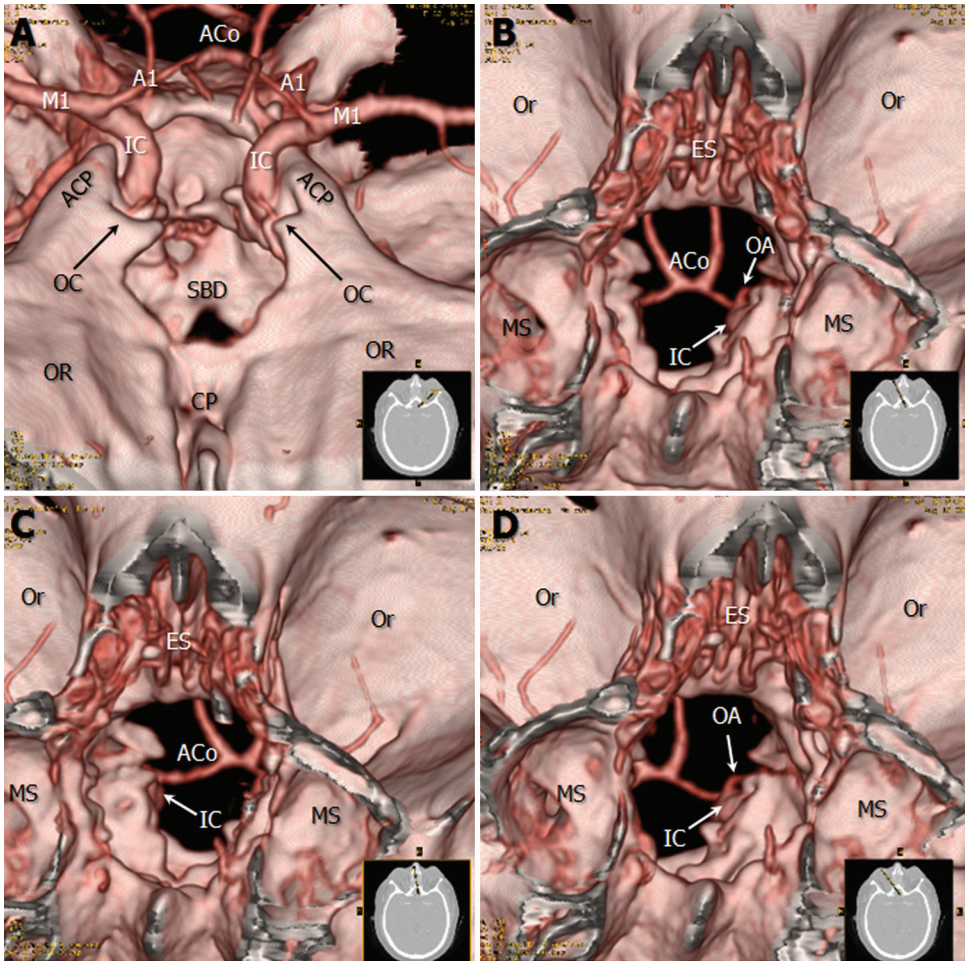

Fig. 5. Case 1. Postoperative 3D reconstructed CT angiograms demonstrating multiple views of the anterior skull base defect (SBD) and surrounding vasculature after a transplanum transtuberculum approach with bilateral optic canal decompression. **A:** View looking from above showing removal of the planum sphenoidale, tuberculum sellae, and both medial optic canals (OC). **B:** A midline endonasal view demonstrating the anterior communicating artery complex in the suprasellar space. The left internal carotid artery (IC) and ophthalmic artery are also visualized. **C and D:** Side-angled views mimicking the view from a 30° endoscope looking toward the right optic canal **(C)** and left optic canal **(D)**. Note that both optic canals have been unroofed medially. ACP = anterior clinoid process; A1 = A_1 segment of anterior cerebral artery; CP = cribriform plate; ES = ethmoid sinus; M1 = M_1 segment of middle cerebral artery; MS = maxillary sinus; OR = orbital roof; Or = orbit.

gland, engorgement of the bilateral cavernous sinuses, and pachymeningeal enhancement and thickening of the retroclival meninges (Fig. 6). Lumbar drainage was discontinued, and the patient improved clinically back to her neurological baseline. Her vision improved to 20/20 in the left eye and 20/60 in the right with significant resolution of the prior visual field deficit at 6 weeks' follow-up. There was no postoperative CSF leakage.

Discussion

Transcranial Approaches for Tuberculum Sellae Meningiomas

The surgical removal of tuberculum sellae meningiomas remains a formidable challenge because of their deep location and intimate involvement with critical neurovascular structures, including the optic apparatus, pituitary stalk, and anterior cerebral artery complex and associated perforators. Total surgical removal, including the tumor, involved dural attachment, and hyperostotic bone, is the most optimal strategy in preventing recurrence.[5,9,43]

Tuberculum sellae meningiomas have traditionally been approached through a transcranial route. In the microneurosurgical era, numerous reports have been published on using a unilateral or bilateral subfrontal, bifrontal interhemispheric, supraorbital, eyebrow keyhole supraorbital, frontolateral, frontotemporal/pterional, orbitopterional, or orbitozygomatic approach.[5,23,27,29,34,46–49,55] In a meta-analysis of modern transcranial microsurgical series by de Divitiis et al.,[16] total resection was achieved in 90% with visual improvement in 59% and visual preservation in 30%. The mortality rate was 2.8%. The complication of postoperative visual deterioration has been reported in up to 20% of cases.[10,14,23,29,50,53] Other reported craniotomy-related complications have included olfactory nerve damage resulting in anosmia, CSF leak requiring additional transnasal surgery, hemorrhagic infarction resulting in shunt-dependent hydrocephalus, wound infection requiring bone

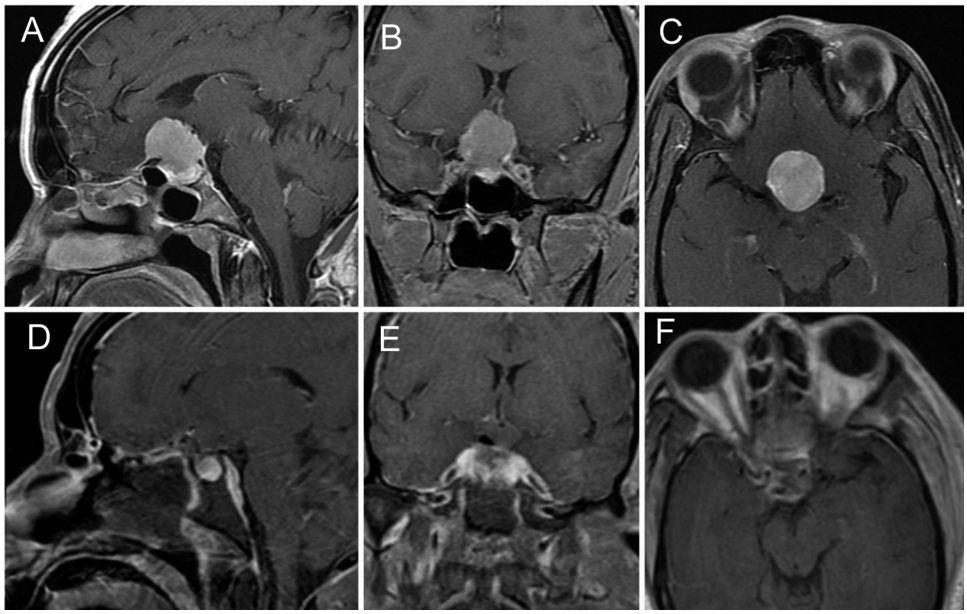

Fig. 6. Case 2. **A–C:** Preoperative T1-weighted post-Gd sagittal **(A)**, coronal **(B)**, and axial **(C)** MR images demonstrating a tuberculum sellae meningioma with suprasellar extension. Hyperostosis of the tuberculum sellae is seen on the sagittal view **(A)**. Complete Simpson Grade I resection including underlying hyperostotic bone was performed using the endoscopic endonasal extended transsphenoidal approach. **D–F:** Postoperative T1-weighted post-Gd sagittal **(D)**, coronal **(E)**, and axial **(F)** MR images showing gross-total resection of the tumor. The patient experienced transient neurological worsening from lumbar drain–induced intracranial hypotension. Note the interval enlargement of the pituitary gland **(D)**, venous engorgement of the bilateral cavernous sinuses **(E)**, and the pachymeningeal enhancement and thickening of the retroclival dura that is characteristic of intracranial hypotension. The patient returned to her neurological baseline after clamping and removal of the lumbar drain.

flap removal, cerebral edema, and venous infarction.[43,47] In general, transcranial approaches usually require some degree of brain retraction and manipulation of neurovascular structures to obtain complete removal. Benjamin and Russell[5] noted that one disadvantage of the pterional approach was that it was difficult to remove tumor located underneath the ipsilateral optic nerve without some manipulation. Intracanalicular tumor extension is also on the inferomedial side of the optic canal, which is difficult to visualize from an ipsilateral anterolateral approach.

The supraorbital approach, as originally described by Jane et al.,[30] is essentially a supraorbital unilateral frontal craniotomy that incorporates the orbital rim as a 1-piece bone flap that is performed through a coronal incision. Removal of the supraorbital rim provides a more basal approach to the tumor, thereby minimizing brain retraction. The working corridor is primarily through an anterior subfrontal route, and access to the suprasellar and parachiasmatic structures can be achieved. Al-Mefty and colleagues[1,43] advocated the advantages of unroofing both optic canals and drilling hyperostotic bone at the tuberculum sellae and planum sphenoidale. This is likely attributed to a more anterior subfrontal trajectory rather than a lateral transsylvian trajectory. Others have described a minimally invasive "keyhole" supraorbital approach that utilizes a smaller supraorbital craniotomy without orbital rim resection through a smaller eyebrow skin incision.[24,54] In a recent report by a group performing endonasal and keyhole supraorbital approaches for tuberculum sellae meningiomas,[24] the keyhole supraorbital approach was recommended for larger tumors (> 3.0–3.5 cm), those extending lateral to the supraclinoid arteries, or those with vascular encasement. Endonasal approaches were generally reserved for smaller, less invasive tumors. However, some have questioned the ability to adequately decompress the optic canals and to drill involved basal bone through a more limited keyhole opening.[43] This may be due to the potential for limited instrument maneuverability because of a smaller working corridor. In addition, the size of the pericranial flap for reconstruction is also smaller due to a smaller eyebrow incision, and the cosmetic result is debatable since the incision can still be visible on the face in contrast to an incision behind the hairline. In general, supraorbital approaches lack the lateral angle of attack that a transsylvian exposure affords, and are limited in accessing suprasellar lesions that extend lateral to the ipsilateral oculomotor nerve.[48] An orbitozygomatic approach can, therefore, combine the advantages of both supraorbital and lateral transsylvian routes.[4]

Evolution of Endoscopic Endonasal Approaches

The endoscopic endonasal extended transsphenoidal (transplanum transtuberculum) route provides a direct midline approach to the suprasellar region without any brain retraction or neurovascular manipulation. This approach has several advantages over transcranial approaches including early extradural optic nerve decompression bilaterally, early devascularization of the tumor resulting in a relatively bloodless tumor debulking, immediate and safe internal decompression of the tumor, excellent visualization of the infrachiasmatic perforators and inferomedial aspect of the optic nerve and op-

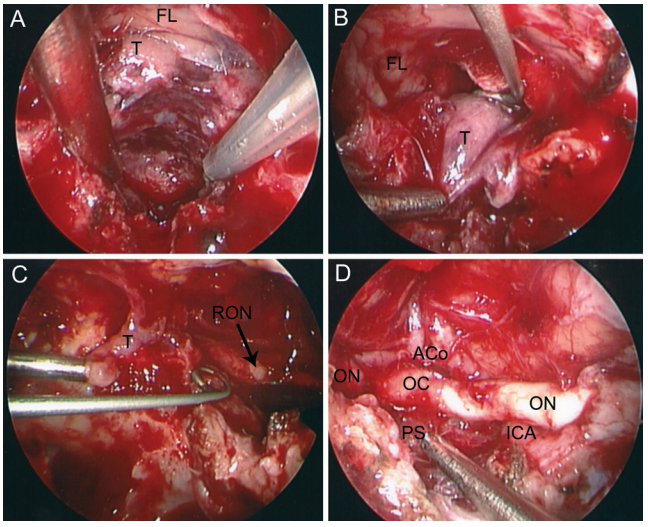

Fig. 7. Case 2. Intraoperative photographs demonstrating tumor removal with a 30° endoscope. **A:** The tumor (T) in the suprasellar space has been exposed and intracapsular debulking is performed using an ultrasonic aspirator. **B:** Meticulous bimanual extracapsular microsurgical dissection is performed to dissect the tumor from the frontal lobe (FL) and neurovascular structures. **C:** A 30° endoscopic view demonstrating removal of intracanalicular tumor that had extended into the inferomedial canal of the right optic nerve (RON). **D:** Final view of the suprasellar space demonstrating complete tumor removal with preservation of the critical structures: optic nerves, optic chiasm (OC), anterior communicating artery complex, pituitary stalk, and left internal carotid artery (ICA).

tic canal, and radical removal of the dural attachment and involved hyperostotic bone at the skull base. Unlike transcranial approaches in which tumor debulking can proceed more safely once both optic nerves are identified,[5] the endonasal approach allows for early internal decompression at its devascularized base so that extracapsular dissection away from the critical structures can be performed without any manipulation of the brain. By maintaining microsurgical principles, bimanual dissection and preservation of the arachnoid planes facilitates tumor removal. We emphasize extraarachnoid dissection of the tumor, that is, the plane of dissection be maintained between the tumor capsule and the tumor arachnoid (not the cisternal arachnoid), whenever possible, to minimize injury to surrounding critical neurovascular structures. Because the trajectory of approach is from below the optic apparatus, the endoscopic endonasal approach allows excellent visualization of the infrachiasmatic perforators and the inferomedial aspect of the optic nerves and optic canal (regions that are difficult to visualize from above with a transcranial approach).

The feasibility and success of the endoscopic endonasal approach are based on earlier work described in microsurgical extended transsphenoidal series.[12,13,21,24,31,35] Since the advent of the extended transsphenoidal approach, described initially in 1987 by Weiss,[60] and later by Mason et al. in 1997,[45] there has been increased interest in transnasal transsphenoidal access to suprasellar lesions beyond the confines of the sella turcica, such as tuberculum sellae meningiomas and supradiaphragmatic craniopharyngiomas.[12,13,21,24,31,35,40] This was initially described using a speculum-based sublabial submucosal transseptal approach, with drilling of the transplanum transtuberculum corridor for transdiaphragmatic exposure of the suprasellar region. Others have implemented an endonasal submucosal, and also a direct endonasal microsurgical route with successful removal of tuberculum sellae meningiomas.[12,13,21,24] Couldwell et al.[13] reported gross-total removal in 7 of 11 tuberculum sellae meningiomas with one complication of monocular blindness. Fatemi et al.[24] reported complete removal in 7 (50%) of 14 patients and near-total removal in 3 patients (21%), with visual improvement in 82% and visual worsening in 7%.

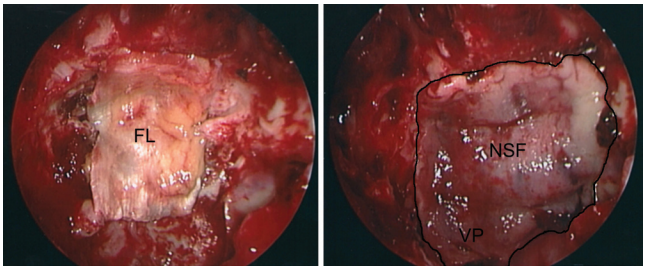

Fig. 8. Case 2. Intraoperative photographs demonstrating multilayer reconstruction of the skull base dural defect. An autologous fascia lata (FL) graft is placed as the initial layer followed by coverage with a vascularized pedicled nasoseptal flap *(black outline)*. NSF = nasoseptal flap; VP = vascular pedicle.

However, illumination becomes compromised at very high magnifications of the microscope. In addition, the operative corridor and field of view of the surgical target are limited by the aperture of the distal end of the speculum. The line of sight and surgical freedom of instrument maneuverability are also restricted by the blades of the nasal speculum. An additional relaxing nasal alar incision is sometimes made to accommodate for the nasal speculum.[12] The endoscope offers superior illumination with a wide panoramic view of the surgical target from the planum sphenoidale to the clival recess, and from one medial OCR to the other. Unlike the microscope, the endoscope also allows high magnification of the surgical target without compromise of illumination by bringing the light source and lens directly up to the target. The purely endoscopic endonasal approach allows a direct view of the inferomedial aspect of the optic nerves and optic canals bilaterally as well as the infrachiasmatic perforators.[26] This advantage facilitates safe, extracapsular dissection of the tumor off of the visual apparatus with preservation of the pituitary stalk and vascular structures. The use of angled endoscopes and angled instruments also allows for removal of intracanalicular extension of tumor. Since the pattern of tumor extension is most often through the inferomedial aspect of the optic canal, an endoscopic approach from below is very favorable for visualizing this region. Although some have reported the use of the endoscope for "looking around" and assessing the degree of resection after a speculum-based microsurgical approach (endoscope-assisted microsurgical resection),[12,13,21,31] tumor removal is still performed under microscopic and not endoscopic visualization. Thus, the advantages of the endoscope are not fully capitalized. While we recognize that the microscope and endoscope are both tools of visualization, the purely endoscopic endo-

nasal approach simultaneously combines the benefits of an extracranial transnasal route to the skull base and the superior visualization of the endoscope. This advantage allows for tumor removal and dissection of the critical structures under direct and continuous endoscopic visualization with increased range of instrument maneuverability that was previously encumbered by the nasal speculum.

Gardner et al.[26] reported complete Simpson Grade I resection in 11 (85%) of 13 tuberculum sellae meningiomas with extension into the optic canals by using a purely endoscopic endonasal approach. There were no instances of postoperative visual deterioration. This was attributed to an inferior and medial approach to the tumor to allow early decompression of the optic nerves and careful meticulous dissection of the tumor without manipulation of already compromised and ischemic optic nerves. Preservation of the infrachiasmatic perforators was also critical for visual improvement or preservation. In a report by de Divitiis et al.,[16] complete removal was achieved in 6 of 7 patients. Visual improvement was observed in 5 patients, and none had postoperative visual worsening.

Optic Canal Involvement in Tuberculum Sellae Meningiomas

Tuberculum sellae meningiomas can frequently extend into one or both optic canals, with reports as high as 67%–77% of cases.[43,49,55] Mahmoud et al.[43] reported unilateral involvement in 28% and bilateral in 40% of cases. Optic canal involvement appears to correlate with preoperative visual dysfunction.[55] Visual loss usually starts in one eye and can subsequently progress to involve the contralateral eye, if left untreated.[2,9] The presence of asymmetrical visual findings is highly indicative of optic canal involvement,[52] as seen in both patients described in this report. Unaddressed residual tumors left within the optic canal after surgery could result in persistent visual loss, visual deterioration, and future tumor recurrence.[56] This has led to several authors in recommending early optic nerve decompression and removal of intracanalicular tumor, which has resulted in favorable visual outcomes.[2,5,14,27,29,43,44,49,51,55,56] Visual improvement has been reported as high as 78%–91% in some series.[43,46,55]

The technique for early optic nerve decompression and release is generally performed using a frontotemporal pterional, supraorbital, or orbitozygomatic approach that includes a posterior orbitotomy, extradural anterior clinoidectomy, optic canal unroofing, and division of the falciform ligament.[46,55] Once the optic nerve is released, the site of constriction is often discolored where the nerve meets the falciform ligament and bony entrance of the optic canal.[46,49] Further division of the dura propria along the longitudinal axis of the optic nerve sheath and division of the distal dural ring allows further mobilization of the internal carotid artery to optimize optic nerve decompression and exposure of the optic nerve within the optic canal to facilitate intracanalicular tumor removal.[18–20] Tumor that is infiltrating the dura propria can also be removed. Using this technique, a 270° decompression from above can be achieved. However, when using an anterolateral skull base approach, such as a pterional approach, limitations in accessing the inferomedial aspect of the ipsilateral optic canal and performing wide near-circumferential decompression of the contralateral optic canal can be encountered because of the oblique, off-midline trajectory. In a review of tuberculum sellae meningiomas removed using a pterional approach, Benjamin and Russell[5] noted that tumor located beneath the ipsilateral optic nerve and tumor extension on the inferomedial side of the optic canal was difficult to visualize and access. From the pterional perspective, it may not be safe to open the contralateral optic canal circumferentially throughout its entire length.[19] Nevertheless, the inferomedial aspect of the contralateral optic nerve is easier to visualize from the ipsilateral anterolateral approach.

One of the major criticisms of the endoscopic endonasal approach is the inability to address optic canal involvement in tuberculum sellae meningiomas.[26,43] However, intracanalicular tumor commonly occupies the inferomedial aspect of the optic canal,[3,53] which is readily accessible via an approach from below. Interestingly, several proponents of pterional approaches have mentioned that the major disadvantage of the pterional approach is the difficulty in dissecting tumor from the inferomedial aspect of the ipsilateral optic nerve.[5,46] Even after optic nerve release, there is still some risk for visual deterioration after manipulating an ischemic compromised optic nerve. Because the approach is midline, the endoscopic endonasal approach allows early extradural decompression of both optic nerves, and intracanalicular tumor can be readily removed from the inferomedial aspects of both optic canals, which are the "difficult to reach" places in a pterional approach. We open the medial aspect of the dural sheath toward the posterior orbit to release the constricted optic nerve (Figs. 4 and 7). This technique is analogous to incising the falciform ligament and dural sheath in a transcranial approach. Care is taken to dissect the tumor from the optic canal with preservation of the ophthalmic artery and its small branches, which contribute to the pial network supply to the optic nerve.[6] However, when considering an endonasal approach, one should consider the limitations of optic canal decompression from below. From the endonasal approach, the inferomedial and superomedial aspects of the optic canal are readily exposed. However, the superior, superolateral, and lateral aspects of the optic canal cannot be safely accessed from below because of obstruction by the optic nerve. Thus, careful examination of preoperative imaging is necessary to determine if there is lateral extension of the dural attachment superiorly over the optic canals and anterior clinoid processes. If so, a transcranial approach would be a better choice of approach to address optic canal involvement and resect the laterally based dural attachment.

In a recent meta-analysis comparing visual outcomes of transcranial versus transsphenoidal approaches, postoperative visual improvement was seen in 75% of transsphenoidal approaches and 58.4% of transcranial approaches.[16] There was no visual worsening in the transsphenoidal series, whereas 12.9% had visual worsening in the transcranial series. The authors attribute this to minimal surgical manipulation of the optic nerves with preservation of the vascular supply to the undersurface of the optic apparatus when approached endonasally from below. This is largely due to extraarachnoid dissection to maintain the protective layer of arachnoid over the blood supply.

Limitations of the Endoscopic Endonasal Approach

One of the major criticisms of endoscopic endonasal surgery for tuberculum sellae meningiomas and other intradural tumors is the higher rate of CSF leak when compared with transcranial results. In the microsurgical transsphenoidal series, the CSF leak rate has been reported to be as high as 21%.[22] In the endoscopic endonasal series, the CSF leak rate has ranged from 10% to 28%.[15,37] However, these results did not incorporate the use of a vascularized nasoseptal flap for reconstruction.[28,33] The latter technique is an important innovation in endoscopic endonasal skull base surgery, which offers robust, vascularized tissue for coverage of skull base defects to optimize tissue healing and prevention of CSF leaks. This tissue is analogous to the pericranial flap that is used in reconstruction after transbasal and craniofacial approaches.[38,41] Emerging reports have demonstrated a significantly reduced CSF leak rate to 5.4% when reconstruction is performed with a pedicled nasoseptal flap.[26,33]

The extent of optic canal decompression and removal of intracanalicular tumor from the endonasal approach is also limited to the superomedial and inferomedial aspects of the optic nerve. The superior aspect of the optic canal becomes more difficult to decompress, and the superolateral and lateral aspects of the optic canal become rather inaccessible from below. Although tumor along the medial aspect of the optic nerves can be readily removed endonasally, tumor involvement along the lateral compartments of the optic canal cannot be safely accessed. The exposure and ability to perform safe resection during the endoscopic endonasal approach also becomes limited when the dural attachment of the tumor extends laterally past the optic canals and along the orbital roof and anterior clinoid process. In these instances, complete Simpson Grade I removal cannot be reasonably obtained. Therefore, in cases with larger, widely based meningiomas exhibiting lateral extension over the optic canals and orbital roofs, we prefer to choose a transcranial approach, such as a pterional or orbitozygomatic approach. The presence of vascular encasement on preoperative imaging may preclude total removal and may not be an optimal approach for the endonasal route because of the difficulty in gaining adequate control and repair in the event of neurovascular injury. In these instances, a transcranial approach is probably more prudent. Nevertheless, it is important to recognize that vascular encasement can also preclude total removal during a transcranial approach as well.

Another criticism of the endoscopic approach is the lack of stereoscopic vision that is afforded by the microscope. However, with increased experience, knowledge of the endoscopic anatomy, dynamic mobilization of the endoscope, and integration of tactile and visuospatial cues, a sense of depth perception can be acquired. The advent of 3D endoscopes (Visionsense, Ltd.) has now greatly enhanced the subjective depth perception for the operating surgeon.[57] These endoscopes are able to render a single 3D view similar to the human eye by using dual channel technology that incorporates information from 2 distinct perspectives. We have used 3D endoscopes for endonasal removal of craniopharyngiomas,[39] pituitary tumors, and sinonasal tumors. This new technology is an important addition to the armamentarium of endoscopic skull base surgery and complements current high-definition 2D endoscopes.

Conclusions

The purely endoscopic endonasal extended transsphenoidal approach offers a direct midline trajectory and immediate access to tuberculum sellae meningiomas without brain retraction and manipulation of neurovascular structures. In carefully selected patients, complete tumor removal including intracanalicular tumor, dural attachment, and involved hyperostotic bone can be achieved. Excellent visualization of the suprasellar region and the inferomedial aspects of both optic canals allows for extracapsular, extraarachnoid dissection of the tumor from the critical structures using bimanual microsurgical dissection. This approach can be considered a viable approach for properly selected patients in experienced hands.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Liu, Eloy. Acquisition of data: Liu, Christiano, Patel, Eloy. Analysis and interpretation of data: Liu, Christiano, Patel. Drafting the article: Liu, Christiano, Patel, Tubbs. Critically revising the article: all authors. Approved the final version of the paper on behalf of all authors: Liu. Administrative/technical/material support: Liu, Christiano, Patel. Study supervision: Liu.

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Surgical nuances for removal of olfactory groove meningiomas using the endoscopic endonasal transcribriform approach

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Olfactory groove meningiomas represent 10% of intracranial meningiomas and arise in the midline of the anterior cranial fossa along the dura of the cribriform plate and planum sphenoidale. Hyperostosis of the adjacent underlying bone is common, and further extension into ethmoid sinuses and nasal cavity can occur in 15%–25% of cases. Radical tumor resection including the involved dural attachment and underlying hyperostotic bone offers the best chance of a Simpson Grade I resection to minimize recurrence. Incomplete removal of involved hyperostotic bone can result in tumor recurrence at the cribriform plate with extension into the paranasal sinuses. Resection has traditionally been performed using a bifrontal or pterional approach, both of which require some degree of brain retraction or manipulation to expose the tumor.

The endoscopic endonasal transcribriform approach offers the most direct and immediate exposure to the tumor without brain retraction and manipulation of neurovascular structures. An endonasal "keyhole craniectomy" is performed in the ventral skull base directly over the basal dural attachment, extending from the posterior wall of the frontal sinus to the planum sphenoidale and tuberculum sellae in the anteroposterior plane, and from one medial orbit to the other in the coronal plane. Excellent panoramic visualization of the keyhole skull base defect can be obtained with a 30° endoscope after performing a modified Lothrop procedure. Because the dural attachment is adjacent to the paranasal sinuses, early devascularization and total Simpson Grade I removal of the tumor including the dural attachment and underlying hyperostotic bone can be achieved in properly selected patients. This approach is also very suitable for meningiomas that have recurred or extended into the paranasal sinuses. Extracapsular, extraarachnoid dissection of the tumor from the frontal lobes and neurovascular structures can be performed using conventional bimanual microsurgical techniques.

In this report, we review the surgical technique and describe our operative nuances for removal of olfactory groove meningiomas, including recurrent tumors with extension into the nasal cavity, using a purely endoscopic endonasal transcribriform approach. In addition, we discuss the advantages, limitations, patient selection, and complications of this approach. We specifically highlight our technique for multilayer reconstruction of large anterior skull base dural defects using fascia lata and acellular dermal allograft supplemented by bilateral vascularized pedicled nasoseptal flaps. Three new cases of endoscopically resected olfactory groove meningiomas are also presented.
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Key Words • endoscopic endonasal approach • transcribriform approach • anterior skull base tumor • olfactory groove meningioma • modified Lothrop procedure • skull base reconstruction

Olfactory groove meningiomas arise in the midline of the anterior cranial fossa along the dura of the cribriform plate and planum sphenoidale, and comprise approximately 10% of intracranial meningiomas.[1,16,30,38] Because of their subfrontal location, many of these tumors are quite large by the time they are diagnosed.[16] Hyperostosis of the adjacent underlying bone is common, and further extension into the ethmoid sinuses and nasal cavity can occur in about 15% of cases.[2,9,16,22,34,39,41] Total Simpson Grade I resection of meningiomas including dural attachment and underlying tumor-infiltrated bone is critical in preventing future recurrence.[37] Most surgeons have preferred a more conservative (Simpson Grade II) approach, not resecting the hyperostotic cribriform plate and entering the paranasal sinuses, because of the risk of postoperative CSF leakage.[2,9,35,38,41] However, this has been associated with tumor recurrence, with rates of recurrence averaging about

Abbreviation used in this paper: OCR = opticocarotid recess.

23%[30] and reported to be as high as 41% at 10 years.[28] The most common sites of recurrence are at the anterior skull base and paranasal sinuses, specifically the cribriform plate and ethmoid sinuses.[30]

The most common surgical approaches for removing olfactory groove meningiomas are the bifrontal transbasal and pterional approaches. When using a midline transbasal approach, the surgical corridor is through either an interhemispheric or a bilateral subfrontal route. This requires ligation and division of the superior sagittal sinus, which entails some risk of venous infarction and cerebral edema.[29] When using a pterional approach, the corridor is through a unilateral subfrontal or transsylvian route. Although the contralateral frontal lobe is left undisturbed, the trajectory is oblique with loss of midline orientation, thereby limiting access to the cribriform plate and paranasal sinuses. Additional cranial base techniques with extended osteotomies, such as removal of the supraorbital bar (extended transbasal approach, subcranial approach) or orbital rim (orbitozygomatic approach, supraorbital approach), can be applied as well to increase exposure and minimize brain retraction. Nevertheless, these transcranial approaches all require some degree of brain retraction and manipulation of neurovascular structures. Associated complications include frontal lobe edema, venous infarction, hematoma, CSF leak, bone flap infection, and pneumocephalus, with a mortality rate of 5% reported in one series.[29] Because the blood supply to the tumor is at the base of the dural attachment, considerable brain displacement and subsequent debulking is required before the tumor blood supply can be interrupted.

Recently, there has been increased interest in endoscopic endonasal approaches for the removal of anterior skull base meningiomas,[7,8,12,14,21] and this continues to be a topic of debate. The endoscopic endonasal transcribriform approach offers the most direct and immediate exposure to the tumor without having to apply brain retraction and manipulate neurovascular structures. A panoramic view of the ventral skull base can be obtained from the frontal sinuses to the planum sphenoidale in the anteroposterior view, and from one medial orbital wall to the other in the coronal view (Fig. 1). Because the site of dural attachment is adjacent to the paranasal sinuses, early devascularization of the tumor and subsequent radical resection of the tumor, dural attachment, and involved hyperostotic bone (Simpson Grade I) can be achieved in properly selected patients. This endonasal approach is also very suitable for those meningiomas that have recurred or extended into the paranasal sinuses. Extracapsular, extraarachnoid dissection of the tumor from the frontal lobes and neurovascular structures can be performed using conventional bimanual microsurgical techniques. Reconstruction of large anterior skull base defects and prevention of CSF leakage remains a challenge. However, with the introduction of newer techniques including vascularized flaps, the rate of CSF leakage has dramatically declined.[12,20]

In this report, we review the surgical technique and describe our operative nuances for removal of olfactory groove meningiomas, including recurrent tumors in the nasal cavity, using a purely endoscopic endonasal transcribriform approach. In addition, we discuss patient selection and the advantages, limitations, and complications of this approach. Our modified technique for endoscopic reconstruction of large skull base defects to prevent CSF leakage is highlighted using a multilayer technique with autologous fascia lata, acellular dermal allograft, and bilateral vascularized nasoseptal flaps (Fig. 2). We discuss cases previously published in the literature and report 3 additional cases of olfactory groove meningiomas (1 new tumor, 2 recurrent tumors involving the paranasal sinuses) treated with endoscopic endonasal resection (Fig. 3).

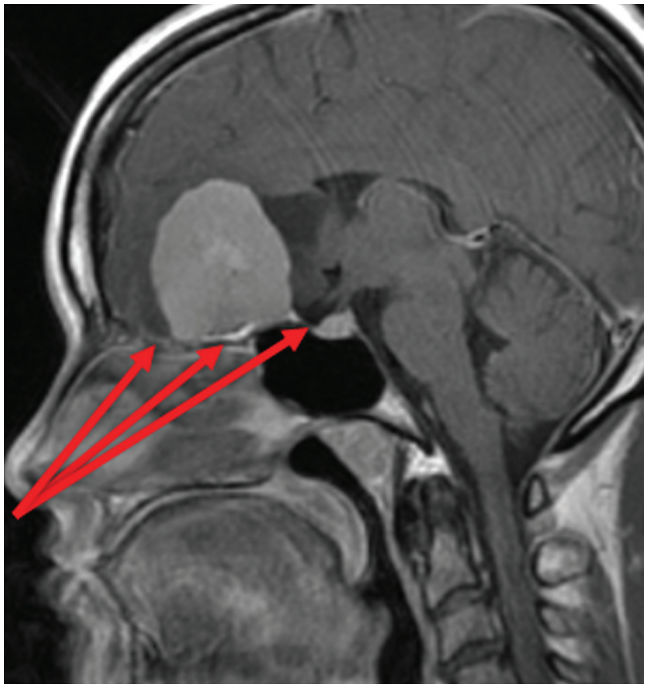

Fig. 1. Case 1. Preoperative sagittal T1-weighted Gd-enhanced MR image demonstrating a large olfactory groove meningioma that extends from the cribriform plate anteriorly to the tuberculum sellae posteriorly. The *red arrows* indicate the range of exposure that can be obtained with an endoscopic endonasal approach to the entire ventral skull base from the crista galli to the tuberculum sellae.

Surgical Technique: Endoscopic Endonasal Transcribriform Approach

Patient Positioning

The patient is positioned supine with the bed slightly reflexed so that the head is 15° above the heart to facilitate venous return. After the head is placed in a Mayfield head holder with 3-pin fixation, the neck is slightly extended to enhance the trajectory to the anterior skull base. We prefer additional lateral flexion of the head toward the left shoulder with slight rotation of the head toward the right shoulder to facilitate comfortable access to the nose when the surgeon stands on the patient's right side. The endotracheal tube is also taped toward the left side of the mouth so that it does not crowd the surgeon's access to the nose. Frameless stereotactic navigation for image guidance is used to guide the degree of bone removal at the skull base. Navigation using CT angiography is helpful for identifying bony anatomy, anticipating the thickness of the cribriform

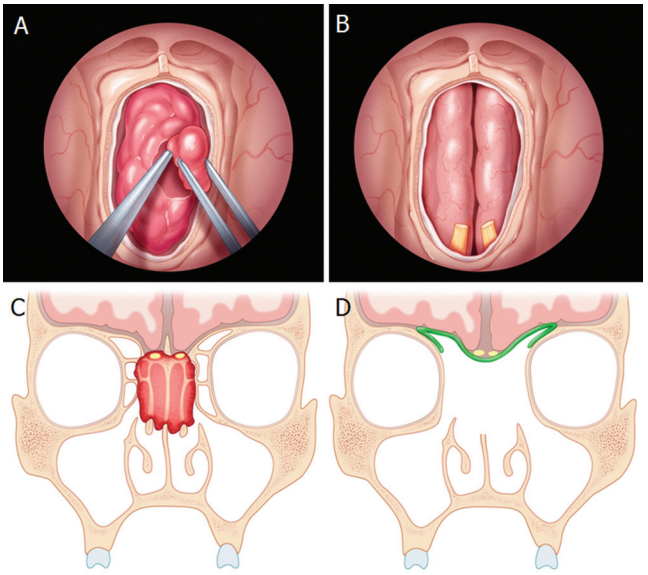

Fig. 2. Illustration demonstrating the endoscopic endonasal transcribriform approach for resection of an olfactory groove meningioma and subsequent repair of a large osteodural defect. **A:** Intracapsular debulking of the tumor is performed to facilitate collapse of the tumor capsule for subsequent extraarachnoid extracapsular dissection from the critical structures. **B:** Following tumor removal, the bilateral frontal lobes and olfactory nerves can be visualized through the large dural defect. A panoramic view of the ventral skull base extending from the posterior wall of the frontal sinus to the planum sphenoidale can be obtained with a 30° endoscope. **C:** Coronal view demonstrating a recurrent olfactory groove meningioma arising from the cribriform plate and extending into the paranasal sinuses. **D:** Coronal view demonstrating the technique of AlloDerm graft repair (highlighted in *green*). A single piece of AlloDerm is positioned intracranially underneath the edges of the bony defect with the outer margins of the graft extending extracranially to overlay the de-epithelialized margins of the bony defect. The graft is wedged into position using gentamicin-soaked Gelfoam pledgets. The weight of the brain helps buttress the graft to keep it in position. From Eloy JA, Tessema B, Casiano RR: Surgical approaches to the anterior cranial fossa, in Kennedy DW, Hwang PH (eds): **Rhinology: Diseases of the Nose, Sinuses, and Skull Base.** Thieme Medical Publishers, with permission.

plate during drilling, tumor localization, and predicting the proximity of critical neighboring vessels. The nose, nares, and midface are prepared with povidone-iodine (Betadine) solution. A thigh incision is also prepared for harvest of an autologous fascia lata graft, which is used during dural reconstruction. Oxymetazoline hydrochloride (Afrin)–soaked pledgets are placed into the nasal cavity. Intravenous antibiotics and 10 mg of dexamethasone are administered at the start of the operation. Anticonvulsants and mannitol are not given for endonasal approaches to olfactory groove meningiomas because the tumor removal is performed in an extraarachnoid fashion without brain retraction or manipulation. We also do not use intraoperative lumbar drainage because there is no need for brain relaxation or brain retraction for this procedure.

General Principles for Endoscopic Skull Base Surgery

In our institution, we use a multidisciplinary team approach when performing endonasal endoscopic skull base surgery. All procedures are performed by a skull base neurosurgeon (J.K.L.) working simultaneously with an otolaryngologist (J.A.E.) specializing in endoscopic sinus and skull base surgery. A so-called "3- to 4-handed binarial technique" is used, with both surgeons working simultaneously through both nostrils without the use of a nasal speculum. The otolaryngologist performs the initial endonasal exposure of the anterior skull base using a 4-mm-diameter, 18-cm-length, 30° endoscope (Karl Storz) that is aimed superiorly. During the transcribriform skull base drilling and subsequent intradural tumor removal, the neurosurgeon uses traditional bimanual microsurgical dissection techniques with instruments inserted into each nostril. For a right-handed surgeon, the suction is primarily in the left hand inserted into the right nostril, and a dissecting tool (drill, tissue aspirator, microdissector, microscissors, or bipolar cautery) is in the right hand inserted into the left nostril. We prefer not to use the scope holder so that the otolaryngologist can provide dynamic movement of the endoscope to enhance depth perception and continuous visualization of desired surgical targets. The 30° endoscope is aimed superiorly toward the skull base so that a direct "looking-up" view of the cribriform plate is obtained. We recommend placing the endoscope at the 6 o'clock position in the right nostril, with suction at the 12 o'clock position, so that the neurosurgeon is working "above" the lens of the scope. We have found that this technique minimizes problems related to our instruments bumping into each other when working in tight spaces.

Although most surgeons report using a 0° endoscope for the exposure and subsequent tumor removal,[7,12] we prefer to use a 30° endoscope as our workhorse. In our experience, the 30° endoscope allows us to achieve the same degree of surgical exposure as a 0° endoscope, and it also has the additional benefit of angled viewing capabilities for looking around corners. Therefore, frequent exchange between the two endoscopes is unnecessary. Our clinical observations are in agreement with the findings in an anatomical study by Batra et al.,[3] in which the 30° endoscope provided the best view from the frontal sinus to the planum sphenoidale with the least distortion compared with both 0° and 70° endoscopes.

Paranasal Sinus Exposure

After injecting the nasal septum and the tail and anterosuperior attachment of the middle turbinates with 1% lidocaine with epinephrine (1:100,000 dilution), both inferior turbinates are lateralized with a Goldman elevator. Depending on the size of the tumor, the middle turbinates may need to be resected to create more working room. Otherwise, they can be lateralized. If the tumor extends intranasally, as is the case in some recurrent meningiomas, the approach starts with endoscopic endonasal debulking with a 4-mm rotation-suction microdebrider with the objective of identifying the stalk of the tumor. Key elements such as the nasal septum, lateral nasal wall, and posterior nasal choanae are identified. Bilateral maxillary antrostomies are routinely performed to prevent iatrogenic sinusitis and to expose the orbital floor as a major anatomical landmark. A wide bilateral sphenoidotomy is performed to expose the sella turcica, carotid protuberances, bilateral optic canals, tuberculum sellae, and pla-

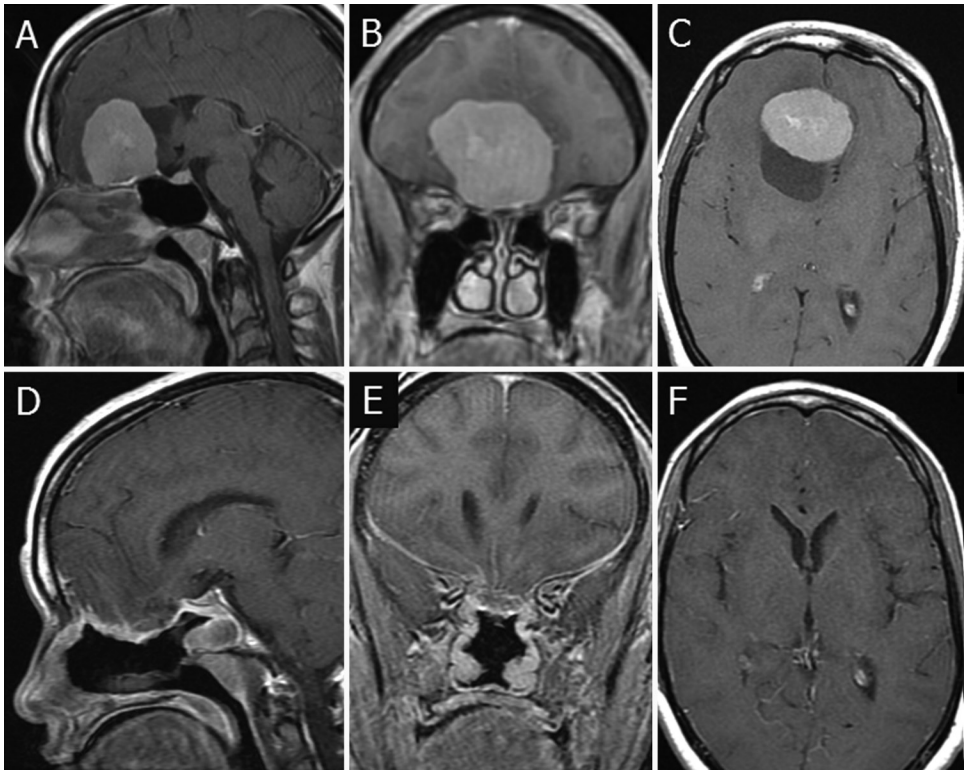

Fig. 3. Case 1. **A–C:** Preoperative sagittal **(A)**, coronal **(B)**, and axial **(C)** T1-weighted Gd-enhanced MR images demonstrating a large olfactory groove meningioma extending from the cribriform plate to the tuberculum sellae. **D–F:** Delayed postoperative sagittal **(D)**, coronal **(E)**, and axial **(F)** MR images obtained 3 months after surgery demonstrating gross-total resection of the tumor achieved via an endoscopic endonasal approach. Basal enhancement represents granulation and reepithelialization of the AlloDerm reconstruction by the sinonasal mucosa.

num sphenoidale. It is important to identify the medial and lateral opticocarotid recesses (OCRs), which are key landmarks in endoscopic skull base surgery. The medial OCR is a pneumatization of the middle clinoid process and represents an indentation in the bone that is formed at the medial junction of the parasellar carotid canal and the optic canal. The lateral OCR is a pneumatization of the anterior clinoid process and is located at the lateral junction of the parasellar carotid canal and the optic canal. The medial OCR is a useful landmark in identifying the optic nerve as it joins the middle clinoid process. The planum sphenoidale and the optic nerves mark the posterior boundary of the anterior skull base exposure.

To expose the entire cribriform plate, particularly for large tumors that extend lateral to the middle turbinates (Fig. 3), bilateral total ethmoidectomies are performed to expose the junction of the lamina papyracea with the fovea ethmoidalis. During the posterior ethmoidectomy, it is important to recognize an Onodi cell, which is a posterior ethmoid cell that is positioned superolateral to the sphenoid sinus. This is an important anatomical variant because the optic nerve and carotid artery often course through the lateral aspect of these Onodi cells.

At this juncture, we prefer to harvest bilateral pedicled vascularized nasoseptal flaps for subsequent skull base reconstruction. The flaps are harvested in a manner similar to that described by Hadad et al.,[15] and rotated inferiorly into the posterior nasopharynx. This allows further exposure of the anterior skull base while protecting the vascular pedicle from inadvertent injury that can compromise the integrity and effectiveness of the flaps. Resecting 1.5–2 cm of the posterior aspect of the nasal septum allows triangulation of surgical instruments through both nostrils so that bimanual microsurgical dissection can be performed.

Endoscopic Modified Lothrop Procedure

The anterior extent of the exposure is created by performing an extended frontal sinusotomy (modified Lothrop procedure). This portion of the procedure starts with localization of the frontal recess and ostia bilaterally. A superior septectomy is performed anterior to the cribriform plate (anterior to the tumor) and is connected to the already made posterior septectomy. This maneuver allows a panoramic view of the cribriform plate and also facilitates triangulation of bilateral instruments at the surgical target.[7] Up-angled 2-0 and 3-0 bone curettes are then used to create and enlarge one common frontal sinusotomy (Lothrop cavity) by removing the intersinus and intrasinus septations, thereby exposing the posterior frontal sinus wall. The nasofrontal beak is subsequently thinned down using large cutting burs once the posterior wall of the common frontal sinus cavity is visualized. The endoscopic modified Lothrop procedure is a key technical portion in the endoscopic transcribriform approach because it provides exposure of the posterior table of the frontal sinus, which is an important landmark delineating the anterior border of the bony resection and

also acts as a shelf for tucking graft material during skull base reconstruction.[3,36] This procedure has served as an important adjunct for exposure of the anterior skull base and complex frontal sinus pathology. Wide opening of the frontal sinuses promotes drainage and minimizes the risk of postoperative frontal stenosis and iatrogenic mucocele formation.[3]

Transcribriform "Keyhole" Craniectomy

Once the endoscopic modified Lothrop procedure, total ethmoidectomy, and wide sphenoidotomy have been performed, a wide panoramic view of the entire ventral skull base from the frontal sinuses to the sphenoid sinuses is achieved. Next, an endonasal "keyhole craniectomy" of the ventral skull base is performed using a high-speed drill with copious irrigation (Fig. 4). The boundaries of the craniectomy extend from the posterior wall of the frontal sinus anteriorly to the planum sphenoidale posteriorly. The lateral boundaries are the lamina papyracea (medial orbital walls) bilaterally. The cribriform plate is carefully drilled away using a self-irrigating high-speed curved endonasal diamond drill (Medtronic Xomed) with copious irrigation. The curve of the drill is directed superiorly to adequately reach the anterior skull base. In addition, we use a double-barrel suction-irrigator that allows continuous self-irrigation and suction to keep the surgical field clear of bone dust while cooling the drill tip to prevent overheating near critical neurovascular structures. Although the extent of bone removal is tailored to the location of the tumor and dural attachment, it is important to perform a wide osteotomy so that there is no residual bone obstructing the surgeon's line of sight or hindering the maneuverability of instruments. When dealing with tumors that extend more superiorly, more bone is removed anteriorly so that an adequate anterosuperior trajectory over the top of the tumor can be obtained during extracapsular dissection of the tumor. Nevertheless, it is important to leave a bony shelf of the posterior frontal sinus wall, if possible, as this serves as a ledge for tucking inlay grafts at the time of reconstruction. Bone removal starts at the posterior table of the frontal sinus anteriorly and ends at the planum sphenoidale posteriorly. If the tumor extends more posteriorly, removal of the tuberculum sellae and medial OCRs can be performed, if needed. Bony resection of the cribriform plate is carried out laterally to include the fovea ethmoidalis from one lamina papyracea to the other.

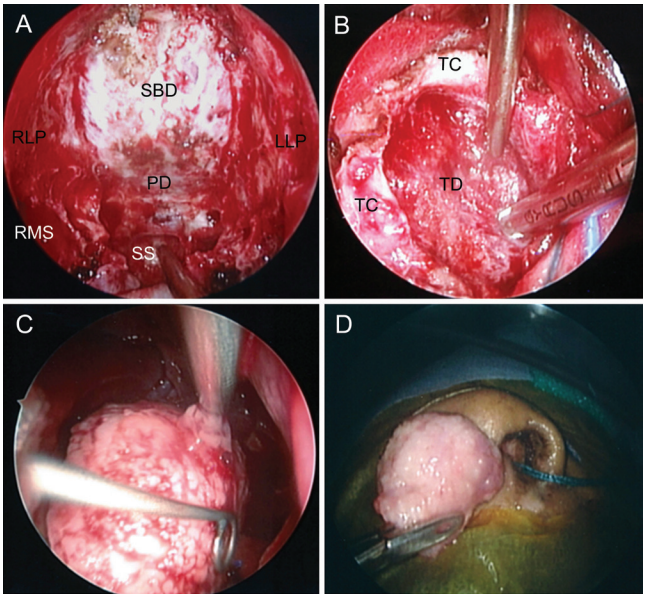

Fig. 4. Case 1. Intraoperative photographs demonstrating tumor removal with a 30° endoscope. **A:** A panoramic view of the ventral skull base keyhole craniectomy defect (SBD) extending from the back of the frontal bone to the sella turcica, obtained with a 30° endoscope looking superiorly. Bone removal extends laterally from one lamina papyracea to the other. The tuberculum sellae was removed because the tumor extended posteriorly to this region. **B:** Intracapsular tumor debulking (TD) of this fibrous tumor was performed with the use of a microdebrider to facilitate collapse of the tumor capsule (TC) for subsequent extraarachnoid extracapsular dissection from the critical structures. **C and D:** Once the tumor capsule had been dissected free from all of the surrounding neurovascular structures, the tumor could be safely delivered through the nose. LLP = left lamina papyracea; PD = planum dura; RLP = right lamina papyracea; RMS = right maxillary sinus; SBD = skull base defect; SS = sphenoid sinus.

During drilling, it is imperative to identify the anterior and posterior ethmoid arteries. Coagulation and division of these arteries contribute to early devascularization of the meningioma since these vessels provide significant blood supply to the tumor. Care is taken not to let the proximal portion of the vessel retract back into the orbit before adequate coagulation, as this can result in an orbital hematoma and proptosis. The crista galli, which can be hyperostotic in some cases of olfactory groove meningiomas, is carefully drilled down and removed.

Before opening the dura, meticulous hemostasis is obtained and careful inspection of the bony opening with intraoperative navigation is performed to ensure that there is adequate exposure of the basal attachment of the tumor. Any residual bony overhang that is obstructing the line of sight or hindering surgical freedom of instruments is removed. Further tumor devascularization is achieved by coagulating the exposed dura and the anterior falcine artery using a pistol-grip endoscopic bipolar forceps (Karl Storz).[12,19]

Intradural Exposure and Tumor Resection

A No. 15 blade and endoscopic pistol-grip scissors are used to make a rectangular incision around the region of the dural attachment. Anteriorly, the falx is coagulated and divided toward the incisura to untether the dural attachment. An extended tip endonasal ultrasonic aspirator (Integra LifeSciences) is used for intracapsular tumor debulking. Some meningiomas may be quite fibrous and unresponsive to the ultrasonic aspirator. In these cases, we have used an up-angled rotation-suction microdebrider (Gyrus, Olympus) that effectively debulks fibrous tumors of the anterior skull base (Fig. 4). It is imperative that tumor debulking with the microdebrider or ultrasonic aspirator remain intracapsular, so as not to breach the tumor capsule. Since the tumor's blood supply has been already devascularized during the extradural approach, the tumor debulking is relatively hypovascular.

After adequate central debulking, extracapsular dissection is performed to collapse the tumor capsule. This allows the tumor capsule to be gathered and brought into

the cribriform keyhole defect from a lateral to medial direction. Natural pulsations of the brain also facilitate medialization and delivery of the tumor capsule into the skull base opening. Although the width of the tumor may be larger than the width of the cribriform defect, delivery of large tumors through a relatively smaller bony opening is possible using this keyhole technique, as long as the dural attachment does not extend laterally beyond junction of the lamina papyracea and the fovea ethmoidalis. It is imperative to maintain bimanual microsurgical dissection techniques during extracapsular dissection so as to preserve the arachnoid planes.

Anatomically, meningiomas are dural-based tumors and displace the arachnoid ahead of them as they grow. Therefore they are extraarachnoid structures situated in the subdural space.[6] If possible, it is helpful to identify the "double arachnoid" layer, which is comprised of tumor arachnoid and cisternal arachnoid; in larger tumors, this may appear as a single layer of arachnoid. Nevertheless, extraarachnoid extracapsular dissection is best performed between the tumor capsule and the tumor arachnoid, and not the cisternal arachnoid. Preservation of these arachnoid layers facilitates safer microsurgical dissection of the tumor from critical neurovascular structures, such as the orbitofrontal, frontopolar, or anterior cerebral arteries. In larger tumors with significant edema on preoperative T2-weighted images, one should anticipate the possibility of subpial invasion and recruitment of pial blood supply. Meticulous microsurgical extracapsular dissection can be performed with gentle countertraction on the tumor capsule with the suction instrument in one hand, and the bipolar dissection forceps in the other hand (Fig. 4). It is paramount to avoid premature "pulling" of the tumor capsule before it has been completely dissected free from the surrounding brain and vascular structures, so as to avoid a catastrophic vascular avulsion. If there is tumor tissue adherent to a major vessel or perforator, it is safer to leave a small residual tumor that can be treated later with radiosurgery.

Closure and Skull Base Reconstruction

Successful tumor resection is not complete without meticulous multilayer reconstruction of the skull base dural defect to prevent CSF leakage. In a recent anatomical study,[3] the average boundaries of the anterior skull base defect were 33.7 mm (range 29–40 mm) in the anteroposterior direction (posterior wall of frontal sinus to planum sphenoidale), and 23.5 mm (range 20–27 mm) and 19.1 mm (range 17–22 mm) in the transverse direction (orbit to orbit) at the level of the anterior ethmoidal artery and posterior ethmoidal artery, respectively. Although the dimensions of the skull base and dural defect vary among individual patients, these dimensions can be helpful in estimating the size of the grafts to fashion. The dimensions of each graft layer should be larger than the dimensions of the dural and bony defect, when using the following reconstruction technique that we have developed.

For repair of these large anterior skull base defects that extend all the way from the posterior wall of the frontal sinus anteriorly to the planum sphenoidale posteriorly, we use a multilayer reconstruction technique (Fig. 5). An autologous fascia lata graft is placed intradurally as an inlay graft. This initial layer converts a "high-flow leak" to a "low-flow leak." Several pieces of Surgicel are placed over the bony defect to temporarily hold the graft in place. Next, a layer of thick implantable acellular dermal allograft (AlloDerm, LifeCell Corp.) is tucked at least 1 cm circumferentially between the remaining dural cuff and the edge of the bony defect using gentamicin-soaked Gelfoam pledgets (Figs. 2D and 5C and D).[11] The redundant edges of the acellular dermal graft serve as an overlay while the tucked portions act as an inlay.[13] The previously harvested bilateral pedicled nasoseptal flaps are then rotated over the acellular dermal graft. A thin layer of fibrin matrix (Tisseel, Baxter), or polymerized hydrogel (DuraSeal, Confluent Surgical) is placed over the multilayer closure. Dural sealant should not be placed in between the dural closure and the nasoseptal flap, as this may prevent flap adherence. Several pieces of gentamicin-soaked Gelfoam pledgets are placed over the repair, which is further buttressed by a Merocel nasal tampon (Medtronic Xomed) covered with bacitracin ointment. The patient is maintained on antibiotics until the packs are removed approximately 10 days after surgery. We do not routinely use postoperative lumbar drainage because the patient is already in a CSF hypovolemic state at the end of surgery. Further lumbar drainage can increase the risk of intracranial hypotension or tension pneumocephalus. We

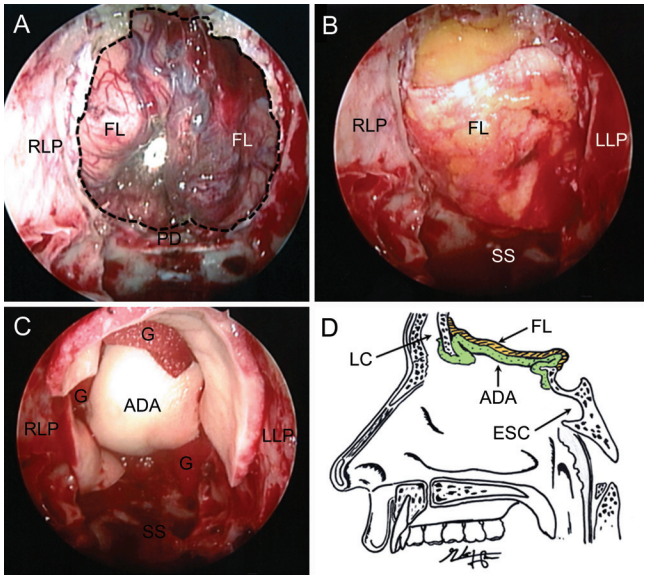

Fig. 5. Case 1. **A–C:** Intraoperative photographs demonstrating multilayer reconstruction of the skull base dural defect. **A:** View of the dural defect (outlined by *dashed lines*). Bilateral frontal lobes (FL) are visualized through the dural defect. **B:** An initial layer of autologous fascia lata (FL) is tucked underneath the edges of the dura as inlay graft to convert a "high-flow" defect to a "low-flow" defect. **C:** A single piece of acellular dermal allograft (ADA) is positioned intracranially underneath the edges of the bony defect with the outer margins of the graft extending extracranially to overlay the de-epithelialized margins of the bony defect. The graft is wedged into position using gentamicin-soaked Gelfoam pledgets (G). **D:** Drawing (sagittal view) demonstrating the multilayer reconstruction with the acellular dermal allograft tucked underneath the bony defect. The reconstruction is completed with rotation of bilateral vascularized pedicled nasoseptal flaps (not shown) to cover the AlloDerm repair followed by application of DuraSeal. ESC = expanded sphenoid cavity; LC = Lothrop cavity.

feel that our reconstruction technique is also somewhat dependent on restoration of CSF pressures to allow the brain to buttress the inlay grafts against the skull base. Without lumbar drainage, patients are able to mobilize earlier with less risk of low-pressure headaches and thromboembolic complications.[13]

Illustrative Cases

Case 1

This 43-year-old woman with a known 1.5-cm olfactory groove meningioma detected 3 years prior presented with progressive headaches and absence of olfaction. A follow-up MR imaging study demonstrated an enlarging 4-cm olfactory groove meningioma with an associated tumor cyst resulting in cerebral edema with mass effect on the frontal lobes (Figs. 3–6). Hyperostosis at the cribriform plate was also seen on preoperative CT (Fig. 6). The patient underwent an endoscopic endonasal transcribriform approach for resection of the tumor. The tuberculum sellae was removed because the tumor extended posteriorly in this region. A microdebrider was used to debulk the tumor because the tumor was very fibrous and unresponsive to an ultrasonic aspirator (Fig. 4B). Extracapsular dissection of the tumor from the surrounding critical structures was performed without brain retraction or neurovascular manipulation. A Simpson Grade I tumor resection was performed including removal of the dural attachment and underlying hyperostotic bone (Fig. 4). Multilayer reconstruction was performed using autologous fascia lata, AlloDerm, and vascularized nasoseptal flaps (Fig. 5). No lumbar drainage was used. Postoperative MR imaging demonstrated gross total resection of the tumor. The patient was neurologically intact after surgery without any CSF leakage. At 3 months' follow-up, nasal endoscopy demonstrated excellent re-epithelialization of the ventral skull base repair that was noted on the follow-up MR imaging (Fig. 3).

Case 2

This 40-year-old woman presented with a 3-month history of nasal congestion and frontal headaches. Three years previously, she had undergone a bifrontal craniotomy for treatment of an olfactory groove meningioma at another institution. Magnetic resonance imaging demonstrated recurrent meningioma arising from the cribriform plate and planum sphenoidale with extension into the paranasal sinuses (Fig. 7). Significant hyperostosis of the anterior skull base extending from the crista galli to the planum sphenoidale was seen on preoperative CT (Fig. 8). An endoscopic endonasal transcribriform approach was performed. A modified Lothrop procedure facilitated exposure of the ventral skull base from the posterior wall of the frontal sinus to the planum sphenoidale. A Simpson Grade I total resection was achieved by excising all of the hyperostotic bone and dural attachment at the cribriform plate with tumor-free margins (Fig. 9). The anterior skull base defect was reconstructed with an autologous fascia lata inlay graft and an AlloDerm inlay/outerlay graft, followed by bilateral vascularized nasoseptal flaps. No lumbar drainage was used. The patient remained neurologically intact without CSF leakage in the immediate postoperative period and at 6 weeks' follow-up. Nasal endoscopy also demonstrated excellent re-epithelialization of the ventral skull base repair.

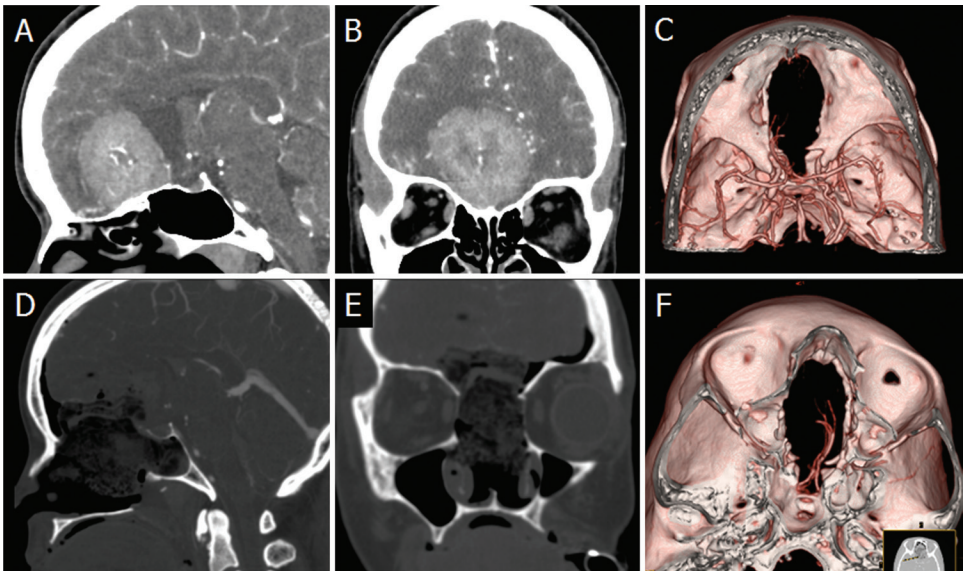

Fig. 6. Case 1. **A and B:** Preoperative sagittal **(A)** and coronal **(B)** contrast-enhanced CT reconstructions demonstrating a large olfactory groove meningioma with hyperostosis of the cribriform plate. **D and E:** Postoperative sagittal **(D)** and coronal **(E)** contrast-enhanced CT reconstructions demonstrating the extent of bone resection extending from the back of the frontal bone to the sella turcica in the sagittal view, and from medial orbit to medial orbit in the coronal view. Note that the patient did not have a frontal sinus. **C and F:** Postoperative 3D reconstructed CT angiograms demonstrating multiple views of the anterior skull base defect and surrounding vasculature after a transcribriform approach. **C:** View looking from above demonstrating a large anterior skull base defect. **F:** View looking up from below mimicking the endonasal endoscopic view of the ventral anterior skull base defect with the anterior cerebral arteries in the distance.

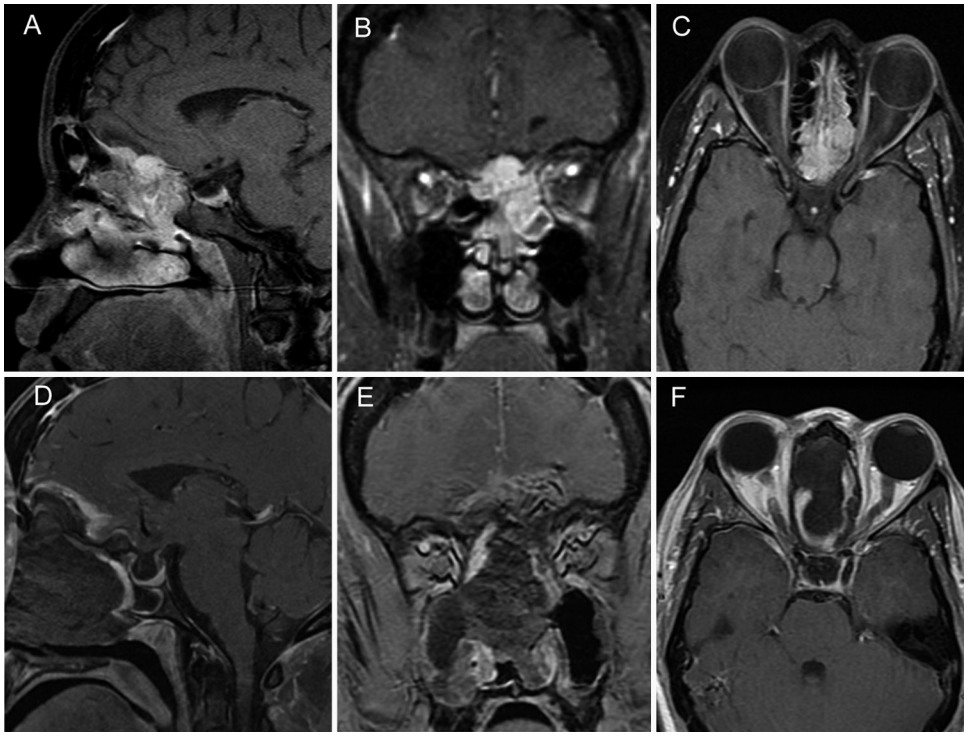

Fig. 7. Case 2. **A–C:** Preoperative sagittal **(A)**, coronal **(B)**, and axial **(C)** T1-weighted Gd-enhanced MR images demonstrating a recurrent olfactory meningioma arising from the cribriform plate and planum sphenoidale with extension into the paranasal sinuses. **D–F:** Postoperative sagittal **(D)**, coronal **(E)**, and axial **(F)** T1-weighted Gd-enhanced MR images showing gross total resection of the tumor using an endoscopic endonasal approach. Enhancement at the ventral skull base represents the vascularized nasoseptal flap with some postoperative changes.

Case 3

This 53-year-old woman, who had undergone 2 previous bifrontal craniotomies for resection of an olfactory groove meningioma at another institution, presented with progressive growth of recurrence at the skull base with extension into the paranasal sinuses. Magnetic resonance imaging also demonstrated enhancement extending laterally over both orbital roofs suggestive of tumor (Fig. 10). An endoscopic endonasal approach alone was felt to be inadequate to resect the laterally extending tumor. Therefore, a combined bifrontal transbasal and endoscopic endonasal approach was performed to resect the anterior skull base and paranasal sinus tumor. From the transcranial exposure, the tumor was resected from the orbital roofs, anterior clinoid process, and along the lesser wing of the sphenoid. The cribriform plate was drilled out from above, and resection of paranasal sinus tumor was carried out. Endonasal endoscopic inspection from below identified more tumor that was not visualized from above, which was removed with a rotation-suction microdebrider. A near-total resection was achieved because microscopic residual tumor was observed infiltrating the left optic nerve. A safe plane of dissection could not be identified.

Multilayer reconstruction was performed with a watertight closure using an autologous temporalis fascia graft that was sewn primarily to the dural defect from above. An AlloDerm graft was tacked down in 4 corners to cover the fascial closure from above. Since there was no pericranial flap available (used in previous surgery),

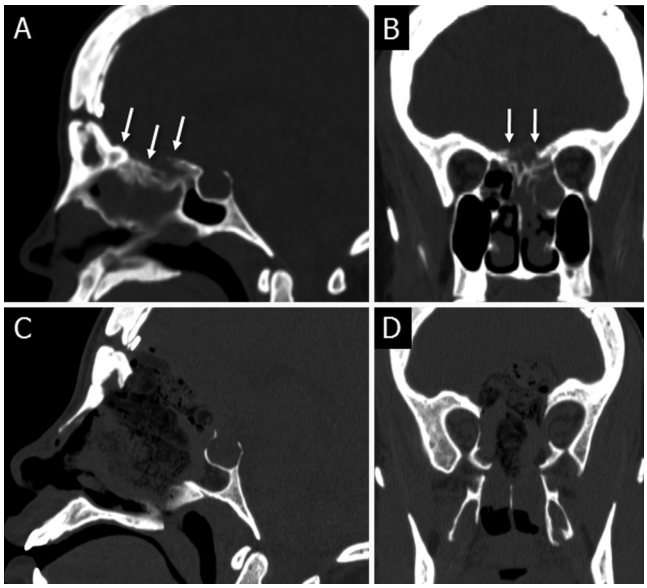

Fig. 8. Case 2. **A and B:** Preoperative sagittal **(A)** and coronal **(B)** CT reconstructions showing recurrence with extensive hyperostosis at the ventral skull base *(white arrows)*. Note the previous bifrontal craniotomy defect at the frontal sinus. **C and D:** Postoperative sagittal **(C)** and coronal **(D)** CT reconstructions (after an endoscopic endonasal approach) demonstrating a maximal ventral skull base defect extending from the posterior table of the frontal sinus to the anterior sella in the sagittal view, and from medial orbit to medial orbit in the coronal view.

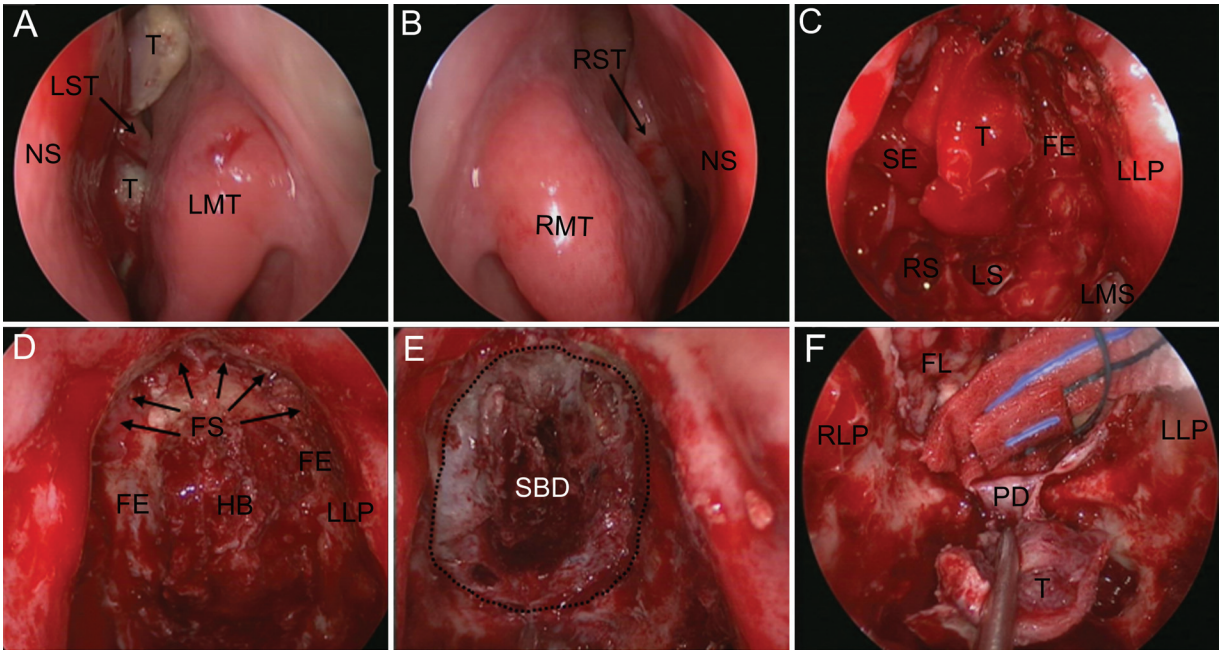

Fig. 9. Case 2. Intraoperative photographs obtained via a 30° endoscope. **A:** View of the left nasal cavity demonstrating recurrent tumor (T) in the olfactory recess. **B:** View of the right nasal cavity showing the normal anatomical landmarks. This view did not reveal any tumor. **C:** The recurrent tumor (T) arising from the ventral skull base is visualized after a total ethmoidectomy, sphenoidotomy, superior septectomy, and modified Lothrop procedure. **D:** A single frontal sinus (FS, *arrows*) is created with an endoscopic modified Lothrop procedure. The keyhole craniectomy includes the hyperostotic bone (HB) at the cribriform plate and both fovea ethmoidalis (FE). **E:** After bony removal, a panoramic view of the ventral skull base defect (SBD) is demonstrated from the posterior wall of the frontal sinus to the planum sphenoidale in the anteroposterior dimension, and from one lamina papyracea to the other in the horizontal dimension. **F:** Removal of the remaining tumor (T) at the anterior skull base is performed by excising a rectangular dural defect in an anterior to posterior fashion. The last cut is made across the planum dura (PD). The frontal lobes (FL) are protected by cottonoid paddies. LLP = left lamina papyracea; LMS = left maxillary sinus; LMT = left middle turbinate; LS = left sphenoid sinus; LST = left superior turbinate; NS = nasal septum; RLP = right lamina papyracea; RMT = right middle turbinate; RS = right sphenoid sinus; RST = right superior turbinate; SE = superior ethmoid cells; T = tumor.

the closure was supplemented by a vascularized nasoseptal flap from below. No lumbar drainage was used after surgery. The patient remained neurologically intact with normal vision (20/25 visual acuity, normal visual fields) in the immediate postoperative period and at the 1-year follow-up examination. There was no postoperative CSF leakage, and follow-up nasal endoscopy at 9 months after surgery demonstrated excellent re-epithelialization of the ventral skull base reconstruction.

Discussion

Endoscopic Endonasal "Keyhole" Removal of Olfactory Groove Meningiomas

The endoscopic endonasal transcribriform approach offers several surgical advantages for removal of olfactory groove meningiomas. Because these tumors originate at the cribriform plate, the endonasal route provides a natural corridor of access to the tumor and allows the most direct approach, without any brain retraction or manipulation of neurovascular structures to obtain adequate exposure (Fig. 1). In cases of convexity meningiomas, a craniotomy is made directly over the dural attachment of the tumor. Similarly, in treating olfactory groove meningiomas, the endonasal "keyhole craniectomy" is made in the cranial base directly over the basal dural attachment, allowing for early devascularization of the tumor (Figs. 4A and 6C and 6F). The anatomical limits of the endonasal keyhole exposure are the posterior table of the frontal sinuses anteriorly, the medial orbits laterally, and the planum sphenoidale posteriorly. Further removal of the planum sphenoidale and tuberculum sellae can be performed, if necessary, for treatment of tumors that have more posterior extension (as in Case 1, Figs. 3–6). The endoscopic view, particularly with a 30° endoscope aimed superiorly, provides an unparalleled panoramic view of the entire ventral skull base (Figs. 4 and 5).

In many cases, the greatest diameter of the tumor in the coronal view is often wider than the width of the endoscopic corridor (from medial orbit to medial orbit). To deliver larger tumors through a relatively smaller keyhole opening, aggressive intratumoral debulking is required to promote collapse of the tumor capsule, thereby making the tumor smaller. The natural pulsations of the brain and any preexisting intracranial pressure both facilitate medialization of capsular walls into the cranial base keyhole opening as the brain gradually reexpands during sequential tumor debulking and extracapsular dissection from surrounding structures. For this reason, we do not use intraoperative mannitol or lumbar drainage. Because these tumors are anatomically subdural extraarachnoid structures with an arachnoid barrier that separates the tumor capsule from the neurovascular structures, extra-

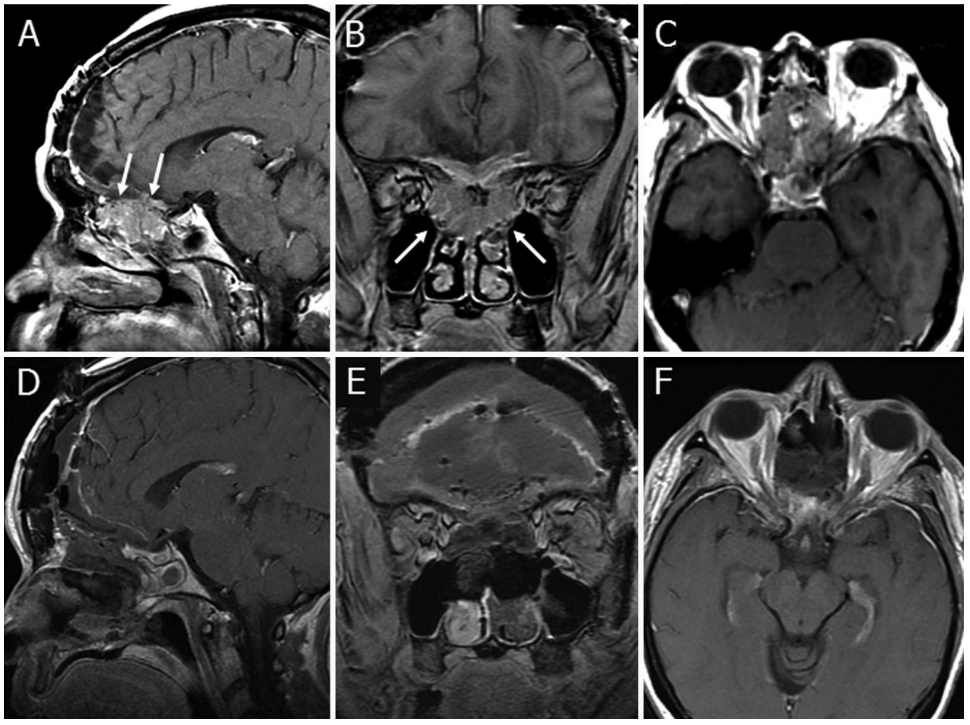

Fig. 10. Case 3. **A–C:** Preoperative sagittal **(A)**, coronal **(B)**, and axial **(C)** Gd-enhanced T1-weighted MR images demonstrating a recurrent olfactory groove meningioma arising from the anterior skull base with extension into the paranasal sinuses. Note the dural enhancement extending laterally over the orbital roofs **(B)**. A combined transcranial and endoscopic endonasal approach was performed. Tumor extending along the lesser wing of the sphenoid was removed transcranially. The intranasal tumor was removed endoscopically from below. Since there was no pericranial flap available (used in prior surgery), reconstruction was performed with a watertight closure using an autologous temporalis fascia graft that was supplemented by a vascularized nasoseptal flap from below. **D–F:** Postoperative sagittal **(D)**, coronal **(E)**, and axial **(F)** Gd-enhanced MR images demonstrating near-total resection. Microscopic tumor that was adherent to the left optic nerve was left behind.

capsular dissection with preservation of the arachnoid planes minimizes the risk of neurovascular injury. We emphasize maintaining the plane of dissection between the tumor capsule and the tumor arachnoid, not the cisternal arachnoid, whenever possible. It is important to recognize that larger tumors may recruit pial blood supply and may even exhibit subpial invasion. It is paramount to perform meticulous dissection of these vessels from the tumor capsule and to ensure that the tumor is completely dissected free from the surrounding brain before any attempt to deliver the tumor capsule, so as to avoid avulsion injury of vascular structures (Fig. 4C and D).

In properly selected patients, radical Simpson Grade I tumor removal can be achieved with the endoscopic endonasal transcribriform approach because the nature of the approach incorporates removal of the underlying hyperostotic bone and dural attachment to access the tumor. The endonasal approach is also very suitable for resecting meningiomas that have recurred or invaded into the paranasal sinuses, as demonstrated in Cases 2 and 3 (Figs. 7–10). Careful examination of preoperative neuroimages is critical for selecting patients for endoscopic resection. If the dural attachment is confined between the medial walls of the orbit, then the endonasal approach may be considered. On the other hand, if the dural attachment extends laterally over the orbital roofs and along the lesser wing of the sphenoid (as in Case 3), complete removal of the tumor, including the dural attachment, may not be possible. In these cases, we would consider a transcranial approach, preferably a bifrontal transbasal interhemispheric approach, if radical resection were the goal. Some authors have reported intentionally performing subtotal debulking via an endoscopic endonasal approach with the goal of relieving mass effect in patients with advanced age and medical comorbidities.[12]

In some instances, a combined transcranial and endonasal endoscopic approach can be considered for some tumors with lateral extension and paranasal sinus invasion.[5,10,24,25,42,43] The patient in our Case 3 (Fig. 10) was treated with such a combined approach because she presented with a recurrence in the paranasal sinuses and skull base with dural enhancement extending laterally over the orbital roofs. Although an endonasal approach alone is able to address the sinonasal tumor and cribriform plate involvement, addition of a bifrontal craniotomy allows for wider access and control of laterally extending tumor over the orbital roofs. Conversely, a transcranial approach alone could have addressed the tumor in Case 3, but the patient had previously undergone surgery performed by a different surgeon, and the pericranial flap had already been used. Addition of the endoscopic approach allowed us to harvest a vascularized nasoseptal flap for reconstruction from below when the pericranial flap from above was not available. The superior visualization afforded by the endoscope also allowed us to detect intranasal tumor that was hidden from the microscopic view from above.

It is also important to recognize the presence of any tumor encasement of major vessels, such as the anterior cerebral arteries, on preoperative imaging, as this may preclude total tumor removal, whether the lesion is approached endonasally or transcranially. In situations where tumor is adherent to important vessels, it is safer to leave a remnant than risk a catastrophic vascular injury. In the event of a neurovascular injury, the reality of quickly gaining adequate vascular control, applying aneurysm clips, and performing direct suture repair or bypass is more feasible with a transcranial approach than with an endonasal approach. Therefore, in cases with major vessel encasement on preoperative images, we would strongly consider a transcranial approach, particularly if a gross- to near-total resection is the desired goal.

Reconstruction of Large Anterior Skull Base Defects

One of the major criticisms of endoscopic endonasal skull base surgery is the relatively higher rate of postoperative CSF leakage. In patients with olfactory groove meningiomas, the anterior skull base osteodural defect is much larger than in patients with tuberculum sellae meningiomas (Figs. 6 and 8). These defects usually extend from the posterior wall of the frontal sinus to the planum sphenoidale. Successful reconstruction of these large defects to prevent CSF leakage remains a challenge.

A summary of results of 3 experienced endoscopic teams removing olfactory groove meningiomas endonasally revealed an overall postoperative CSF leak rate of 24% (6 of 25 patients).[7,12,14] In the largest series reported to date (15 patients), Gardner et al.[12] cited 4 cases of CSF leak (26.7%), which were all successfully treated with endonasal reexploration followed by further lumbar drainage. No subsequent craniotomies or permanent CSF diversion procedures were required. De Divitiis et al.[7] reported 1 CSF leak in a series of 4 cases (25%); it was successfully treated with endonasal reexploration. In another recent report, Greenfield et al.[14] reported 1 CSF leak in a series of 6 cases (16.7%), with an additional craniotomy being required to repair the leak. The authors stated that a craniotomy was chosen rather than repeat endonasal surgery because the defect was large and the leak site was just posterior to the frontal sinus and difficult to reach endonasally. It appears that the majority of these reported cases were performed prior to the application of vascularized nasoseptal flaps, as described by Hadad et al.[15] This mucosal flap remains pedicled on the posterior nasal artery and can be rotated to cover a variety of cranial base defects. Because this tissue is vascularized, the flap heals within 5–7 days, thereby quickly forming a mucosalized seal.[12] This technique is analogous to the pericranial flap technique that is frequently used in transbasal and craniofacial approaches from above to repair anterior skull base defects.[23,24] There are emerging reports that demonstrate significant reduction in CSF leakage (down to 5.4%) when reconstruction is performed with vascularized mucosal flaps.[12,20]

In this report, we introduce our technique for repairing large anterior skull base defects that extend all the way from the posterior wall of the frontal sinus anteriorly to the planum sphenoidale posteriorly (Figs. 2D and 5). We use a multilayer reconstruction technique that has its foundations based on a technique previously reported by Germani et al.[13] The autologous fascia lata inlay graft is the initial layer that serves to convert a "high-flow" defect into a "low-flow" defect. The next layer, using acellular dermal allograft (AlloDerm) is the most critical layer; it completely occludes the dural defect and thereby functions as our primary workhorse for repair of large (> 2 cm) anterior skull base defects. We use the technique of Germani et al.,[13] whereby a single piece of AlloDerm is positioned intracranially underneath the edges of the bony defect, with the outer margins of the graft extending extracranially to overlay the de-epithelialized margins of the bony defect. The graft is wedged into position using gentamicin-soaked Gelfoam pledgets (Fig. 5C and D). We rely on the weight of the brain to buttress and hold the intracranial portion of the graft in position and prevent migration. We do not routinely use postoperative lumbar drainage, as this may theoretically defeat the purpose of this repair technique by promoting lowered intracranial pressures. Absence of a lumbar drain also promotes quicker mobilization and shorter hospital stays,[4,13] as well as avoiding the risks of lumbar drain-induced intracranial hypotension and progressive pneumocephalus. Germani et al.[13] reported a CSF leak rate of 3% when using AlloDerm as the sole graft material without any additional vascularized mucosal flaps. In our modified technique, we incorporate bilateral vascularized pedicled nasoseptal flaps on top of the AlloDerm repair as an additional layer of coverage. The length of the nasoseptal flaps may not always reach anteriorly to adequately seal the posterior wall of the frontal sinus. Therefore, we rely on the AlloDerm layer, rather than the nasoseptal flaps, as the primary layer of coverage. The nasoseptal flaps in this technique act as a supplemental layer to promote rapid ingrowth of granulation, vascularization, and re-epithelialization by sinonasal mucosa. Although some have reported difficulty in reaching the posterior wall of the frontal sinus endoscopically to repair dural defects,[14] we have found that this region can be readily accessed and visualized by performing a modified Lothrop procedure with 30° and 70° endoscopes.[3] With this technique, large skull base defects that extend anteriorly to the posterior wall of the frontal sinus can be successfully repaired without occlusion of the nasofrontal recess. Therefore, the risk of a delayed mucocele is not a concern with this method of repair. Additional craniotomy may not be necessary to repair these anteriorly based dural defects. Although our preliminary results appear favorable, longer follow-up and a larger number of patients are warranted to further assess the efficacy of this technique.

The risk of CSF leak after transcranial removal of olfactory groove meningiomas is not insignificant either, particularly if the hyperostotic cribriform plate is removed to access tumor extension into the paranasal sinuses. Obeid and Al-Mefty[30] reported a CSF leak rate of 20% (3 of 15 patients) after radical excision that included removal of hyperostotic bone and tumor extending into paranasal sinuses. One of these patients required an additional operative repair, whereas the other 2 cases resolved with lumbar drainage. In a report of 80 patients by Spektor et al.,[40] 10 patients (12.5%) had postoperative CSF

leakage and 4 patients (5%) had meningitis, resulting in 1 postoperative death. This reemphasizes the importance of meticulous multilayer reconstruction of the cranial base, whether the operative approach is endonasal or transcranial.

Hyperostosis and Invasion Into Paranasal Sinuses

Olfactory groove meningiomas tend to have a rather high rate of recurrence (30% at 5 years and 41% at 10 years), which is often attributable to incomplete resection, particularly of the involved underlying bone at the cranial base.[28] Radical Simpson Grade I removal including the dural attachment and involved bone, when safely possible, remains the best option for minimizing recurrence. Interestingly in Simpson's original report, Grade I resection was possible only in 1 of 14 patients with olfactory groove meningiomas because of tumor involvement of the cranial base. This stems from the thinking that violation of the cranial base and entrance into the paranasal sinuses increases the risk of CSF leakage and meningitis. Thus, most surgeons have taken a more conservative approach, usually a Simpson Grade II resection, without aggressive resection of the involved bone at the cranial base. However, mere cauterization of the dural attachment or even dural resection alone without removal of bone involvement may not be sufficient to minimize recurrence.[1,2,9,18,27,28,37]

It is not uncommon for olfactory groove meningiomas to exhibit hyperostosis of the anterior skull base because they frequently involve the underlying bone (Fig. 8).[1,2,9,17,26,30–32] This rate of hyperostosis has been reported to be as high as 86%,[30] and it appears to be a result of tumor invasion rather than a reactive association to the tumor.[32,33] Because olfactory groove meningiomas arise from the region of the cribriform plate and planum sphenoidale, they can invade the adjacent ethmoid and sphenoid sinuses. Derome and Guiot[10] reported that 15% of olfactory groove meningiomas extended into the paranasal sinuses. In a more contemporary series of 80 patients, Spektor et al.[40] found 26.3% of cases with paranasal sinus invasion. As such, the ethmoid sinuses and cribriform plate are frequent sites for tumor recurrence, with extension into the paranasal sinuses and nasal cavity in patients who have undergone conservative Simpson Grade 2 resections. In our report, all 3 patients exhibited underlying hyperostosis at the cribriform plate, which was the likely source of tumor recurrence into the paranasal sinuses in 2 patients. In a study by Obeid and Al-Mefty,[30] all 6 patients who presented with recurrent olfactory groove meningiomas had hyperostotic bone involvement at the cranial base.

Therefore, to minimize recurrence, a Simpson Grade I removal should be performed that includes the dural attachment, underlying hyperostotic bone, and any paranasal sinus extension. In more contemporary transcranial series that advocate this more radical approach, the rate of total resection has ranged from 85% to 93.3%, with a postoperative CSF leak rate ranging from 0% to 20%.[16,29,30,40] Although the number of patients who have undergone endoscopic resection is limited, the extent of resection and rates of CSF leak appear comparable to those of transcranial series. In a recent endoscopic series by Gardner et al.,[12] 10 (83%) of 12 patients underwent gross-total or near-total resection with a CSF leak rate of 27%. De Divitiis et al.[7] reported total removal in all 4 patients (100%) with olfactory groove meningiomas, with a CSF leak occurring in 1 patient (25%). These reports were prior to application of vascularized nasoseptal mucosal flaps, which appears to be a promising technique for reducing the rate of CSF leaks. Newer studies from the same authors have reported a significant decrease in the overall incidence of CSF leaks to 5.4% after using the nasoseptal flap.[20] When a transcranial approach transgresses the cranial base into the paranasal sinuses, one may consider supplementing the repair with a nasoseptal flap from below, as illustrated in Case 3. Further long-term follow-up is warranted to see whether a radical approach (Simpson Grade I including resection of underlying bone) results in a lower rate of recurrence than a more conservative approach (Simpson Grade II).

Conclusions

The purely endoscopic endonasal transcribriform approach offers a direct midline trajectory and immediate access for removal of olfactory groove meningiomas without brain retraction and manipulation of neurovascular structures. Extracapsular dissection with preservation of the arachnoid planes can be achieved using bimanual microsurgical techniques through a keyhole craniectomy directed at the ventral skull base. In carefully selected patients, complete Simpson Grade I tumor removal including the dural attachment and involved hyperostotic bone can be achieved. Excellent panoramic visualization of the entire ventral skull base extending from the posterior wall of the frontal sinus to the planum sphenoidale can be obtained with a 30° endoscope after performing a modified Lothrop procedure. Successful cranial base reconstruction can be performed using a multilayer fascia lata and AlloDerm technique supplemented by bilateral vascularized nasoseptal flaps. In experienced hands, this approach can be considered a viable alternative for a select group of patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Liu, Eloy. Acquisition of data: all authors. Analysis and interpretation of data: Liu, Christiano, Patel. Drafting the article: Liu, Christiano, Patel, Tubbs. Critically revising the article: all authors. Approved the final version of the paper on behalf of all authors: Liu. Administrative/technical/material support: Christiano, Patel. Study supervision: Liu.

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See the corresponding article in this issue (E3).

Neurosurg Focus 30 (5):E4, 2011

Editorial

Endoscopic endonasal approach to anterior skull base meningiomas

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Since the seminal report of Weiss[5] describing use of the transnasal approach to tuberculum meningiomas, a concatenation of the superb expertise brought forward with endoscopic equipment and techniques refined by our colleagues specializing in otolaryngology/head and neck surgery and a corresponding interest by neurosurgeons in the development of transfacial approaches to intradural pathological conditions of the anterior skull base have led to an increasing interest in the use of this approach.[1] The paper by Liu et al.[3] in this issue of *Neurosurgical Focus* nicely describes the state of the art, state of technology, and limitations of the transnasal surgical approach to olfactory groove meningiomas. The authors also provide a technical overview of the procedure as done at their institution.

Advantages of the Approach

Standard tenets of skull base meningioma surgery include 1) removal of bone to avoid or minimize retraction of the brain for tumor access, and 2) early devascularization of the tumor at its point of attachment. The endonasal approach achieves these goals precisely. Removal of hyperostotic bone with the approach also facilitates a Simpson[4] Grade I resection (removal of the tumor and its bony attachment). The tumor is immediately apparent if the opening is well placed; we have used image guidance (Stealth, Medtronic) for this purpose to tailor our opening accordingly. Furthermore, the approach can address any tumor extension into the adjacent sinuses, which in the past may have been neglected by neurosurgeons. Finally, with this endonasal route, facial incisions are avoided.

Disadvantages of the Approach

The major disadvantage of the midline exposure provided by the endonasal approach is the limitations placed laterally by the orbits. Tumor extension laterally over the superior roof of the orbits may limit the visualization of tumor removal; the authors address this by noting that the tumor may be reduced by intratumoral debulking followed by extracapsular dissection, a standard meningioma resection technique. Although this is true, the challenge is not so much the ability to achieve resection of the mass of tumor, which often naturally delivers itself through the opening, but one of adequate removal of the tumor's dural and bone attachment laterally. The orbits provide a barrier to thorough removal of bone and dura of the anterior skull base beyond the projection the papyracea and the fovea ethmoidalis, which may hinder the removal of the tumor attachment on the superior orbital wall. I personally believe that the bar should be set higher for meningiomas of the anterior skull base than a Simpson Grade I removal. We routinely strive to attain a Simpson Grade 0 (2-cm margin of normal dura; Kinjo et al.[2]) if anatomically feasible for meningioma resection in any location. This should be achievable in most cases if the region of attachment is the olfactory groove. If the approach limits the possibility of achieving a Grade 0 resection because of lateral extension of the tumor over the orbits, then a transcranial approach is chosen. These tumors can be removed with facility from a limited unilateral frontal or frontotemporal approach with minimal morbidity, with equal or reduced length of stay in the hospital in comparison with an endonasal approach. It is our firm belief that the resection should not be compromised on the basis of the approach used in any case. It also remains to be determined whether the endonasal approach will provide as much durable tumor control as contemporary transcranial approaches for this reason.

The risk associated with creating any large defect in the anterior skull base is CSF leak. With improved closure techniques, including the vascularized nasoseptal flap, this risk has been reduced from roughly 25% in studies reported in the early endoscopic literature to closer to 5% in the contemporary literature. This is still a significant deterrent to use of the endonasal approach. By definition, the opening will always be larger when approaching the tumor from below than the defect created by a Simpson Grade I removal from above. Closure is critical, and the authors describe a technique that has been successful in their hands. The risks of morbidity and mortality associated with a potential CSF leak should not be downplayed during the critical appraisal of these approaches. It is a morbid and potentially lethal complication. We too have found that the use of dermal allograft (AlloDerm, LifeCell Corp.) has facilitated closure of all endonasal leaks, and this material is routinely used in other skull base locations by our group.

Another lesser disadvantage with the endonasal endoscopic approach is that important cranial nerves and arteries are identified later in the dissection than when the transcranial approach is used. They are identified near the end of tumor removal and may already have been manipulated if they are adherent to the tumor. The surgeon must pay particular attention to those tumors with surrounding T2-weighted image hyperintensity, in which the pia–arachnoid may have been breached by the tumor, and the extracapsular dissection plane well described by the authors is not present.

In conclusion, the authors have emphasized that the endonasal approach to removal of olfactory groove meningiomas is feasible and provides excellent outcome in well-selected cases (based on size and location). It is a superior approach in lesions with sinus extension (or can be a supplement to a transcranial approach). As the technology and closure techniques improve, it should become routine in training programs and skull base centers. The work of Dr. Liu and others will help refine the indications and advantages for these approaches for meningioma patients. It should be emphasized that the goal of meningioma surgery is resection with the lowest Simpson grade that can be safely achieved, and the choice of approach—when both approaches are safe in experienced hands—should be made with this goal in mind. *(DOI: 10.3171/2011.3.FOCUS1174)*

Disclosure

The author reports no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Level I to III craniofacial approaches based on Barrow classification for treatment of skull base meningiomas: surgical technique, microsurgical anatomy, and case illustrations

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Object. Although craniofacial approaches to the midline skull base have been defined and surgical results have been published, clear descriptions of these complex approaches in a step-wise manner are lacking. The objective of this study is to demonstrate the surgical technique of craniofacial approaches based on Barrow classification (Levels I–III) and to study the microsurgical anatomy pertinent to these complex craniofacial approaches.

Methods. Ten adult cadaveric heads perfused with colored silicone and 24 dry human skulls were used to study the microsurgical anatomy and to demonstrate craniofacial approaches in a step-wise manner. In addition to cadaveric studies, case illustrations of anterior skull base meningiomas were presented to demonstrate the clinical application of the first 3 (Levels I–III) approaches.

Results. Cadaveric head dissection was performed in 10 heads using craniofacial approaches. Ethmoid and sphenoid sinuses, cribriform plate, orbit, planum sphenoidale, clivus, sellar, and parasellar regions were shown at Levels I, II, and III. In 24 human dry skulls (48 sides), a supraorbital notch (85.4%) was observed more frequently than the supraorbital foramen (14.6%). The mean distance between the supraorbital foramen notch to the midline was 21.9 mm on the right side and 21.8 mm on the left. By accepting the middle point of the nasofrontal suture as a landmark, the mean distances to the anterior ethmoidal foramen from the middle point of this suture were 32 mm on the right side and 34 mm on the left. The mean distance between the anterior and posterior ethmoidal foramina was 12.3 mm on both sides; the mean distance between the posterior ethmoidal foramen and distal opening of the optic canal was 7.1 mm on the right side and 7.3 mm on the left.

Conclusions. Barrow classification is a simple and stepwise system to better understand the surgical anatomy and refine the techniques in performing these complex craniofacial approaches. On the other hand, thorough anatomical knowledge of the midline skull base and variations of the neurovascular structures is crucial to perform successful craniofacial approaches. *(DOI: 10.3171/2011.3.FOCUS1110)*

Key Words • **anterior cranial fossa** • **craniofacial approach** • **meningioma** • **microsurgical anatomy** • **surgical technique**

Midline craniofacial approaches provide various routes for reaching lesions from the ACF down to the upper cervical spinal cord. For lesions situated in the midline, they are advantageous over the lateral approaches (that is, orbitozygomatic-pterional craniotomy and transpetrosal approaches), which have some disadvantages such as critical structures surrounding the lesions, long working distances, and limited operative maneuverability.[3] Midline craniofacial approaches provide direct access to the lesions and involve fewer neurovascular structures on the surgical avenue than the lateral approaches.[13,14,16,21]

Since its early description by Smith in 1954 and Ketchan in 1963, the basic transbasal approach and its modifications have been coined under various and often confusing names, including the extended cranial approach, subcranial approach, and telecanthal approach.[7,11,18,19,25,26] The Barrow group created a new classification system that simplified the description of these complex approaches to find a common terminology and better understand the surgical anatomy.[10,12]

Numerous reports exist regarding the indications, techniques, and variations of craniofacial approaches in the neurosurgical literature. The purpose of this study is to describe the technical aspects of craniofacial approaches in cadaveric dissections in a stepwise manner.

Abbreviation used in this paper: ACF = anterior cranial fossa.

Recent advances in general endoscopic techniques have led to advances in endoscopic skull base surgery as well. Nowadays, many of the lesions that required complex skull base surgical approaches may be amenable to endoscopic techniques. However, there are still particularly complex and difficult cases that require craniofacial approaches. This report consolidates the approaches for the first 3 of the 5 different levels in stepwise cadaveric dissections. It also describes the relationships of important anatomical landmarks, foramina, and sutures in 24 dry skulls. Surgical case examples consisting of meningiomas of the ACF in which 3 of these approaches (Levels I–III) were used are presented, along with the relevant microsurgical anatomy, to demonstrate the applications and indications of each craniofacial approach.

Methods

Ten cadaveric heads were injected with colored silicone (red for arteries, blue for veins) to demonstrate craniofacial approaches based on the Barrow classification. Step-by-step dissections were performed to demonstrate the differences of each approach. In addition, important anatomical landmarks and techniques were demonstrated on cadaveric heads. Clinical case illustrations are presented to show applications for the first 3 craniofacial approaches.

The supraorbital foramen or notch is the first bony landmark seen during surgery when performing Level I, II, and III craniofacial approaches. This passage can be either in the form of a foramen or a notch. The type of passage in each dry skull was evaluated, and the distance from the supraorbital foramen or notch to midline was measured. The nasofrontal suture was considered a useful and simple anatomical landmark during Level I, II, and III craniofacial approaches. The distances between the anterior and posterior ethmoidal foramina and the optic canal were also measured.

Surgical Techniques

Level I Craniofacial Approach and Illustrative Cases

Removal of the inferior frontal bone and the orbital roofs provides a direct flat view to the ACF floor. The key to this modification is elevation of bilateral supraorbital bars and an osteotomy made in the nasofrontal suture without detachment of the medial canthal ligaments.

A bicoronal (tragus to tragus) scalp incision was used for this approach (Fig. 1 left). The incision must be posterior enough to allow the dissection of an adequate length of the periosteal (pericranial) flap. Care should be taken not to incise the periosteum along with the galea because the periosteum can be dissected further posteriorly to harvest more periosteum for reconstruction if necessary (Fig. 1 right). This flap is used for reconstruction of the ACF (Fig. 1 right). Since lateral orbital wall exposure is not needed for Level I and II approaches, there is no need to reflect the temporalis muscle. However, a 2–3-cm incision can be made away from the subgaleal fat pad where the frontotemporal branch of the facial nerve courses to

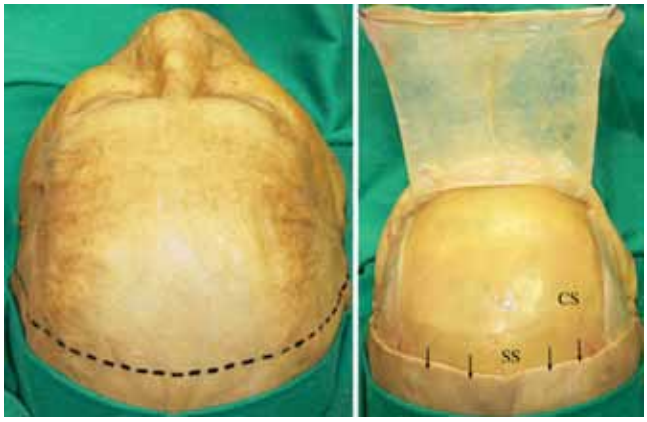

Fig. 1. Photographs. **Left:** The tragus-to-tragus bicoronal scalp incision. **Right:** The cadaveric dissection showing the pedicled, vascularized periosteal (pericranial) layer, which is used to reconstruct the ACF. Part of this layer can also be used for duraplasty. More flap can be obtained by further undermining of the galea posteriorly *(arrows)*. CS = coronal suture; SS = sagittal suture.

expose the so-called keyhole region on both sides. These also can be used for bur hole placement. For Level III approaches, subfascial or interfascial temporalis muscle dissection is performed to expose the pterion, the zygomatic bone, and the frontozygomatic suture. A detailed description of subfascial dissection to expose the zygoma, which is commonly used in the orbitozygomatic approach, is given in previous publications.[24,31] Blunt dissection is used to free the periorbita from the superior, medial, and lateral aspects of the orbital rims. The supraorbital nerves can be freed from the supraorbital notch with blunt dissection. In the case of the supraorbital foramen, a small chisel or drill can be used to free the nerve (Fig. 2). Advancing the scalp reflection to provide adequate exposure to the level of the nasofrontal suture might be difficult in some cases. A useful technique described by Fujitsu et al.[11] involves a midline incision of the procerus muscle, which relaxes the scalp and leads to an easier exposure of the nasion. The initial 2 holes are made at each keyhole region bilaterally, and the other bur holes can be made near or wherever necessary depending on the particular patient's anatomy at the midline. After bifrontal craniotomy is performed (Fig. 3), the dura is reflected from the ACF (Fig. 4). Size and lateral extension of the bifron-

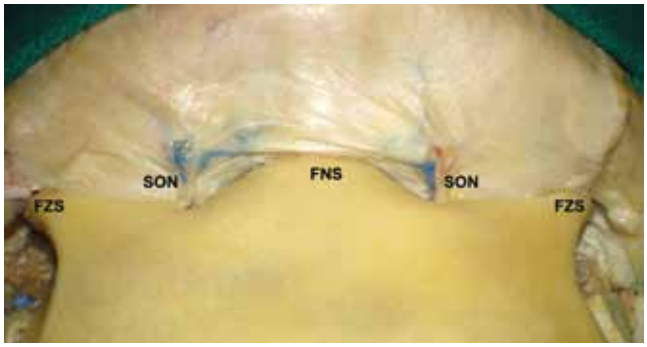

Fig. 2. The supraorbital nerves (SONs) are shown after elevation of the periosteal flap. FNS = frontonasal suture; FZS = frontozygomatic suture.

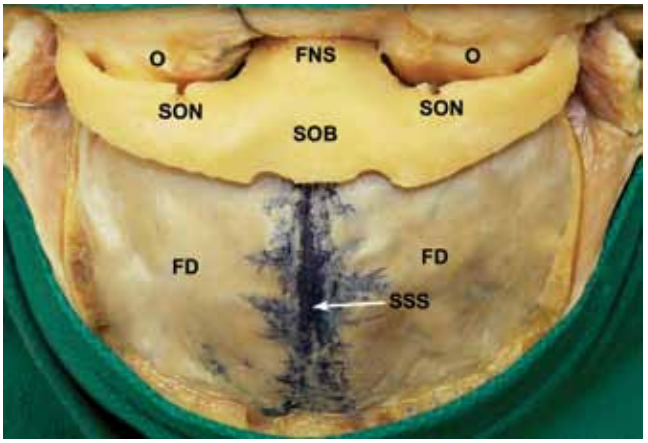

Fig. 3. A bifrontal craniotomy has been performed. Both orbital rims (supraorbital bars) are shown on the cadaver. FD = frontal dura; O = orbit; SOB = supraorbital bar; SON = supraorbital notch; SSS = superior sagittal sinus.

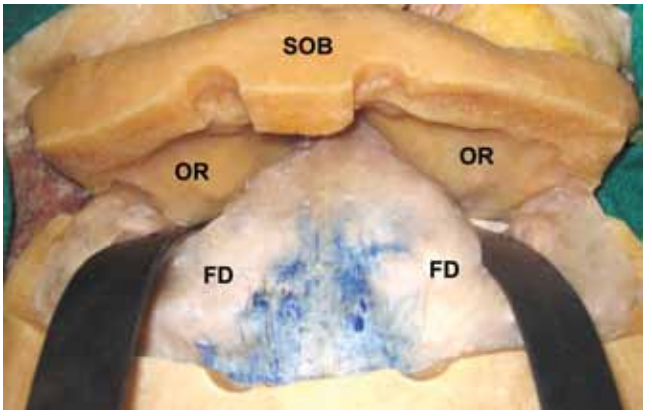

Fig. 4. The orbitofrontal dura has been reflected from both orbital walls. FD = frontal dura; OR = orbital roof.

tal craniotomy are tailored according to size of the lesion and other variables such as the extent of the edema. The frontozygomatic suture is the lateral landmark for an osteotomy made in the supraorbital bar (Fig. 5A). The orbital roofs are cut in an arch that extends posteriorly to incorporate as much of the roof into the bar as possible (Fig. 5B), then anteromedially just lateral to the cribriform plate to the level of the foramen cecum in front of the crista galli (Fig. 5C). The inferomedial landmark is the nasofrontal suture (Fig. 5D). This facilitates exposure of the ACF and cribriform plate (Fig. 5E–H). The exposure is a wide subfrontal one that leaves the nasal bones in place and gives access to the ACF and cribriform plate but not access into the nasopharynx (Fig. 5E–H).

Case 1. This 61-year-old woman presented with a 2-year history of personality change and depression. On workup, she was found to have a very large homogeneously contrast-enhancing mass in the anterior cranial fossa (Fig. 6A–C). Although the origin of this meningioma could not be exactly determined preoperatively, at surgery it was found to be arising from the olfactory groove. She underwent a Level I craniofacial approach with lumbar drain placement (Fig. 6D and E). She made an excellent recovery and went back to her premorbid baseline. Postoperative MR imaging at 2 years did not show any recurrent or residual meningioma (Fig. 6F and G). Of note, she did not have any smelling function before surgery, which remained unchanged.

Case 2. This 57-year-old woman presented with headache and long-standing decreased visual acuity, which progressed to bilateral blindness very recently. Magnetic resonance imaging showed a very large tuberculum sellae meningioma (Fig. 7A–C). She underwent a Level I craniofacial approach and gross-total resection of the meningioma. This is the only case of tuberculum sellae meningioma that we resected via a transbasal approach because of its very large size and optic nerve involvement. Our usual approach of choice at our institutions for the treatment of tuberculum sellae meningiomas is the unilateral cranioorbital or pterional approach. The patient made a remarkable recovery. On follow-up at 6 months, she was able to count fingers bilaterally from approximately 1 m with residual field defects. Follow-up MR imaging at 6 months did not show any residual or recurrent meningioma (Fig. 7D).

Case 3. This 54-year-old woman presented with personality changes and decreased executive functions. Routine neurosurgical examination revealed grossly intact neurological functions except for loss of smelling bilaterally. Magnetic resonance imaging showed a very large anterior fossa meningioma with extensive vasogenic edema (Fig. 8A and B). The patient underwent a Level I craniofacial approach with placement of a lumbar drain. Gross-total resection of the meningioma was achieved. Intraoperatively, the origin of the meningioma could not be determined exactly but was narrowed down to either the olfactory groove or planum sphenoidale. The patient made an excellent recovery with no recurrent meningioma at 2-year follow-up and almost complete resolution of T2 signal changes (Fig. 8C–E).

Level II Craniofacial Approach and Illustrative Case

This approach provides an additional inferior exposure to the Level I approach by removing the nasal bone, which allows access to the nasopharynx and clivus. It is used to expose lesions in the ACF, nasopharynx, clivus, and the orbit.

The orbital bar osteotomies typically include the nasal bone, medial orbital wall, and orbital roof. The lateral orbital wall is not included to a significant extent. The inferior orbital fissure is not incorporated in the osteotomy of the orbital bar (Fig. 9A). With this osteotomy, detachment of the medial canthal ligaments either unilaterally or bilaterally is required (Fig. 9B). The medial canthal ligament lies in front of the lacrimal sac, and the angular vein (the uppermost end of the facial vein) lies in front of the medial canthal ligament (Fig. 9C and D). The nasolacrimal duct continues downward from the lacrimal sac and opens into the inferior nasal meatus.

The flap is reflected anteriorly, exposing the nasal bones and nasal process of the maxilla (Fig. 9A and B). The supraorbital nerves are freed from the supraorbital notch or the foramen with a small chisel or drill. The me-

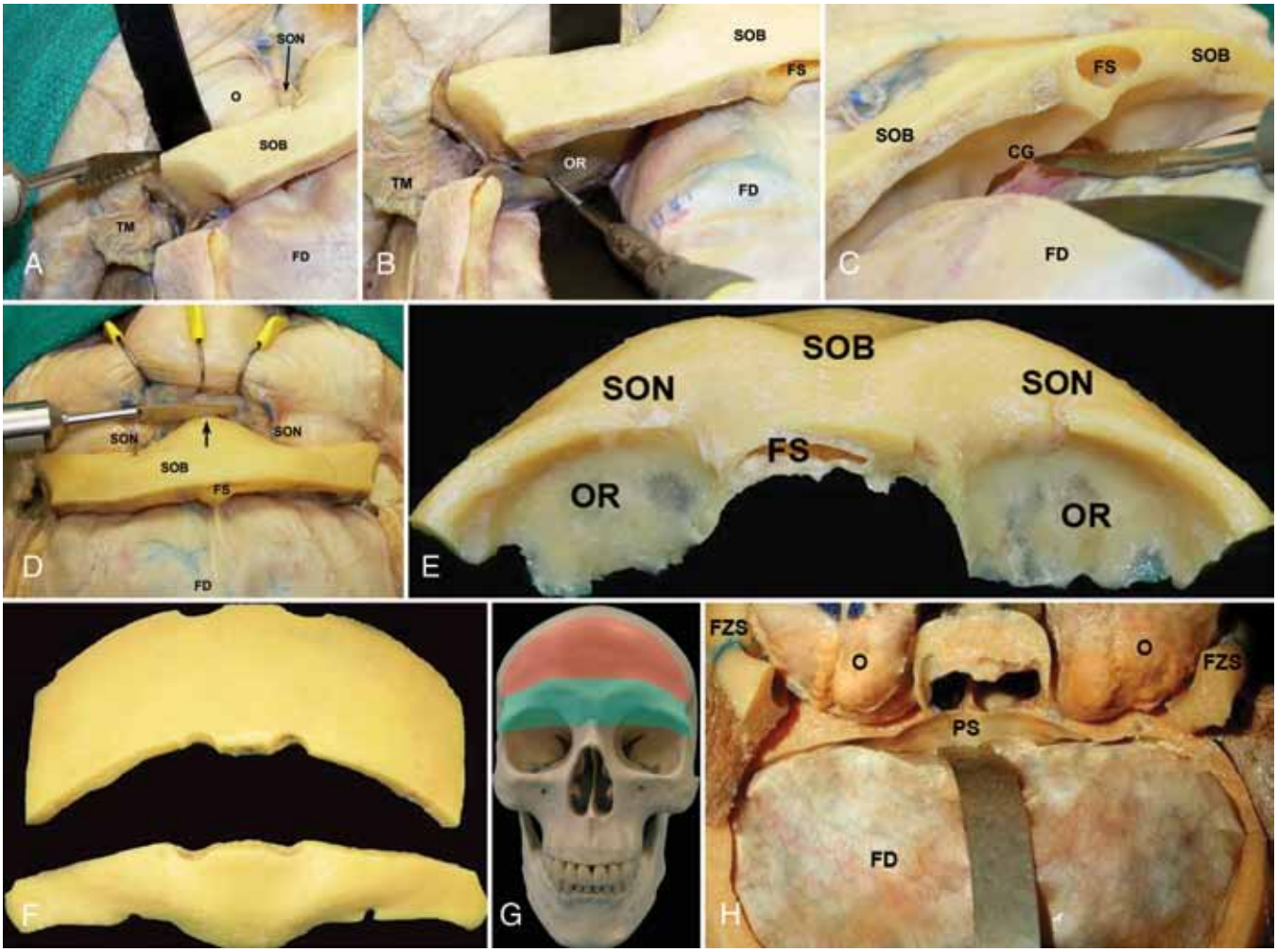

Fig. 5. Demonstration of orbital osteotomy cuts for a Level I craniofacial approach. **A:** The lateral border of the osteotomy is just medial to the frontozygomatic suture. SON = supraorbital nerve. **B:** The osteotomy extends from the orbital bar to the orbital roof (OR) at least 2.5 cm. **C:** The osteotomy continues in the frontal fossa passing over the crista galli (CG). **D:** The nasofrontal suture forms the inferomedial border of the supraorbital osteotomy. The *arrow* indicates the nasofrontal suture. SON = supraorbital nerve. **E:** The supraorbital bar is demonstrated after it has been removed. SON = supraorbital notch. **F:** Demonstration of the bifrontal bone flap and supraorbital bar that have been taken out for the Level I approach. **G:** Color demonstration of the bifrontal craniotomy and supraorbital bar osteotomies on a dry skull. **H:** Final extradural exposure after a Level I approach has been performed. FS = frontal sinus; PS = planum sphenoidale; TM = temporalis muscle.

dial canthal ligaments are taken down, and the upper cartilages are detached from the nasal bones. The nasolacrimal duct is exposed and preserved. A fragment of bone can be retained on the medial canthal ligament for easy, subsequent transnasal wiring. A bifrontal craniotomy and dural dissection are then performed. The cuts across the lateral orbital walls and roofs are the same for the Level I and II craniofacial approaches (Figs. 5 and 9). Medially, the osteotomies extend inferiorly to the nasal aperture. The nasal cuts are made across the nasal process of maxilla, anterior and medial to the nasolacrimal ducts, and then posteriorly along the medial orbital wall to the foramen of the anterior ethmoidal artery (Fig. 9A–D). The frontoethmoid suture is the main anatomical landmark in the medial orbital wall. The anterior and posterior ethmoidal foramen and the optic foramen are usually in the superior localization at this suture and trace in a parallel manner. The anterior ethmoidal foramen can easily be found by following the frontoethmoid suture during this osteotomy. The cut is approximately 1 cm in front of the optic canal. To free the supraorbitonasal bar, a last cut across the frontal crest anterior to the crista galli is made. The supraorbital bar and the nasal orbital complex are osteotomized and removed (Fig. 9F and G).

Case 4. This 40-year-old man presented with loss of smelling, nasal fullness, and mild personality changes over the course of a year. Magnetic resonance imaging revealed a contrast-enhancing mass lesion located in the AFC with extension into the nasal cavity and destructing the cribriform plate (Fig. 10A). He underwent a Level II craniofacial approach with lumbar drain placement (Fig. 10B). The meningioma was totally excised (Fig. 10C), and his postoperative course was uneventful. However, this patient was lost to follow-up.

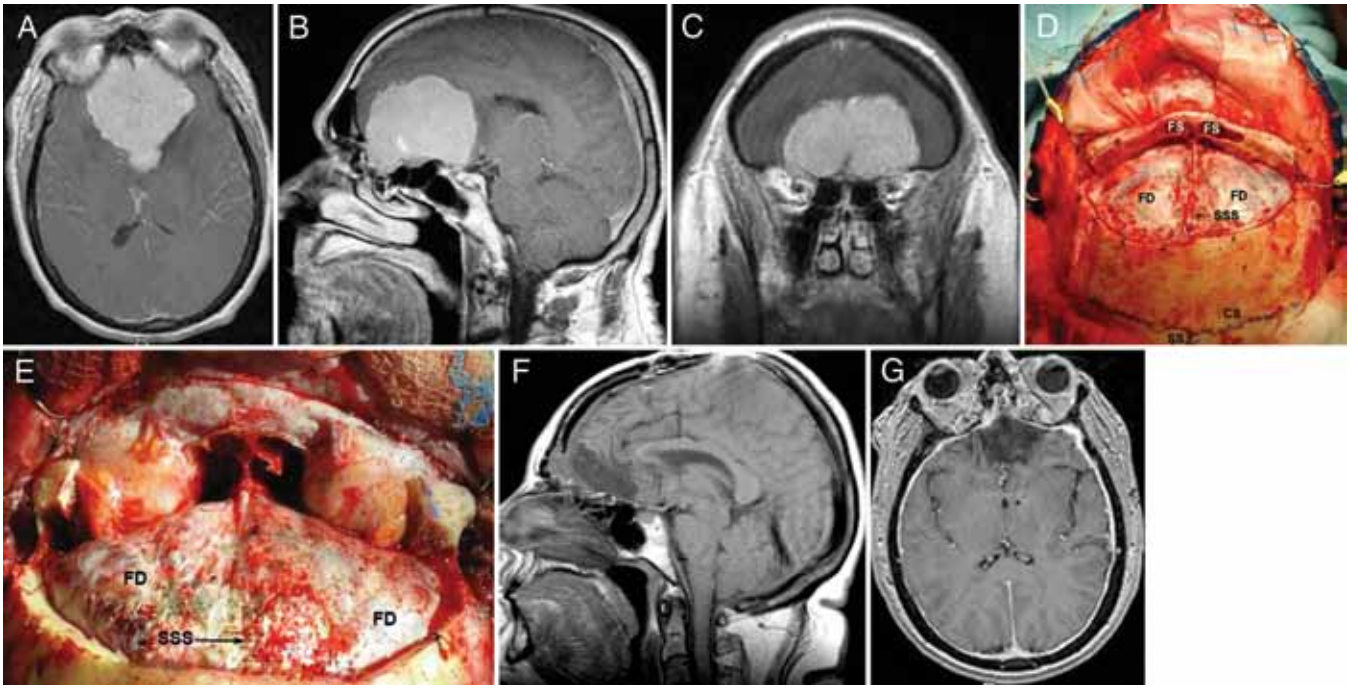

Fig. 6. Case 1. Preoperative T1-weighted postcontrast axial **(A),** sagittal **(B)**, and coronal **(C)** MR images demonstrating a giant olfactory groove meningioma with extension into the cribriform plate and ethmoidal sinus. Intraoperative photographs showing the epidural exposure after bifrontal craniotomy **(D)** and supraorbital bar removal **(E)**. Postoperative T1-weighted postcontrast sagittal **(F)** and axial (**G)** MR images obtained 2 years later do not show any residual or recurrent meningioma.

Level III Craniofacial Approach and Illustrative Case

The indications for a Level III craniofacial approach are to expose large ACF, nasopharyngeal, and clival lesions. The method of dissection is identical to that used in the Level II craniofacial approach. The osteotomy includes the lateral orbital walls from the level of the inferior orbital fissure as part of the supraorbital fragment (Fig. 11). To expose the inferior orbital fissure, zygoma, and superolateral orbital rim, the temporalis fascia is elevated in the subfascial plane between the muscle and deep fascia (Fig. 12). Approximately 2.5 cm of the orbital roof should be included in this cut so as to minimize the possibility of a postoperative pulsatile enophthalmos (Fig. 13A and B). Most of the superior orbital roof can be included in the fragment to facilitate the lateral retraction of the globe. Osteotomies are performed to remove the frontonasoorbital unit, leaving the cribriform plate exposed. Under direct vision, an osteotomy is performed posterior to the cribriform plate through the planum sphenoidale. The final cut is made through the ethmoid bone and nasal mucosa. Care should be taken to preserve a generous cuff of nasal mucosa attached inferiorly to the cribriform plate. This final maneuver completes the separation of the cribriform plate from all bony connections and leaves it attached to the base of the frontal dura with the olfactory nerve rootlets left intact. The frontal lobes, with the dura intact, can be elevated generously to access the involved area (Fig. 13C and D).

Case 5. This 22-year-old man presented with a large mass lesion located in the frontal region that had invaded the nasopharynx, paranasal sinuses, sella turcica, sphenoid sinus, and nasal cavity. This mass lesion extended into the bilateral orbital fissures more on the right than left (Fig. 14A and B). The patient underwent a Level III craniofacial approach because of periorbital involvement and involvement of the superior orbital fissures. The preoperative differential diagnosis was meningioma. The lateral walls of the orbits were also cut, and the tumor was totally removed (Fig. 14C). The histopathological diagnosis was juvenile ossifying fibroma. This case was included to demonstrate the utility of this approach (Level III) when the mass is very extensive and compresses both orbits from the medial to lateral direction.

Results

The anatomical structures in the frontoorbital region and their relationship should be well known for Level I, II, and III craniofacial approaches. The supraorbital notch or foramen is the first structure that is recognized during the surgery for all 3 approaches. The supraorbital artery and the nerve pass between the periorbita and the superior levator palpebrae muscle and leave from the supraorbital foramen or notch. The supraorbital nerve innervates the sensation of the upper eyelid, conjunctiva, and skin of the forehead up to the lambdoid suture. The freeing of this nerve during surgery is easier if it traverses through a notch rather than the foramen. Our study demonstrates that the opening of the notch might be either narrow or wide. The dimension of the opening of the supraorbital notch is important in that the risk of damaging the nerve during surgery can be minimized if the opening is wide. In our study, the notch occurred in 85.4% of specimens and the foramen occurred in 14.6% of specimens. The

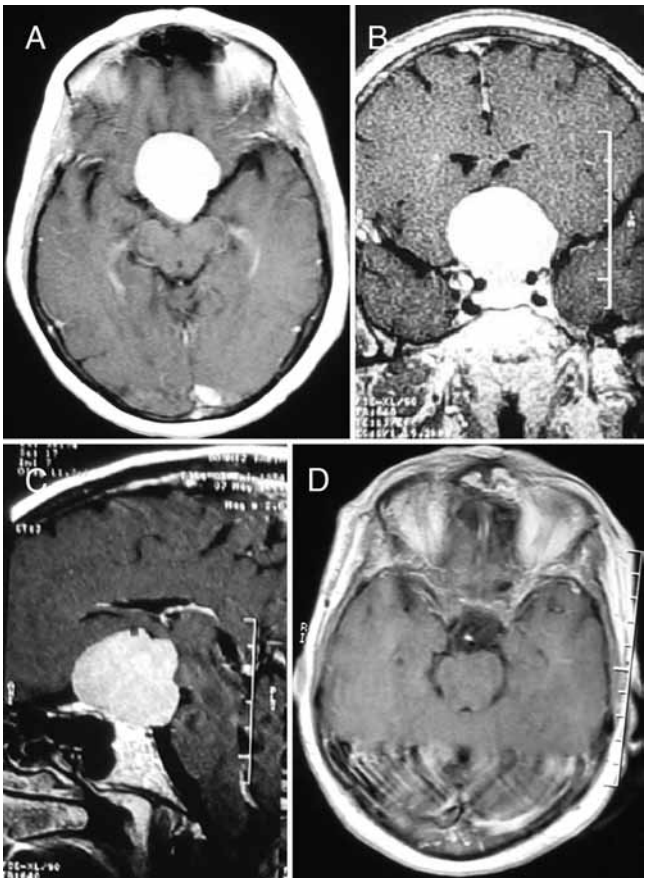

Fig. 7. Case 2. **A–C:** Preoperative T1-weighted, postcontrast axial **(A)**, coronal **(B)**, and sagittal **(C)** MR images showing a very large tuberculum sellae meningioma. **D:** Postoperative T1-weighted, postcontrast axial MR image demonstrating gross-total tumor resection at the 6-month follow-up.

opening of the notch was wide in 68.7% of cases and narrow in 16.7% of cases. Distances for important anatomical structures in the frontoorbital region are given in Table 1.

TABLE 1: Frontoorbital region measurements

Distances Btwn Anatomical Structures	Mean Distance in mm (range)	
	Rt Side	Lt Side
supraorbital foramen notch & midline	21.9 (14.8–25.8)	21.8 (18.5–26.3)
nasofrontal suture & anterior ethmoidal foramen	32.0 (31–34.5)	34.0 (32.5–36)
anterior & posterior ethmoidal foramina	12.3 (8.8–16.8)	12.3 (7.6–16.7)
posterior ethmoidal foramen & optic foramen	7.1 (5.9–10)	7.3 (4.6–10.8)

Discussion

Lesions of the ACF, especially those with extension into the orbits, clivus, paranasal sinuses, and nasopharynx are surgically challenging. The complex and critical anatomy of the neurovascular structures in this region can cause significant problems for the surgeon and the patient. The ultimate goal in surgical management is maximum resection of the tumor with minimal morbidity. Craniofacial surgical techniques have been described to accomplish these goals.[3,4,10,12,13,21,27] Beals et al.[3] listed the important features in the selection of the craniofacial approach as 1) the location and size of the lesion, 2) the tumor type and its biological behavior, 3) the patient's age, and 4) the surgeon's preference and experience. Based on these considerations, they developed the Barrow classification scheme, which simplifies the description of the craniofacial approaches and provides a common terminology.[3,4,21] This classification system, which is based on selecting the most appropriate angle of approach to the anatomical location of the tumor, can help the surgeon to plan appropriate surgical strategies for lesions of this region. This system is simple and useful for planning surgical treatment.

The first 3 of these 5 different levels of craniofacial approaches (Levels I–III) access the midline skull base from a superior trajectory (Fig. 15), whereas Levels IV and V provide access to the midline skull base via Le Fort I or II osteotomies. Levels IV and V are used primarily for oncological resection of extensive neoplastic processes of the paranasal sinuses and nasopharynx. For the first 3 levels of craniofacial approaches, the face is degloved from above using a bicoronal incision, and facial disassembly is built around a supraorbital bar. The subfrontal access achieved by removing the supraorbital bar (Level I) is extended vertically downward by removing the nasal complex and medial orbital walls on the supraorbital bar (Level II), exposing the entire midline skull base down to the craniocervical junction. Greater horizontal exposure is achieved by removing the lateral orbital walls with the supraorbital-nasal bar (Level III) and retracting the globes laterally.

In the literature relevant to craniofacial approaches, the supraorbital notch was seen in 69.9% of cases but the supraorbital foramen was only seen in 28.9% of cases.[8] In our study, the notch was seen in 85.4% of cases and the foramen in 14.6%. The opening of the notch was wide in 68.7% of cases and narrow in 16.7% of cases. The distance between the midline and supraorbital foramen or notch was 21.9 mm on the right side and 21.8 mm on the left.

The medial orbital wall is rectangular in shape and makes the lateral wall at the ethmoid sinuses. The medial orbital wall is very thin and has anterior and posterior ethmoidal foramen. In this region, the distances between the anatomical structures and nasofrontal suture is important. Proximity of the optic nerve to the posterior ethmoidal foramen is an important point that should be kept in mind. In the literature, the mean distances between the posterior ethmoidal foramen and the optic foramen have been reported to be 5.34 ± 2.81 mm on the right side and 4.9 ± 3.35 mm on the left.[1] In the present study, the mean distances between the posterior ethmoidal foramen and the optic foramen were 7.1 mm on the right side and 7.3 mm on the left. Furthermore, an additional foramen was found in 35.4% of cases between the anterior and the posterior ethmoidal foramina in cadaveric specimens.

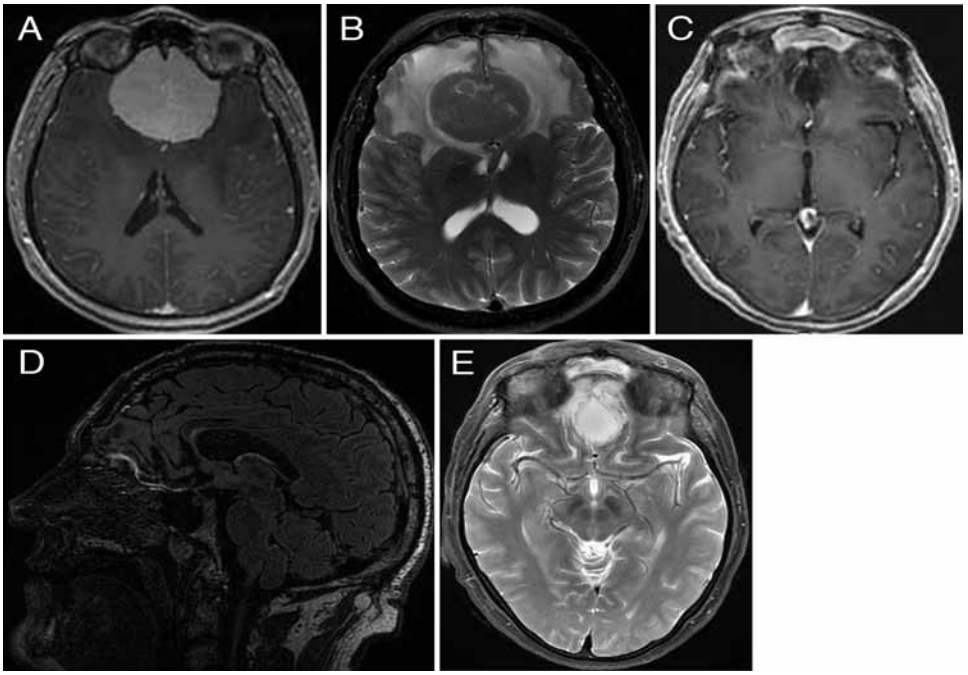

Fig. 8. Case 3. **A and B:** Preoperative T1-weighted postcontrast axial **(A)** and T2-weighted axial **(B)** MR images showing a very large meningioma of the ACF associated with extensive vasogenic edema. The meningioma extends toward the tuberculum/diaphragma sellae. **C–E:** Images obtained 2 years postoperatively. Postcontrast axial T1-weighted MR image **(C)**. There are almost no residual T2 signal changes on T2-weighted FLAIR sagittal **(D)** and T2-weighted axial **(E)** MR images.

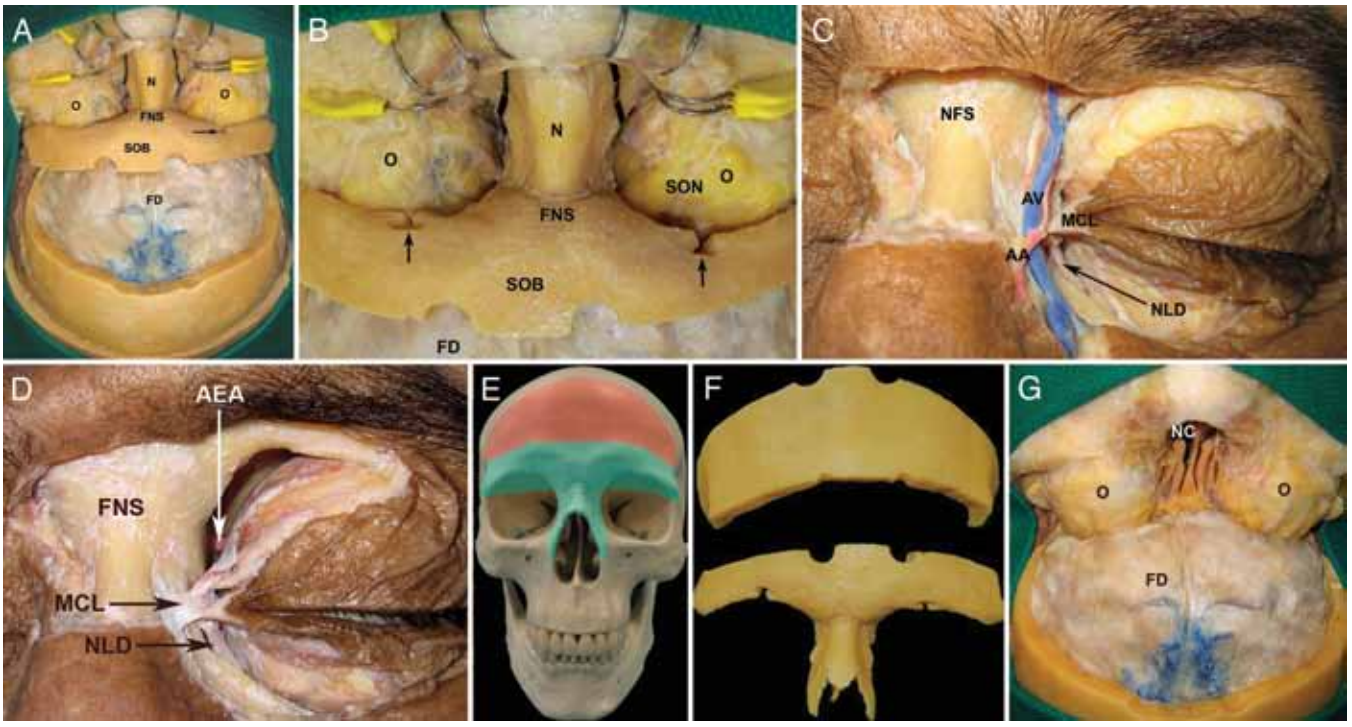

Fig. 9. Demonstration of osteotomy cuts for the Level II craniofacial approach. **A:** Overview of the Level II craniofacial approach. **B:** After a bifrontal craniotomy is performed, the location of the nasal bone osteotomies are demonstrated by *dashed lines* in a higher magnification. *Arrows* indicate the supraorbital notch. SON = supraorbital nerve. **C:** Demonstration of the medial canthal ligament (MCL) in a separate cadaveric dissection. This ligament lies in front of the lacrimal sac. The angular vein (AV) lies in front of the medial canthal ligament. The *arrow* points to the nasolacrimal duct (NLD). **D:** Further dissection of the anterior ethmoidal artery (AEA). The anterior ethmoidal artery is in the lamina papyracea of the medial orbital wall at the anterior ethmoidal foramen. **E:** Color demonstration of the bifrontal craniotomy and nasoorbital osteotomies on a dry skull. **F:** Demonstration of the bifrontal bone flap and supraorbital bar with nasal bone osteotomies. **G:** Final extradural exposure after the Level II approach. AA = angular artery; N = nasal bone; NC = nasal cavity; NFS = nasofrontal suture.

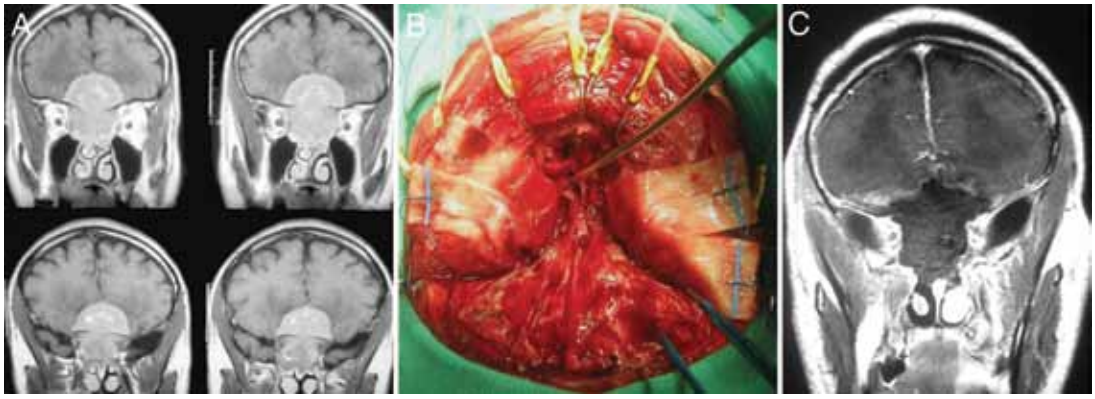

Fig. 10. Case 4. **A:** Preoperative T1-weighted postcontrast coronal MR images showing a large anterior skull base meningioma extending into the nasal cavity. **B:** Intraoperative photograph showing the final view after removal of the tumor. **C:** Postoperative T1-weighted postcontrast coronal MR image demonstrating gross total-tumor resection at the 6-month follow-up.

The anterior ethmoidal artery usually courses between the second and third lamellae and is responsible for supplying the anterior ethmoidal cells, the frontal sinus, the anterior third of the nasal septum, and the lateral wall of the adjacent nasal cavity.[29] Embolization might be of significant advantage to prevent a large amount of operative blood loss during the surgical procedures for large tumors of the ACF, especially for highly vascular neoplastic lesions. Embolization for anterior and posterior ethmoidal arteries is usually performed through the ophthalmic artery.[28] During the interventional procedure, the rate of visual compromise is up to 10%.[20,22] The brain retraction during the application of Level I, II, and III craniofacial approaches might be diminished by a broad removal of the bone in the cranial base and proper and early exposure of arterial feeders. When endovascular embolization is not feasible, the early control of blood supply to the tumor minimizes blood loss and leads to decreased surgical risk. In a large series of cranial base tumors, 12% of patients were not eligible for embolization because a suitable vessel was not available. It was reported that 9% of patients had experienced permanent major complications, and 12.6% of patients presented minor neurological complications.[23] In general, we prefer no preoperative embolization of the meningiomas involving the ACF to avoid additional risk of the embolization procedures.

Three important locations exist for proximal microsurgical access to these vessels. One location is in the

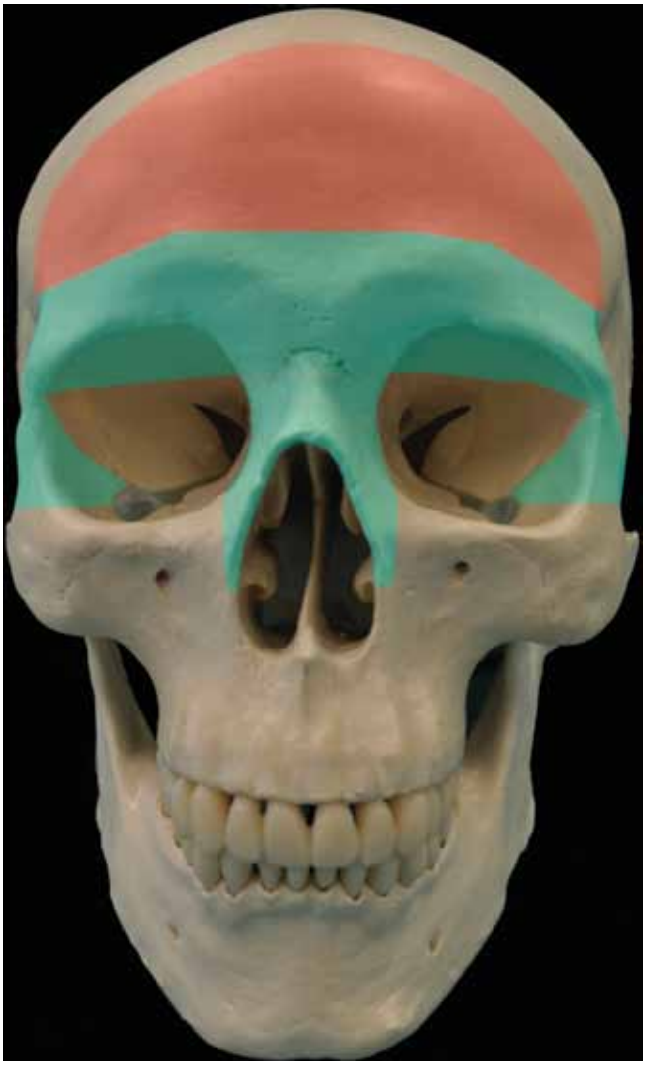

Fig. 11. Color demonstration of the bifrontal craniotomy along with osteotomies for the Level III approach is shown on a dry skull.

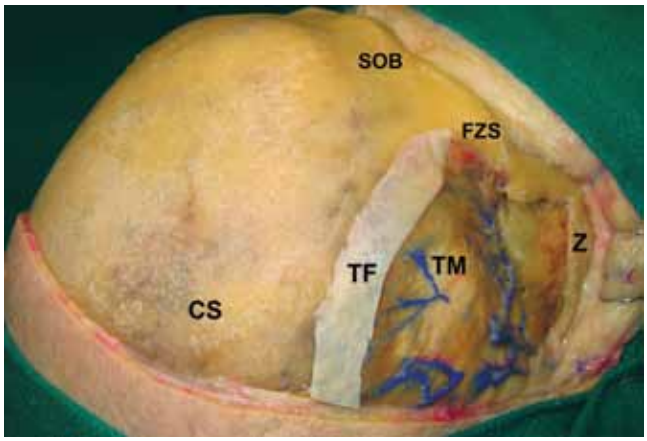

Fig. 12. Cadaveric dissection showing the exposure of the zygoma (Z) and superolateral orbital rim. The temporalis fascia (TF) has been elevated in the subfascial plane between the muscle and deep fascia.

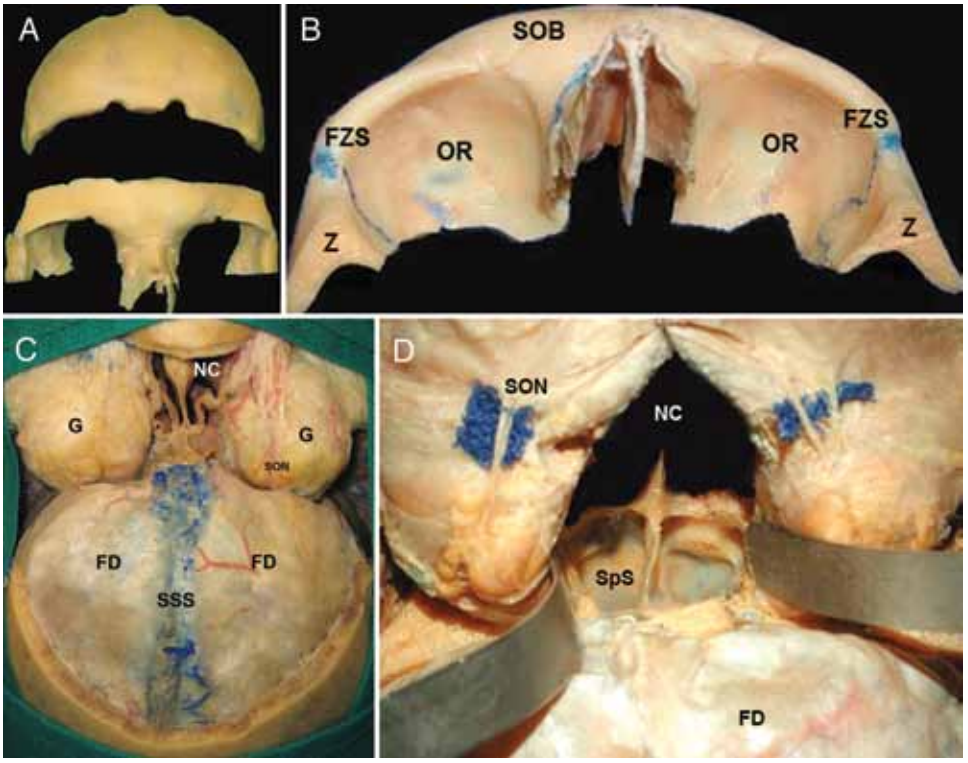

Fig. 13. **A:** Final overview of the bifrontal bone flap and nasoorbital bar in a Level III approach. **B:** Approximately 2.5 cm of the orbital roof should be included for supraorbital osteotomies. **C:** The final extradural exposure of the anterior cranial fossa, both globes (G), and ethmoidal sinus via a Level III approach in a cadaveric specimen. **D:** A Level III approach facilitates the lateral retraction of the globe. SON = supraorbital nerve; SpS = sphenoid sinus.

lamina papyracea of the medial orbital wall at the anterior ethmoidal foramen,[1] which is located 32 mm on the right side and 34 mm from the middle point of the nasofrontal suture in our study (Fig. 9D). Another site is at the lateral ethmoid wall as the anterior ethmoidal artery traverses the anterior ethmoidal foramen and travels in the anterior ethmoidal canal (Fig. 16 left). The anterior ethmoidal canal is between the second and third lamellae of the ethmoid sinus, and in 60 of 70 cases it was attached to the base of the cranium.[28,29] These findings are consistent with our dissections, showing that the anterior ethmoidal artery usually travels in a bony canal through the ethmoid sinus, requiring careful bone removal at the level of the floor of the anterior cranial fossa to identify and control the anterior ethmoidal artery at the lateral ethmoid wall. A third location for proximal control is extradurally at the cribriform plate (Fig. 16 right).

Level I craniofacial approaches are used to access tumors of the anterior skull base and those that extend into the superior orbital region. It improves the exposure of a traditional bifrontal craniotomy by removing the ledge of bone inferiorly that typically houses the frontal sinuses to create a flat or tangential view along the anterior cranial fossa. Feiz-Erfan et al.[10] recommended a Level I craniofacial approach for tumors located primarily extradurally or for large midline meningiomas. In agreement with their findings, a Level I approach is the most commonly used approach by our group in the resection of large olfactory

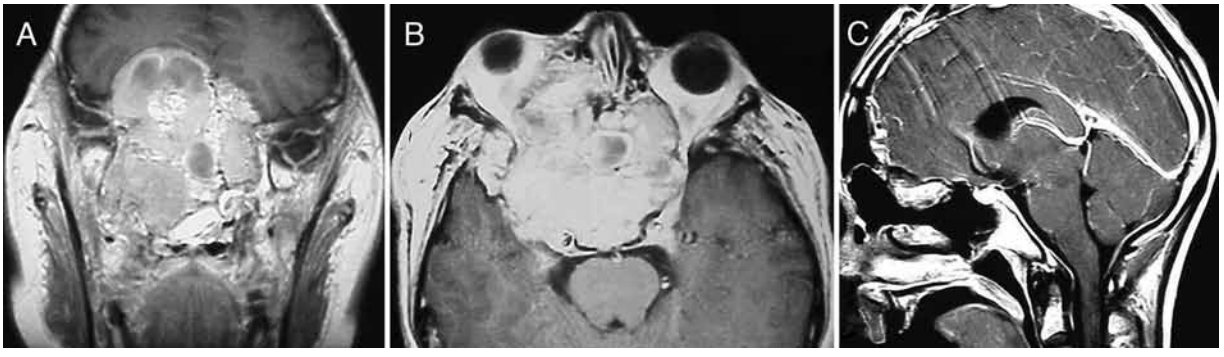

Fig. 14. Case 5. Preoperative T1-weighted postcontrast coronal **(A)** and axial **(B)** MR images showing a giant mass lesion located in the ACF, invading the nasopharynx, paranasal sinuses, sella turcica, sphenoid sinus, and nasal cavity. Postoperative T1-weighted postcontrast sagittal MR image **(C)** demonstrating gross-total tumor resection.

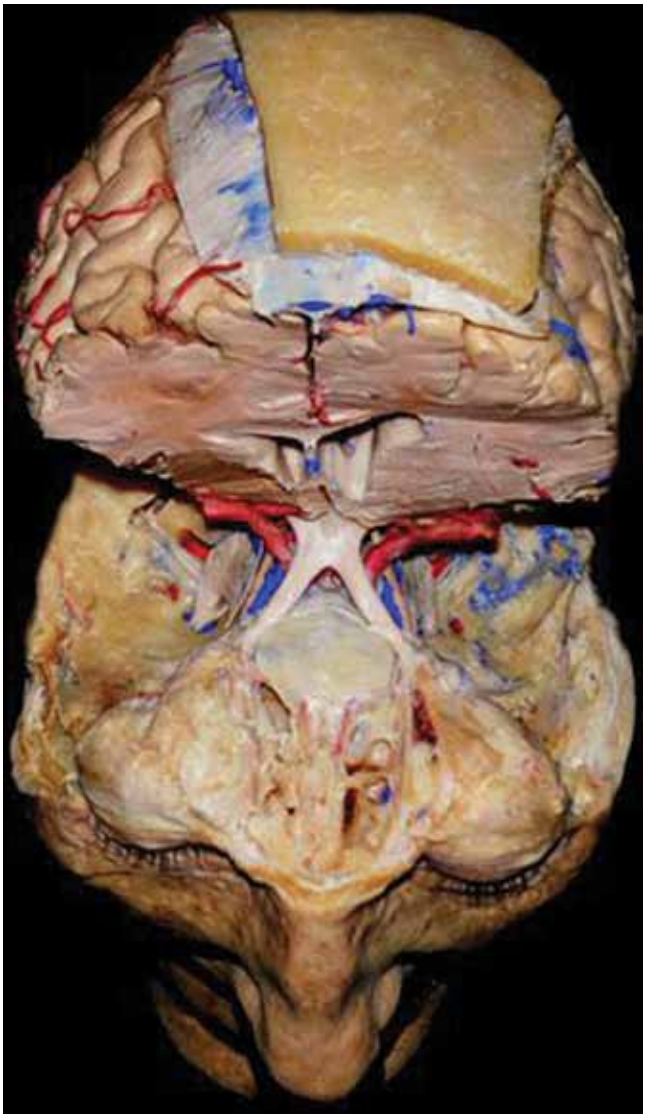

Fig. 15. Overview of cadaveric dissection showing superior trajectory obtained in Level I–III craniofacial approaches.

groove or planum sphenoidale meningiomas reaching approximately 5 cm in size and associated with extensive vasogenic edema (Figs. 6 and 8). Although some authors would use unilateral approaches in these meningiomas,[30] we believe a Level I approach significantly minimizes brain retraction, gives direct tangential view to the lesion, and carries minimal to no risk for cosmetic problems in our hands (data not shown). The disadvantage of this approach over pterional or cranioorbital approaches is that the surgeon remains blind to the optic nerves and internal carotid arteries in the early stage of microsurgical dissection.

Level II and III craniofacial approaches provide additional inferior exposure. Removal of the nasal complex provides wider access to the nasopharynx, the ethmoid and sphenoid sinuses, and the clivus (Fig. 17). A Level III craniofacial approach was developed to access large anterior cranial fossa lesions, nasopharyngeal lesions, and clival lesions with anterior extension. This approach is similar to

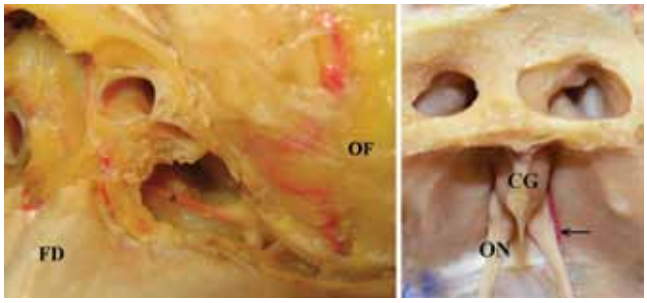

Fig. 16. **Left:** Anterior ethmoidal artery at the lateral ethmoid wall traverses the anterior ethmoidal foramen and courses in the anterior ethmoidal canal. The *asterisk* indicates the anterior ethmoidal artery. **Right:** The anterior ethmoidal artery has been exposed extradurally at the cribriform plate. The *arrow* indicates the anterior ethmoidal artery. OF = orbital fat; ON = olfactory nerve.

the Level II approach but is augmented by including the lateral orbital wall on the frontonasal fragment. The addition of a lateral orbital wall osteotomy facilitates retraction of the globes, an otherwise potentially hazardous maneuver that can be associated with diminished vision. This approach potentially decreases retraction pressure on the globes, and in addition it allows exposure of lesions with lateral extension into the superior and inferior orbital fissures and medial aspect of the infratemporal fossa. Level II and Level III craniofacial approaches offer slightly more exposure of the clivus than the Level I approach. However, at present, we rarely use these 2 approaches because of the

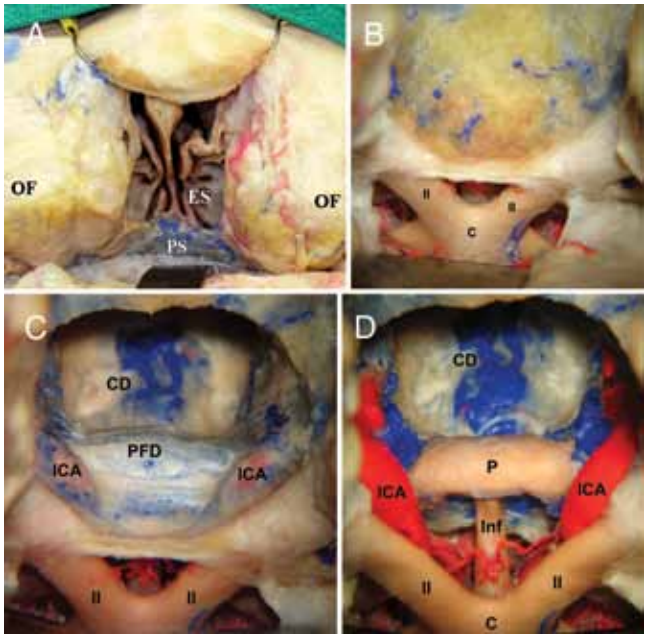

Fig. 17. **A:** The ethmoid sinus (ES) and planum sphenoidale (PS) are demonstrated in a cadaveric specimen after a Level II craniofacial approach has been performed. **B:** Demonstration of intracranial intradural and extracranial optic nerves (II) and chiasm (C) after a Level II craniofacial approach has been performed. **C:** After the sphenoid sinus has been removed, clival dura (CD), the dura of the pituitary fossa (PFD), and both cavernous internal carotid arteries (ICA) are revealed. **D:** After further resection of the dura, the intradural structures are seen. inf = infundibulum; P = pituitary gland.

extensive work and associated cosmetic problems in the postoperative period.

When performing a Level II or III approach on a tumor that does not involve the cribriform plate, the integrity of the cribriform plate and olfactory nerves can be preserved. A circumferential cribriform plate osteotomy permits greater exposure because it is easy to see beyond the cribriform plate onto the planum sphenoidale. This technique also reduces the risk of CSF leak and preserves olfaction.[15,17,21] Chandler et al.[7] found this maneuver to hinder their approach and not result in clinically significant preservation of olfaction.

Anterior approaches to midline skull base lesions have important advantages. First, these techniques capitalize on a midline plane, which is relatively avascular and critical neurovascular structures do not represent obstacles. Second, the direction of the surgery is straight at the bulk of the lesion with a short working distance. Facial incisions are seldom needed, and facial degloving and disassembly are far less complicated than expected. Craniofacial approaches provide the neurosurgeon the greatest chance of preserving neurological function and completely resecting the lesion.[16] The absence of intraoperative shifts in skull base surgery provides the opportunity to use neuronavigation reliably and accurately and enhance the surgeon's ability to localize and verify the anatomical structures.[2]

The use of the endoscope in addition to the surgical microscope has been reported to afford a wide panoramic view in the depths of the surgical field.[2,5] Pure endoscopic approaches have emerged as a feasible alternative to the craniofacial resection. They are reported to have comparable results in terms of the extent of resection and superior results in terms of the complication and recurrence rates, hospital stay, and the added benefit of desirable cosmetic outcomes in selected cases.[6,9,17] However, in most of the cases with a malignant skull base pathology, open resection is still the best option to achieve oncological resection, which is the primary prognostic indicator. Moreover, in some selected cases the endoscope can also be used as an adjunct to craniofacial approaches to reduce bone removal and to provide an inferior trajectory.

Conclusions

Craniofacial resections are best performed by a multidisciplinary team comprising a neurosurgeon, a craniofacial surgeon, and an otolaryngologist. Craniofacial approaches to the midline skull base provide access for the safe removal of complex lesions. A better understanding of the interaction of surgical anatomy with the nature and extent of the lesion, along with refinements of each approach, are of great importance in improving outcomes and avoiding complications.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Başkaya, Avcı. Acquisition of data: Başkaya, Avcı, Seçkin, Uluç, Bauer, Izci, Morcos. Analysis and interpretation of data: Başkaya, Avcı, Aktüre, Seçkin, Uluç. Drafting the article: Başkaya, Avcı, Aktüre. Critically revising the article: Başkaya, Avcı. Approved the final version of the paper on behalf of all authors: Başkaya. Statistical analysis: Avcı. Administrative/technical/material support: Başkaya. Study supervision: Başkaya.

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The molecular genetics and tumor pathogenesis of meningiomas and the future directions of meningioma treatments

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Meningiomas are mostly benign, slow-growing tumors of the CNS that originate from arachnoidal cap cells. While monosomy 22 is the most frequent genetic abnormality found in meningiomas, a multitude of other aberrant chromosomal alterations, signaling pathways, and growth factors have been implicated in its pathogenesis. Losses on 22q12.2, a region encoding the tumor suppressor gene *merlin*, represent the most common genetic alterations in early meningioma formation. Malignant meningioma progression, however, is associated with more complex karyotypes and greater genetic instability. Cytogenetic studies of atypical and anaplastic meningiomas revealed gains and losses on chromosomes 9, 10, 14, and 18, with amplifications on chromosome 17. However, the specific gene targets in a majority of these chromosomal abnormalities remain elusive.

Studies have also implicated a myriad of aberrant signaling pathways involved with meningioma tumorigenesis, including those involved with proliferation, angiogenesis, and autocrine loops. Understanding these disrupted pathways will aid in deciphering the relationship between various genetic changes and their downstream effects on meningioma pathogenesis.

Despite advancements in our understanding of meningioma pathogenesis, the conventional treatments, including surgery, radiotherapy, and stereotactic radiosurgery, have remained largely stagnant. Surgery and radiation therapy are curative in the majority of lesions, yet treatment remains challenging for meningiomas that are recurrent, aggressive, or refractory to conventional treatments. Future therapies will include combinations of targeted molecular agents as a result of continued progress in the understanding of genetic and biological changes associated with meningiomas. *(DOI: 10.3171/2011.2.FOCUS1116)*

Key Words • meningioma • signaling pathway • pathogenesis • molecular genetics

Meningiomas are the second most common adult neoplasm of the CNS, and they are mostly benign, slow-growing tumors originating from the arachnoidal cap cells.[97] The annual incidence of meningiomas is 2.3 per 100,000, increases with age, and peaks in the 7th decade of life.[97,98] Overall incidence is greater in females with a 2:1 ratio, yet higher grade meningiomas are more frequent in males.[36,67] Deletions of the *neurofibromatosis Type 2 (NF2)* gene, ionizing radiation, and head trauma are associated with an increased risk, while the role of sex hormones in meningioma development is still uncertain.[5,30] Meningiomas are categorized according to the WHO classification of tumors as benign (Grade I), atypical (Grade II), and anaplastic (Grade III), comprising 80%, 15%–20%, and 1%–3% of all meningiomas, respectively.[97] Benign meningiomas are slow growing and have a 5-year recurrence rate of 5% following gross-total resection.[97] However, management of the more aggressive and higher grade tumors is difficult. Atypical meningiomas have 5-year recurrence rate of 40%, and anaplastic meningiomas have recurrence rates of up to 80%.[97] Stafford et al. reported 5-year survival rates of 76% and 0%, respectively, for patients with atypical and anaplastic meningiomas who underwent multimodal treatment.[112]

Most meningiomas have a good prognosis, and often surgery and adjuvant radiotherapy are curative. However, gross-total resection is not always achievable because the meningioma may be enveloping sensitive neural or vascular structures, and radiation therapy is limited by neuro-

Abbreviations used in this paper: IGF = insulin-like growth factor; LOH = loss of heterozygosity; MEF = mouse embryonic fibroblast; NF2 = neurofibromatosis Type 2; PFS = progression-free survival.

toxicity and tumor size. To date, chemotherapy regimens have been minimally effective in treating meningiomas. Thus, treatment of the remaining subset of aggressive, inoperable, or refractory meningiomas remains challenging. In this review, we describe the current understanding of the molecular pathogenesis and future therapies of meningiomas.

Meningioma Development

Chromosome 22 and the NF2 *Gene*

Meningiomas are the first solid neoplasms to be identified with a characteristic cytogenetic alteration.[94,97] Monosomy 22 is the most frequent genetic abnormality found in meningiomas. This association between the long arm of chromosome 22 (22q) and meningiomas was first studied in patients with NF2. Patients with NF2, a dominantly inherited disorder, commonly present with bilateral vestibular schwannomas, multiple meningiomas, and other nervous system tumors.[59] Roughly 50% of meningiomas have allelic losses in 22q12.2,[59] a region encoding the *NF2* gene. Nearly all NF2-associated meningiomas, and 54%–78% of sporadic meningiomas, have deletions in this region.[94]

The *NF2* gene encodes the tumor suppressor merlin. Amino acid analysis revealed merlin's similarity to the 4.1 family of proteins (specifically, 3 ERM proteins: ezrin, radixin, and moesin), which link integral membrane proteins to the cortical cytoskeleton.[59] A number of studies suggest that merlin has a critical role in controlling cell growth and motility. Mouse embryonic fibroblasts (MEFs) with merlin defects are associated with abnormal cell growth and motility through the destabilization of adherens junctions.[51,106] Mice heterozygous for *NF2* mutations develop a number of motile and metastatic tumors.[73] Both in vivo and in vitro reexpression of wild type merlin leads to reduced tumor growth and decreased cell motility.[24,26,34,80,107] Furthermore, MEFs with inactive *NF2* exhibit irregular contact inhibition-dependent growth arrest, suggesting that merlin has a role in curbing growth rate in high cell density environments.[51,90]

Given the structural similarities between merlin and the ERM proteins, merlin has been implicated in regulating various membrane- and cytoskeleton-based cellular processes, including cell migration, cell-cell contact, and cell proliferation.[37,72] Merlin is localized to the cell membrane and consists of 3 major domains, including an amino-terminal protein 4.1 cell surface glycoprotein-binding domain (FERM domain).[97] While the exact mechanisms by which merlin exerts its growth-regulatory functions in human arachnoidal cells is still unclear, merlin's FERM domain allows it to interact with a number of important cytoskeleton-regulating proteins including paxillin, actin, syntenin, and other ERM proteins.[38,39,97,104,127] Merlin also binds important cell surface signaling proteins, including β1-integrin and CD44.[21,80,90] CD44 is a cell surface receptor involved with mediating cell-cell interaction, cell adhesion, and migration.[80] Merlin signals via extracellular growth pathways by forming internal protein complexes through its interaction with the cytoplasmic tail of CD44 and associations with ERM proteins.[80,117] Morrison et al.[80] proposed that merlin and CD44 form a molecular switch between growth permissive and growth inhibiting conformations, where external cues for growth inhibition (for example, increased cell density) lead to consequent merlin activation.

Most recently, merlin was identified as a novel negative regulator of the mammalian target of rapamycin complex 1 (mTORC1), a critical modulator of cell growth and proliferation. The mTORC1, a serine/threonine kinase sensitive to rapamycin inhibition, is dysregulated in hamartoma syndromes and various cancers.[22,37] The mTORC1 pathway is constitutively active in *NF2* meningioma patients and *NF2* knockout MEFs.[37] Activation of mTORC1 leads to phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) and S6 kinase 1. Consequently, this results in increased protein translation and ribosome biogenesis.[37] Although the exact mechanism is still unclear, merlin inhibits mTORC1 through a novel pathway, independent from the previously established activators of the mTORC1 pathway, which include phosphoinositide 3-kinase–Akt (PI3K) and mitogen-activated protein kinase/extracellular signal-regulated kinase. Thus, inhibition of the mTORC1 pathway, either through rapamycin or disruption of the PI3K pathway, presents a promising route for targeted therapeutics.[37]

Several studies have linked merlin to the Rho/GTPase and Rac/PAK signaling pathways, which are critical regulators of cytoskeleton organization, intracellular proliferation, and transcription signaling. Active Rac and Cdc42 lead to PAK-mediated merlin inactivation via phosphorylation at serine 518, and merlin expression inhibits the Rac/PAK pathways. Merlin also regulates transcription of cyclin D1, a proto-oncogene that encodes a regulatory subunit of cell cycle regulating cyclin–dependent kinase holoenzymes.[126] Merlin inhibits PAK activity and consequently decreases PAK1-dependent upregulation of cyclin D1 during cell cycle progression. Adenovirus-mediated merlin expression in *NF2*-inactivated mesothelioma cells inhibits cell proliferation, decreases cyclin D1 expression, inhibits CDK3 activity, and dephosphorylates pRB.[126] Furthermore, this cell cycle arrest at the G_1 phase can be partially overcome by ectopic expression of cyclin D1, suggesting that cyclin D1 is an important mediator of merlin's growth regulation.

The frequency of *NF2* inactivation varies between WHO Grade I subtypes. While 70%–80% of fibroblastic and transitional meningiomas have *NF2* mutations,[93] only 25% of meningothelial meningiomas and less than 1% of secretory meningiomas possess *NF2* mutations.[59] These findings suggest that there may be cytogenetic differences in tumorigenesis between benign subtypes. For higher grade meningiomas, the frequency of *NF2* mutations is 70% for both atypical and anaplastic tumors, which is roughly the same as the frequency for benign fibroblastic and transitional meningiomas.[93] This suggests that while *NF2* is important for tumor formation, it most likely is not critical in malignant meningioma progression.[59]

Although *NF2* losses are frequently present in meningiomas, studies have failed to find chromosome 22 or *NF2* abnormalities in 40% of sporadic lesions. As such,

it has been inferred that other anomalous pathways may be responsible for tumorigenesis within this population.[59]

DAL-1

Merlin's role in meningioma tumorigenesis led to several studies of the structurally homologous and functionally similar protein 4.1 family. A number of studies have implicated protein 4.1B as a potential tumor suppressor in meningiomas.[20] The *EPB41L3* or *DAL1* gene is located at 18p11.3 and encodes protein 4.1B, a regulator of proliferation and apoptosis.[52] Like merlin, protein 4.1B contains 3 functional regions, including a highly conserved amino-terminal FERM domain (protein 4.1 and ERM binding), a spectrin-actin binding domain, and a carboxy-terminal domain. Each domain is separated by a unique interspersed region, termed U1, U2, and U3. Differentially expressed in adenocarcinoma of the lung-1 (DAL-1) is a smaller protein fragment of protein 4.1B that retains a tumor suppressive property identical to that of protein 4.1B.[20]

Protein 4.1B loss has been demonstrated in meningiomas at the DNA level through in situ hybridization, at the RNA level through reverse transcription–polymerase chain reaction, and at the protein level through Western blot and immunohistochemical analyses.[90] These studies reported that reexpression of protein 4.1B/DAL-1 suppressed meningioma cell growth. The U2 region is the critical tumor suppressive domain of protein 4.1B/DAL-1, and deletion of the U2 domain weakens its suppression of meningioma cell growth. While the exact mechanisms are still unclear, a study by Gerber et al.[20] provided the first molecular insights underlying protein 4.1B/DAL-1 tumor suppression. The study revealed that protein 4.1B/DAL-1 activated the JNK pathway in a U2 domain–dependent fashion. However, no proteins that specifically bind this important U2 domain have yet been identified. Protein 4.1B growth regulation in meningiomas relies on JNK-mediated activation of the Src, Rac1, and mixed-lineage kinase 3 (MLK3) signaling cascades. JNK activation decreased cell growth through reduced expression of cyclin A, hyperphosphorylation of the retinoblastoma protein (Rb), and G_0–G_1 cell cycle growth arrest.[20]

Protein 4.1B has also been found to associate with the 14-3-3 family of proteins near the plasma membrane. These 14-3-3 proteins are protein 4.1B/DAL-1 specific and do not bind with other members of the protein 4.1 family.[90,130] Past studies have implicated 14-3-3 proteins in regulating signal transduction and apoptosis.[130] Further work is necessary to elucidate the functional significance of 4.1B/DAL-1 and 14-3-3 binding in growth regulation. Additionally, TSLC1 is another protein that interacts with protein 4.1B. Reduced expression levels of TSLC1 are correlated with higher grade meningiomas and worse prognosis, while reexpression of TSLC1 in meningioma cells slows growth.[70]

There have been conflicting reports regarding the role of protein 4.1B/DAL-1 in meningioma tumorigenesis. Gutmann et al.[25] initially reported loss of heterozygosity of *4.1B/DAL-1* in 60% of sporadic meningiomas, and attributed the loss of *DAL-1* as an early event in meningioma pathogenesis. A later study of 63 sporadic meningiomas found a much lower frequency of *DAL-1* inactivation than previously reported, and suggested that the locus had a role in meningioma progression rather than initiation.[84] A study of 83 meningiomas found a very low mutation frequency of *4.1B/DAL-1*, and suggested that epigenetic changes may be responsible for *4.1B/DAL-1* silencing in meningiomas.[33,47,68,90] Furthermore, *4.1B/DAL-1* null mice do not have an increased propensity for developing cancer.[59]

Meningioma Progression

While genetic analysis of losses on chromosome 22 has provided a foundation for understanding meningioma pathogenesis, the previously discussed genetic alterations constitute early events in meningioma development.[59,70,97] Benign meningiomas rarely have chromosomal aberrations beyond chromosome 22 losses. More complex karyotypes are associated with more aggressive meningioma behavior.[59] Malignant progression, thought to follow the theory of clonal evolution, is associated with a stepwise cumulative acquisition of chromosomal gains and losses, leading to more aggressive subclones with greater growth advantage.[63,123,132] Atypical and anaplastic meningiomas exhibit much more complex genetic changes than their benign counterparts, with losses on 1p, 10q, 14q, and less frequent losses on 6q and 18q. Higher grades are also associated with chromosomal gains on 1q, 9q, 12q, 15q, 17q, and 20q.[59,70] In addition to these genetic changes, anaplastic meningiomas exhibit more frequent losses on 6q, 10q, 14q, and 9p, with amplification on 17q23 (Fig. 1).[12,54,86,97,123] Epigenetic alterations, including increased CpG island hypermethylation, have also been associated with malignant meningioma progression.

Most of the data from studies aiming to characterize the stepwise progression of meningioma development have been based on cytogenetic analyses of different meningioma grades in various patients. In a cytogenetic analysis of one group of 11 meningioma patients with tumors that exhibited clear progression from benign to higher grades, the authors found a complex karyotype present in the lower grade tumors prior to progression.[1] Contrary to the model of clonal evolution, these findings suggest that this cohort of meningiomas was destined to be malignant.

Candidate Genes Identified Through Chromosomal Losses

Chromosome 1. Chromosome 1p deletions comprise the second most common chromosomal abnormality in meningiomas and are more frequent in higher grade tumors. 1p losses are found in 13%–26% of Grade I, 40%–76% of Grade II, and 70%–100% of Grade III meningiomas.[52] 1p deletions have also been associated with malignant progression in recurrent meningiomas, suggesting that the loss of 1p is associated with meningioma progression rather than initiation. Loss of 1p is also associated with a 30% recurrence rate, whereas only 4.3% of meningiomas recur when 1p is intact.[94] While a number of candidate targets have been studied on 1p, including *CDKN2C*, *RAD54 L*, *EPB41*, *GADD45A*, *RAD54 L*, and *ALPL*, no promising tumor suppressor has yet been found.

Studies of *CDKN2C*, a cell cycle control gene encoding $p18^{INK4C}$ located at 1p32, found one point mutation and

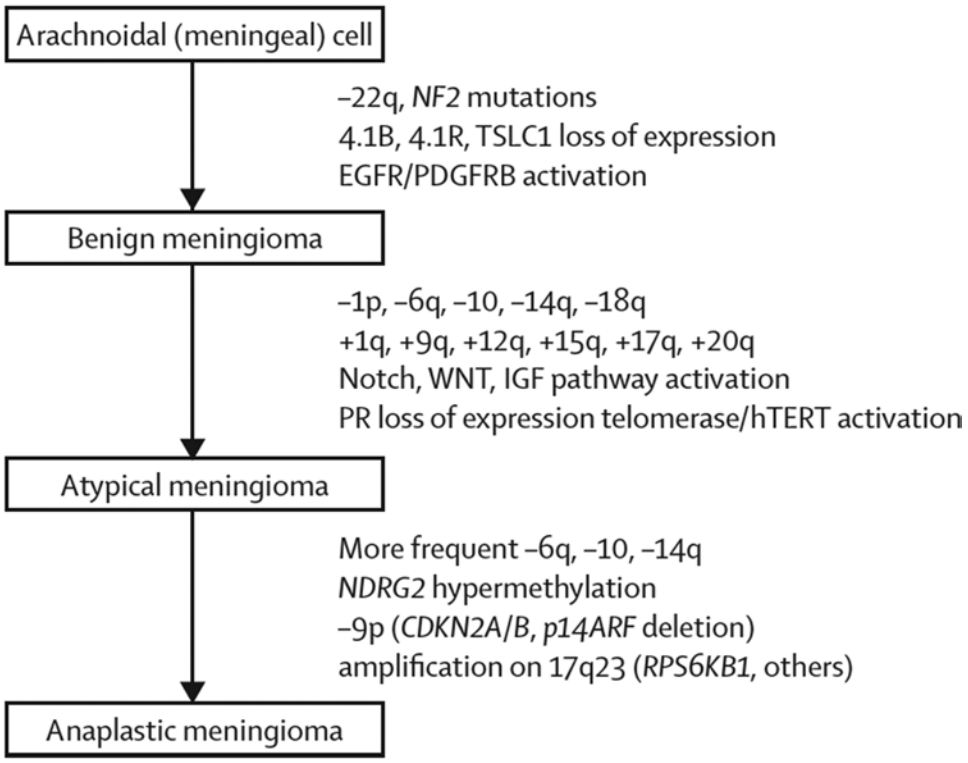

Fig. 1. The genetic alterations underlying meningioma formation and progression. Meningiomas are thought to arise from arachnoidal cells. Losses of 22q and other family 4.1 proteins represent early events in meningioma formation. Higher grade meningiomas are associated with more complex karyotypes, and progression is characterized by the accumulation of chromosomal losses and gains. Loss of 9p is characteristic of anaplastic meningiomas. PR = progesterone receptor. Reprinted from **The Lancet Neurology**, volume 5, Riemenschneider MJ, Perry A, Reifenberger G: Histological classification and molecular genetics of meningiomas, pp 1045–1054, copyright 2006, with permission from Elsevier.

one homozygous deletion at the *INK4C* locus. Inactivating methylation and loss of cytoplasmic p18 was not found, demonstrating that p18 is rarely mutated in atypical and anaplastic meningiomas and is unlikely to be important in meningioma pathogenesis.[59] A study of 29 meningiomas found no mutations in *RAD54 L*, located on 1p32.[52,74] Loss of heterozygosity and expression analysis failed to find expression losses of *EPB41* and *GADD45A*, located on 1p36.2-p34 and 1p31.2-p31.1 respectively.[59]

ALPL, a gene encoding an alkaline phosphatase, is located on 1p36.1-p34.[52,59,97] *ALPL* has drawn interest as a potential tumor suppressor because 1p loss in meningiomas is strongly associated with loss of alkaline phosphatase activity. However, mutational analysis of *ALPL* is still needed.[52]

Liu et al.[59] found that while many of the candidate genes on 1p lack regular genetic losses, epigenetic changes may have an important role in malignant meningioma progression. Their study found transcriptional silencing via abnormal hypermethylation of various promoter-associated CpG islands of cancer-related genetic regions in atypical and anaplastic meningiomas. For example, *TP73* on 1p26.32 has been examined as a candidate gene. While studies have failed to find significant and consistent *TP73* mutations in meningiomas, one methylation status study found *TP73* methylation-mediated inactivation in 10 of 30 meningiomas with 1p losses, and 3 of 30 meningiomas with intact 1p.[52,60,83] This suggests that assessment of the methylation status of other candidate genes may be a promising avenue of future study.

Chromosome 14. Similar to 1p losses, deletions on chromosome 14 are important in meningioma progression.[52] Loss of 1p and 14q are frequent in anaplastic meningiomas and are associated with a worse prognosis.[40,61,65] After losses in chromosome 1 and 2, deletions in chromosome 14 represent the third most common chromosomal abnormality and have been found in up to 31% of Grade I, 40%–70% of Grade II, and up to 100% of Grade III meningiomas.[13,52,58,75,109,116,123] Studies have also found losses of 14p to be a prognostic indicator of tumor recurrence.[13,52,66]

Genomic analysis conducted by Lusis and Gutmann[65] identified *NDRG2* as a potential tumor suppressor on 14q. The authors found that *NDRG2* is frequently inactivated in both anaplastic meningiomas and a subset of lower grade yet clinically aggressive atypical meningiomas. Reduction of *NDRG2* expression was associated with promoter hypermethylation in 40% of anaplastic and atypical meningiomas.[59] Additionally, *NDRG2* mRNA is down-regulated in recurrent meningiomas of all grades relative to primary benign meningiomas.[110] Although the mechanism is unknown, NDRG2 is involved with regulating cell growth, differentiation, and apoptosis.[16,62,65,69,111]

Recently, Zhang et al.[134] identified *maternally expressed gene 3 (MEG3)* as a candidate tumor suppressor located at 14q32. Greater loss of *MEG3* expression and al-

lelic loss are associated with higher tumor grades. While MEG3, a noncoding RNA with antiproliferative functions, is robustly expressed in normal arachnoidal cells, it is absent in the IOMM-Lee and CH157-MN meningioma cell lines. Functional studies suggest that MEG3 mediates its tumor suppressive properties by suppressing DNA synthesis and inhibiting colony formation in the meningioma cell lines. Additionally, MEG3 was found to transactivate p53 (TP53), another tumor suppressor involved in an often dysregulated pathway in anaplastic meningiomas.[70] Of note, while mutations of *TP53* (17q) are common in many other cancers, direct alterations in *TP53* are rare in meningiomas;[9,41,52,70,85,121] instead, regulators of the pathway are often mutated.[70,134]

Chromosome 9. Gains and losses on chromosome 9 in meningiomas have led to identification of a number of candidate genes. Losses at 9p are found in 5% of Grade I, 18% of Grade II, and 38% of Grade III meningiomas,[9,52] and are strongly associated with anaplastic, rather than benign or atypical meningiomas.[52,123] While the actual target genes and tumorigenic mechanisms of many chromosomal losses in meningiomas are still unclear, 9p alterations are associated with specific losses of *CDKN2A/p16*^{INKa} (encoding p16), *p14*^{ARF} (encoding p14), and *CDKN2B/p15*^{ARF} (encoding p15).[70,88] All 3 tumor suppressors are located on 9p21. p14 is a tumor suppressor involved with regulating cell apoptosis through modulation of the p53 pathway, and p16 and p15 control cell cycle progression through the G_1/S-phase checkpoint (Fig. 2).[59]

Loss of *CDKN2A*, *p14*^{ARF}, and *CDKN2B* have been reported in 0% of Grade I, 3% of Grade II, and 38% of Grade III meningiomas.[9,52] Seventy percent of anaplastic meningiomas with 9p21 losses have a considerably shorter survival than 9p21 intact anaplastic meningiomas.[9,28,97] Similarly, Grade III meningiomas with intact *CDKN2A* have better outcomes than those with *CDKN2A* loss.[52] These findings suggest that loss of cell cycle regulation at the G_1/S-phase checkpoint is associated with clinically aggressive tumors and is a critical component of malignant progression.[59]

Other Chromosomal Alterations. Deletions on chromosome 10 are associated with meningioma progression.[52] Losses on chromosome 10 are found in 5%–12% of Grade I, 29%–40% of Grade II, and 40%–58% of Grade III meningiomas;[52,91,109,120,123] however, some studies have suggested that the true frequencies are higher.[52,77,78] A number of candidate genes have been identified at chromosomal region 10q23-q25, namely *PTEN*, *MXI1*, and *DMBT1*. *PTEN* alterations have been found in Cowden syndrome, but rarely in meningiomas. Studies have also failed to identify mutations of *MXI1* or *DMBT1* in meningiomas.[59]

Similarly, the high frequency of chromosome 17 amplification in malignant meningiomas (42%) compared with lower-grade meningiomas (almost 0%) has led to studies of ribosomal protein S6 kinase (*RPS6K*), a proto-oncogene located at 17q23.[52,123] However, *RPS6K* amplifications only occur in a small subset of higher grade meningiomas, despite robust amplification of adjacent loci.[12,52] While *RPS6K* amplification may be important in the progression of a subset of lesions, *RPS6K* does not appear to be the main target of amplification in meningiomas.

Losses in chromosome 18 are frequent in atypical and anaplastic meningiomas, but rare in benign meningiomas. Büschges et al.[11] examined *MADH2*, *MADH4*, *APM-1*, and *DCC*, tumor suppressor genes on chromosome 18q21. However, mutational and LOH analysis of the four genes found only one missense mutation in *APM-1*, suggesting

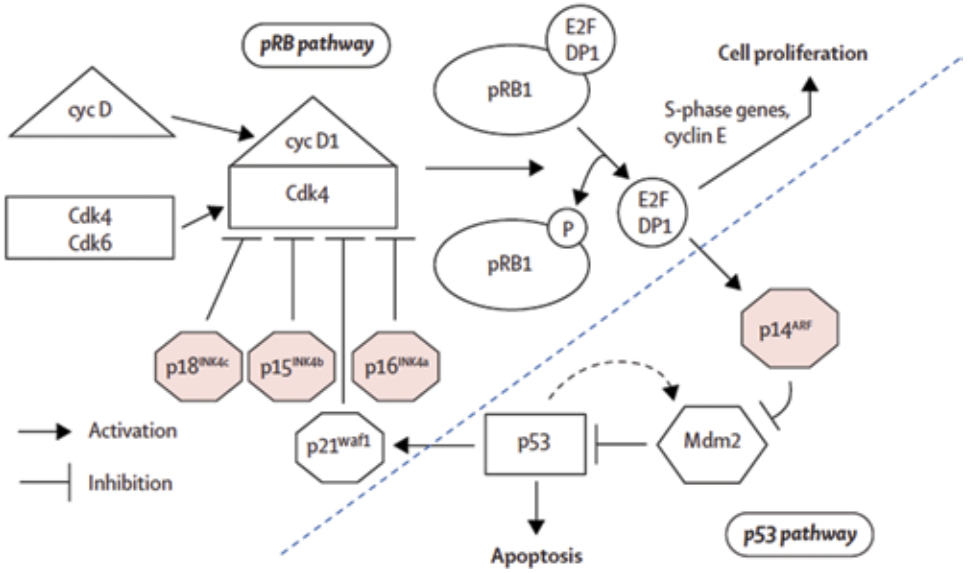

Fig. 2. Cell cycle dysregulation through interrelated p53/pRB pathways. Anaplastic meningiomas characteristically exhibit homozygous deletions and mutations in *p16*^{INK4a}, *p15*^{INK4b}, and *p14*^{ARF}. *p16*^{INK4a} and *p15*^{INK4b} prevent S-phase entry by inhibiting the Cdk4/cyclin D complex. p14^{ARF} negatively regulates MDM2 and removes MDM2-mediated p53 inhibition and degradation. The shaded proteins are affected in meningioma progression. Reprinted from **The Lancet Neurology**, volume 5, Riemenschneider MJ, Perry A, Reifenberger G: Histological classification and molecular genetics of meningiomas, pp 1045–1054, copyright 2006, with permission from Elsevier.

that *MADH2*, *MADH4*, *APM-1*, and *DCC* are not the target inactivated genes in 18q losses in meningioma progression.

Telomerase/hTERT

Telomeres comprise repeat DNA sequences at the ends of chromosomes and function to prevent chromosomal deterioration. Telomeres shorten during successive DNA replication and mitoses, eventually limiting cell division through signaling senescence. Telomerase, a reverse transcriptase that rebuilds the lost telomere repeat sequences, is often reactivated in malignant cancers to sustain chromosomal integrity during aggressive growth. Telomerase is made of the telomerase RNA subunit (hTR) and the reverse transcriptase subunit, hTERT. Expression of *hTERT* mRNA, rather than *hTR* in meningiomas is best correlated with telomerase activity.[59]

Telomerase activation is rare in benign meningiomas, found in only 3%–21% of Grade I meningiomas. However, 58%–92% of atypical and 100% of anaplastic meningiomas demonstrate telomerase activity.[19,52,56,108] In addition to higher grade tumors, telomerase activity is also associated with a higher rate of recurrence and greater malignancy in meningiomas, and may serve as a potential prognostic marker.[52,108]

Signaling Pathways

Considerable progress in deciphering the biological mechanisms underlying meningioma development, growth, and malignant progression has been made through cytogenetic studies analyzing chromosomal abnormalities and identifying specific genes involved with tumorigenesis. However, the majority of the actual targets of these chromosomal alterations remain unknown. Understanding the disrupted signaling pathways regulating tumorigenic processes such as growth, angiogenesis, and apoptosis will not only help bridge the link between the various genetic changes and consequent effects on cellular processes involved in meningioma pathogenesis, but will also provide targets for novel therapeutics.

Cell Cycle Dysregulation—the pRB/p53 Pathways. A number of studies have highlighted the importance of aberrant cell cycle pathways in meningioma progression and malignancy.[59] Anaplastic meningiomas characteristically exhibit homozygous deletions and mutations in *p16*^{INK4a}, *p15*^{INK4b}, and *p14*^{ARF}, which are all important modulators in the retinoblastoma protein (pRB)-dependent and p53-dependent pathways.[9,97] pRB inhibits cell cycle progression at the G_1/S-phase checkpoint by binding and inhibiting E2F transcription factors, a dimer comprising the E2F protein and DP protein (E2F-DP).

Cell cycle progression is normally regulated by cyclin D expression. Under mitogenic signals, cyclin D levels increase, and cyclin D binds to either Cdk4 or Cdk6, which leads to the phosphorylation of pRB. When pRB is phosphorylated, it loses its function, releases active E2F-DP, and allows the transcription of genes critical for the S-phase (Fig. 2). *p16*^{INK4a} and *p15*^{INK4b}, which normally prevent S-phase entry by inhibiting the Cdk4/cyclin D complex, are often mutated in higher-grade meningiomas.[97]

p53 is another important tumor suppressor that can induce cell cycle arrest, DNA repair, and apoptosis. The p53 pathway serves as an important feedback inhibitor of the pRB pathway.[4,97] The mechanism of feedback inhibition occurs via p14^{ARF}. Phosphorylation of pRB and consequent release of E2F-DP not only promote S-phase entry but also leads to increased transcription of *p14*^{ARF}. *p14*^{ARF} promotes p53 activity through negative regulation of the proto-oncogene murine double minute 2 protein (MDM2), which normally binds to p53 and assists in p53 degradation (Fig. 2). However, this regulatory checkpoint is broken in higher-grade meningiomas because of frequent homozygous deletions of *p14*^{ARF}.[4,9,28]

The Hedgehog Pathway. The hedgehog (Hh) signaling pathway is a highly conserved, critical regulator of development during embryogenesis and homeostatic processes.[10,56,118,122] Genetic mutations in the Hh membrane receptor, patched (PTCH), and other downstream proteins have been found in a number of neoplasms including basal cell carcinomas and medulloblastomas.[3,31,44,56] When Hh binds PTCH, PTCH-mediated tonic inhibition of the transmembrane protein Smoothened (SMO) is suppressed.[10,56,118,122] SMO activation initiates a signaling cascade that results in the activation of GLI transcription factors. These include growth activators GLI1 and GLI2, and growth repressor, GLI3, with subsequent transcription of genes implicated in cell growth, proliferation, angiogenesis, matrix remodeling, and stem cell homeostasis.[46,50,56,99] Thus, aberrant Hh pathway activation can have a critical role in tumorigenesis. Recently, Laurendeau et al.[56] examined the mRNA expression patterns of 32 Hh pathway–related genes in 36 meningiomas. The authors found amplifications of 16 genes involved with Hh pathway activation and cell growth, and decreased expression of 7 genes involved with Hh pathway inhibition across all tumor grades. Furthermore, the study identified a number of Hh target genes with significantly increased expression in high-grade meningiomas, in contrast to benign meningiomas. Such targets include *IGF2* and *SPP1* and may serve as potential prognostic markers for malignancy and tumor aggressiveness.[56]

The Notch Pathway. The Notch signaling pathway, involved in intracellular communication, is mediated through the transmembrane proteins Notch1–4. Binding of ligands, which consists of other transmembrane proteins, leads to the proteolytic cleavage of the intracellular domain of Notch.[2,49] This intracellular domain translocates to the nucleus and initiates expression of the Hairy/Enhancer of Split (HES) family of transcriptional regulators. HES then functions as a Notch pathway effector.[2,35] Notch signaling function varies according to cell type and mediates a myriad of cellular processes during embryonic development and later in adult life.[2,8] The role of aberrant Notch signaling in tumor genesis is equally complex and varies from cancer to cancer.[2,14,87,113,131,133]

Gene expression analysis suggests that deregulation of the Notch pathway is a critical component in meningioma development. HES1 expression is increased in all meningioma grades and correlates with increased expression of Notch1, Notch2, and Jagged ligand. TLE2 and TLE3, members of the Groucho/transducin-like enhancer of the Split family of corepressors that modulate HES1 activity,

were specifically upregulated in malignant meningiomas, suggesting that TLE3/HES1 may be associated with more aggressive meningiomas. One study identified tetraploidy and chromosomal instability as possible consequences of notch deregulation in meningiomas.[2] Further studies are necessary to elucidate the mechanism by which abnormal notch activation induces tetraploidy and promotes meningioma pathogenesis.

The PI3K/Akt Pathway and MAPK Pathway. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the mitogen-activated protein kinase (MAPK) pathway are also aberrantly activated in meningiomas. Both pathways are involved in numerous cellular processes including differentiation, growth, and apoptosis. Many meningioma growth factors mediate their activity through these signaling pathways. Activation of PI3K leads to Akt phosphorylation and activation of $p70^{S6K}$ via mammalian target of rapamycin (mTOR), a regulator of many cancer-associated cell processes. Administration of a PI3K inhibitor blocks platelet-derived growth factor stimulation and decreases Akt and $p70^{S6K}$ phosphorylation.[124] Mawrin et al.[71] found high levels of phosphorylated Akt in anaplastic and atypical meningiomas, but not in benign meningiomas. Additionally, wortmannin, an Akt inhibitor, reduced malignant meningioma growth and survival, but did not induce apoptosis.

Other studies have found constitutive activation of the MAPK pathway in benign meningiomas.[42,43,71] Upstream activation of this pathway leads to the activation of Ras, with activation and phosphorylation of both Raf and MAPK.[58,71,105] In the same study, Mawrin et al. found that PD98059, a MAPK inhibitor, slowed cell growth and induced apoptosis in malignant meningiomas. However, reduced amounts of activated MAPK were correlated with increased recurrence of meningiomas suggesting that other pathways are involved with meningioma growth. PD98059 also prevents platelet-derived growth factor–mediated meningioma growth.[71] Overall, in malignant meningiomas, PI3K/Akt activation is associated with aggressive growth, and reduced MAPK activation promotes apoptosis at the cost of increased recurrence rates.

WNT/Beta-Catenin. Recent studies have also expanded on the role of the WNT/β-catenin pathway activation in meningiomas, which was first identified through gene expression studies.[90,103] A later study of the *adenomatous polyposis coli (APC)* gene, a tumor suppressor involved in the WNT pathway, found LOH in 15 of 33 meningioma samples; however, only benign meningiomas exhibited this APC loss.[90,115] E-cadherin, another tumor suppressor and modulator of the WNT pathway, is lost in one-third of meningiomas.[90] In aggressive meningiomas, this loss is often associated with increased translocation of β-catenin to the nucleus.[29,76,90] Additionally, E-cadherin expression is associated with a decrease in both invasiveness and recurrence.[29,90]

Growth Factors and Autocrine Loops

A number of autocrine loops and growth factors have been investigated in meningiomas. The activity of various growth hormones is often mediated through the Ras/Raf MAPK and PI3K/Akt signal transduction pathways. In tumors, alterations in these pathways can contribute to abnormal activation of cellular processes including growth, motility, and angiogenesis without external stimuli.

Platelet-derived growth factor BB (PDGF-BB) and its receptor PDGFR-β are overexpressed in meningiomas.[42,90,129] Expression of PDGF and its receptor are greater in higher grade meningiomas than in benign meningiomas.[124] A recent study suggested that PDGF-BB can mediate its growth regulation through activation of the PI3K/Akt and MAPK pathways.[93] Addition of PDGF-BB to meningioma cells in culture results in increased growth and activation of MAP kinases and c-fos, while anti–PDGF-BB agents can inhibit meningioma cell growth.

A study of 15 meningiomas found expression of epidermal growth factor receptor (EGFR) in all cases, while normal human meningeal tissue did not have detectable EGFR.[90,114] Expression of the EGFR ligands, transforming growth factor alpha (TGF-α), and EGF in meningiomas also contribute to the activation of EGFR through an autocrine loop.[15,27,90] Increased TGFα expression is associated with more aggressive meningioma growth.[124]

Meningiomas also express transforming growth factor-β (TGF-β) and Type I and II TGFβ receptors.[124] Transforming growth factor–β has been demonstrated as a Smad 2/3-mediated inhibitor of meningioma growth. Stromal cell derived factor 1 (SDF1) and its receptor CXCR have been found in human meningiomas, and human SDF1α stimulates growth in meningioma cell cultures. Bone morphogenetic proteins (BMPs) and their receptors (BMPR) have been found to form another autocrine loop involved in proliferation in meningiomas.[93] Other growth factors and receptors investigated in meningiomas include IGF, fibroblast growth factor, placental growth factor, HER2, and somatostatin.[59,64,67]

Angiogenic Pathways

Meningiomas are highly variable with respect to peritumoral brain edema and vascularity.[52] While meningiomas are mainly supplied by meningeal vessels through the external carotid artery, more than half of meningiomas receive additional supply from cerebral-pial vessels.[6,52] Vascular endothelial growth factor A (VEGF-A) and the receptor VEGFR-1 regulate development of neovascularity and peritumoral edema in brain tumors. Studies have found that in meningiomas, 84% expressed VEGF and 67% expressed VEGFR.[93]

While two small studies have suggested that VEGF-A mRNA expression may correlate with meningioma vascularity,[52,101] a larger study by Lamszus et al.[55] of 69 meningiomas did not find such a link between VEGF-A expression and either microvascularity or invasiveness. Despite this result, they did note an association between meningioma grade and VEGF-A levels, with Grade III meningiomas showing a 10-fold and Grade II meningiomas showing a 2-fold increase in VEGF-A relative to benign meningiomas.[52] However, other authors have shown conflicting results for the association between tumor grade and VEGF expression.[93]

Expression levels of VEGF-A are associated with recurrence rates in benign meningiomas.[52,128] While the

mechanisms regulating VEGF in meningiomas are unknown, studies have suggested that increased epidermal growth factor and platelet-derived growth factor can induce VEGF expression. Additionally, both VEGF and hypoxia inducible factor-1 (HIF-1), a transcription factor that regulates VEGF, are expressed in higher levels in meningiomas that have undergone preoperative embolization. Endothelins, peptides involved in angiogenesis, vasoconstriction, and vasodilation, have also been implicated in meningioma angiogenesis and growth.[93]

Sex Steroids

A number of observations have suggested a role for sex hormones in meningioma tumorigenesis. The incidence of meningiomas is more than 2-fold greater in women than in men. Meningiomas have also been reported to undergo increased growth during pregnancy and the luteal phase of the menstrual cycle.[52,102] Additionally, the incidence of meningiomas is increased in patients with breast cancer.[124] While estrogen and androgen receptors are both found in meningiomas, expression of the progesterone receptor is most frequently observed. The progesterone receptor is expressed in 81% of women and 40% of men with meningiomas,[7] and is minimally present in normal arachnoidal cells. Progesterone receptor expression is highest in benign meningiomas (50%–80%), and it is inversely proportional to tumor proliferation and grade.[32,48,89,90,119]

Cyclooxygenase-2

Investigators have begun to examine the potential role of the inflammatory response in meningiomas as a result of numerous case reports and epidemiological studies that suggested head trauma as a risk factor for meningioma formation.[95] Within the inflammatory pathway, cyclooxygenase serves as the rate-limiting catalyst for the biosynthesis of prostaglandins from arachidonic acid. Prostaglandins, a member of the eicosanoid family of biologically active lipid mediators, regulate a variety of critical cellular processes involved with proliferation, adhesion, angiogenesis, suppression of apoptosis, and inflammation.[81] Cyclooxygenase-2 (Cox-2) is an inducible enzyme important in mediating inflammatory responses.[95] The role of Cox-2 in tumorigenesis has also previously been demonstrated through its overexpression in colon, lung, and breast cancers. Ragel et al.[95] found that Cox-2 is highly and universally expressed in meningiomas. Thus, aberrant activity of eicosanoids may mediate tumor development and growth.

Targeted Therapies

The past decade has seen considerable progress in deciphering the myriad of aberrant signaling pathways underlying cell growth, proliferation, and angiogenesis in meningioma development. This progress has helped identify a number of potential therapeutic targets.

A number of drugs targeting growth hormones, growth receptors, and their associated intracellular signaling pathways have been investigated. The North American Brain Tumor Consortium (NABTC) conducted a Phase II study of imatinib mesylate, a PDGF-α and PDGF-β receptor inhibitor, for recurrent meningiomas.[125] In the study, 23 patients with all grades of meningioma were treated with single agent imatinib, starting with 600 mg/day. While the treatment was well tolerated and levels of cytoplasmic imatinib were therapeutically sufficient, the treatment regimen was not significantly effective. For benign meningiomas, median PFS was 3 months, with a 6-month PFS of 45%, while atypical and anaplastic meningiomas demonstrated a median PFS of 2 months, with a 0% 6-month PFS. In a study addressing these results, Gupta et al.[23] found that nelfinavir, a protease inhibitor, potentiates imatinib's efficacy in meningioma cells. Compared with treatment by imatinib alone, the combined treatment resulted in a dose-dependent decrease in tumor survival, growth, and colony formation. Other PDGFR inhibitors, such as sunitinib and CHIR 265, block additional kinases and are currently being investigated.[124]

Other studies have investigated EGFR as another growth hormone receptor target for meningiomas. A recent small Phase II trial examined the efficacy of gefitinib and erlotinib, EGFR inhibitors, in 25 patients with recurrent meningiomas.[82] The 6-month PFS was 25% for benign meningiomas and 29% for atypical and anaplastic meningiomas. Eight patients maintained stable disease. While the treatment was well tolerated, gefitinib and erlotinib did not exhibit significant activity against recurrent meningiomas. Although other EGFR inhibitors exist, very few studies have examined their therapeutic potential for treating meningiomas. The various downstream signaling pathways used by growth factors important in meningioma tumorigenesis provide another therapeutic target. Inhibitors of the MAPK signaling pathway (for example, Raf, MEK inhibitors) and the PI3K pathway (for example, PI3K, Akt, mTOR inhibitors) are worthwhile candidates for future studies.

Another treatment approach to controlling meningioma growth has been inhibiting angiogenesis. Angiogenesis inhibitors have been effective in treating several cancers, including renal cell carcinoma and glioblastomas.[17,45] A number of VEGF and VEGFR inhibitors are available, including ZD6474, PTK787, AEE788, Avastin, and IMC-1C11,[79] and these are currently being tested for use against meningiomas. Additionally, some studies have shown that inhibitors of growth factors, signal transduction pathways, and angiogenesis may induce radiation sensitivity in meningiomas.[18,100] Thus, these inhibitors may be used synergistically with radiation therapies.

The involvement of Cox-2 in meningiomas has led investigators to examine the efficacy of various nonsteroidal antiinflammatory drugs as a therapeutic agent. One such agent is celecoxib, a selective Cox-2 inhibitor. Treatment with celecoxib demonstrated a dose-dependent growth inhibition of both the IOMM-lee cell line and benign meningioma cells in culture.[95] Celecoxib decreased tumor microvascularity, increased cell apoptosis, and decreased Cox-2 and VEGF expression in vivo in a mouse xenograph model.[96] In addition to Cox-2, Pfister et al.[92] identified a number of other potential therapeutic targets involved in eicosanoid formation that are highly

expressed in meningiomas, including the enzymes Cox-1, 5-LO, and PTGER4. Future clinical trials are necessary to determine the potential efficacy of Cox-2 inhibitors and other nonsteroidal antiinflammatory drugs in treating meningiomas.

Challenges and Future Directions

One of the largest obstacles in the development of novel targeted therapies for meningiomas is the limited understanding of the molecular pathogenesis underlying their formation, growth, and progression. A lack of adequate cell lines and animal models for meningiomas has made study of this tumor challenging. While a number of studies have identified common chromosomal aberrations, the majority of the specific genes affected remain unknown. Beyond cytogenetic studies, others have begun to unravel the numerous abnormal signaling pathways involved with tumorigenesis including cell cycle dysregulation, aberrant growth, and angiogenesis. Meningiomas exhibit increased activity in a number of growth factors, growth factor receptors, and their downstream signaling pathways. However, it is difficult to identify which pathways are most critical and which targets are most therapeutically promising. Additionally, the lack of data on the natural course of untreated meningiomas has made it challenging to gauge the benefits of novel therapeutics. A number of studies have reported periods of disease stabilization, but it is possible that placebo may have achieved comparable results. This is especially true in benign and slow-growing meningiomas. Lastly, only a limited number of patients with meningiomas require more than surgery and radiotherapy, thus creating enrollment difficulties for a number of studies.

Despite advancements in our understanding of meningioma pathogenesis, the conventional treatments, including surgery, radiotherapy, and stereotactic radiosurgery, have remained largely stagnant. While these options can be curative for the majority of meningiomas, there exists a subset of inoperable and refractory meningiomas with inadequate treatment options. Current chemotherapy regimens and hormonal therapies have shown minimal activity against meningiomas. A number of potential targets have been tested, and several studies are currently being conducted; however, none has proven particularly effective to date. Future therapies will include combinations of targeted molecular agents, and this will most likely be accomplished through continued progress in the understanding of the genetic and biological changes associated with meningiomas.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Yang, Nagasawa, Stramotas, Yew. Acquisition of data: Yang, Choy, Kim, Nagasawa, Stramotas, Yew. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Yang, Choy, Kim, Nagasawa, Yew, Gopen, Parsa. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Yang. Administrative/technical/material support: Yang. Study supervision: Yang.

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Molecular genetics of meningiomas: a systematic review of the current literature and potential basis for future treatment paradigms

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Although a majority of meningiomas are benign neoplasms, those occurring at the cranial base may be challenging tumors to treat because of extensive tissue invasion, an inability to achieve gross-total microscopic resection, and local tumor recurrence and/or progression. A more comprehensive understanding of the genetic abnormalities associated with meningioma tumorigenesis, growth, and invasion may provide novel targets for grading assessments and individualizing molecular therapies for skull base meningiomas. The authors performed a review of the current literature to identify genes that have been associated with the formation and/or progression of meningiomas. Mutations in the *NF2* gene have been most commonly implicated in the formation of the majority of meningiomas. Inactivation of other tumor suppressor genes, including *DAL-1* and various tissue inhibitors of matrix metalloproteinases, upregulation of several oncogenes including *c-sis* and *STAT3*, and signaling dysregulation of pathways such as the Wnt pathway, have each been found to play important, and perhaps, complementary roles in meningioma development, progression, and recurrence. Identification of these genetic factors using genome-wide association studies and high-throughput genomics may provide data for future individualized treatment strategies.
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Key Words • **meningioma** • **genetics** • **skull base** • **DNA sequencing** • **genomics**

Meningiomas are among the most common primary intracranial tumors, with a reported incidence of 4.4 per 100,000 person-years.[99] The true prevalence is likely even greater, as incidental meningiomas have been reported in 2.3% of autopsy examinations.[61] Most commonly diagnosed in middle-aged and elderly patients, cranial meningiomas are roughly 10-fold more common than spinal meningiomas.[84] Meningiomas located at the base of the skull may present a unique therapeutic challenge, based on local invasion of critical neurovascular structures that often limit the ability to eradicate the burden of disease. Gross-total resection can be difficult to achieve without significant operative morbidity, and although radiosurgery is frequently implemented as an adjunctive strategy for residual tumor, it is often contraindicated due to extensive tumor burden or proximity to eloquent, radiosensitive tissue.[14,15,71,100]

The majority of meningiomas are benign, but a subset display histologically or clinically more aggressive behavior. The WHO classification distinguishes these tumors as Grade I (benign), Grade II (atypical), or Grade III (anaplastic/malignant).[69] Although 90% of meningiomas are slow-growing Grade I tumors, these can cause significant morbidity via mass effect on neighboring structures. Atypical meningiomas account for 6%–8% of cases, whereas 2%–3% are frankly malignant tumors associated with brain invasion, early recurrence, and decreased progression-free and overall survival.[52] A diagnosis of anaplastic meningiomas, for instance, is characterized by a median survival time of less than 2 years.[70]

Grade I meningiomas are typically classified as one of the following histopathological subtypes: meningothelial, fibroblastic, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, or metaplastic. Grade II meningiomas, on the other hand, are typically more aggressive clear cell and chordoid tumors, and Grade III meningiomas are usually rhabdoid or papillary subtypes.[46,84] The genetic and molecular bases for the wide variety of biological behavior and histopathological subtypes that are encountered clinically remains

Abbreviations used in this paper: GWAS = genome-wide association studies; Hh = hedgehog; LOH = loss of heterozygosity; MMP = matrix metalloproteinase; SNP = single nucleotide polymorphism; TCGA = The Cancer Genome Atlas; TIMP = tissue inhibitor of metalloproteinase; Wnt = wingless.

to be determined. In comparison with primary intraaxial brain tumors such as gliomas, the genetics of meningiomas are poorly understood and relatively understudied.

A further understanding of the genes and signaling pathways associated with meningioma formation, growth, and transformation is likely to provide a foundation for future assessment of histological and clinical behavior and response to potential gene therapies and individualized treatment regimens. This information would be particularly constructive in evaluating potential treatment plans for cranial base meningiomas, the management of which is already challenging with currently available surgical and radiation treatment paradigms. The authors present a systematic review of the genes currently associated with the development, progression, and recurrence of meningiomas. The article then provides a brief discussion of potential future avenues of research and targeted therapeutic paradigms employing novel genetic techniques such as next-generation sequencing data analysis and high throughput genomics.

Genetics

Tumor Suppressor Genes

Tumor suppressor genes are those that encode proteins whose function is to inhibit the development of neoplastic processes. These genes generally follow the 2-hit hypothesis originally proposed by Knudson in 1971,[42] in which both alleles for a particular tumor suppressor gene must be rendered ineffective for the cell to escape its normal regulatory processes. The most common tumor suppressor genes that have been associated with the development of meningiomas are *NF2*, *DAL-1*, and various tissue inhibitors of matrix metalloproteinases *(TIMPs)*. In addition, the short arm of chromosome 9 has been shown to harbor several genes related to tumor suppression, including *CDKN2A, CDKN2B*, and *p14ARF*.

The *NF2* gene is a tumor suppressor gene that is commonly involved in the development of meningiomas and other neoplasms of the central and peripheral nervous system (Table 1). Using linkage analysis, the *NF2* gene has been localized to chromosome 22q; biallelic inactivation of the *NF2* gene results in loss of the merlin protein and may be associated with the development of multiple meningiomas and schwannomas (Type II neurofibromatosis).[25,83] In addition, approximately 60% of patients with sporadic meningiomas are also found to have loss of the *NF2* gene.[16,17,56] Recent analysis of the merlin protein has demonstrated that its function in the protein 4.1 family as part of the actin cytoskeleton is intimately involved in the regulation of cell proliferation and cell growth in human tumor cells.[30,86,93] Alterations in the merlin protein could therefore substantially affect cell shape and favor the appearance of more mesenchymal-like phenotypes rather than epithelioid-like ones. With respect to this histopathology, only 28.5% of meningothelial meningiomas show reduced *NF2* expression in comparison with 86% of other meningioma subtypes.[23] Based on the frequency with which meningothelial subtypes typically occur at the anterior skull base, Kros et al.[43] used LOH analysis, karyotyping, and fluorescence in situ hybridization in 42 cases of sporadic meningiomas, demonstrating a significant correlation between tumor localization at the anterior skull base and an intact chromosome 22q.

DAL-1 (differentially expressed in adenocarcinoma of the lung) is another gene that is part of the protein 4.1 superfamily, and encodes the 4.1B protein. Loss of heterozygosity of *DAL-1* at chromosome 18p11.3 was originally reported in 60% of sporadic meningiomas.[32] While loss of *DAL-1* was initially believed to be an early event in the tumorigenesis pathway of meningiomas, Nunes et al.[63] reported that only 12 (19%) of 62 meningiomas analyzed as part of their study had LOH of *DAL-1*. Eleven of those 12 also had LOH of the *NF2* gene, which suggested that *DAL-1* may be involved in the progression rather than initiation of meningioma formation. They also found that 3 of 4 WHO Grade II meningiomas had monosomy of chromosome 18, while large deletions of 18p were found in only 2 of 13 WHO Grade I meningiomas.

Tissue inhibitors of metalloproteinases are proteins that regulate MMP activity and help to regulate cell proliferation, apoptosis, and angiogenesis.[24] Both the *TIMP1* and *TIMP3* genes have been implicated in the aggressive behavior and invasion of meningiomas. Halaka et al.[33] reported that invasive meningiomas produce significantly lower levels of TIMP-1 compared with noninvasive meningiomas. Because TIMP-1 functions to inhibit MMP-9

TABLE 1: Meningioma tumor suppressor genes

Gene	Locus	Product	Function	Meningioma Effect
NF2	22q12.2	merlin protein	links cell membrane proteins to cytoskeleton	early event tumorigenesis[93]
DAL-1	18p11.32	4.1B protein	links cell membrane proteins to cytoskeleton	early event tumorigenesis,[32] progression[63]
TIMP1	Xp11.3-p11.23	metalloproteinase inhibitor 1	inhibits MMP-9 activity	meningioma invasion[33,58]
TIMP3	22q13.1	metalloproteinase inhibitor 3	inhibits MMP-2 and MMP-9 activity	higher meningioma grade[4]
CDKN2A	9p21.3	p16 protein	cell cycle control	higher meningioma grade[7,31]
CDKN2B	9p21.3	p15 protein	cell cycle control	higher meningioma grade[7,31]
p14ARF	9p21.3	p14arf protein	cell cycle control	higher meningioma grade[7]
NDRG2	14q11.2	NDRG2 protein	possible cell growth & apoptosis; N-myc target	higher meningioma grade,[47] meningioma recurrence[85]
BAM22	22q12.2	beta adaptin	endocytosis	possible early event tumorigenesis[72]
DLC1	8p22-p21.3	DLC1 protein	rho GTPase activator	meningioma replication rate[34]

activity, Mizoue et al.[58] examined the role of the TIMP-1/MMP-9 balance using a cell immunoblot assay in 20 meningiomas. They found that reduced secretion of TIMP-1 was associated with an increase in the infiltrative capacity of meningiomas. Paek et al.[65] compared 10 patients with confirmed microcystic meningiomas to a control group of 6 patients with meningothelial, atypical, or transitional subtypes using immunohistochemistry and real-time reverse transcriptase polymerase chain reaction. They found that patients harboring microcystic meningiomas had relative mean values of TIMP-1 that were lower than their control group, suggesting that a TIMP-1/MM-9 imbalance was associated with the formation of microcysts. The role of TIMP-3 in the behavior of meningiomas was recently demonstrated by sequencing 50 meningiomas, of which 27 were WHO Grade I, 11 were WHO Grade II, and 12 were WHO Grade III.[4] In this study, the authors demonstrated that *TIMP3* inactivation via methylation was associated with a more aggressive and higher-grade meningioma phenotype; *TIMP3* promoter hypermethylation was observed in 67% of anaplastic meningiomas, compared with 22% of atypical and 17% of benign meningiomas.

Chromosome 9 is of particular importance in the development of malignant meningiomas because of 3 notable tumor suppressor genes located on its short arm. *CDKN2A* and *CDKN2B* are genes located at 9p21 that regulate cell cycle progression at the G_1/S-phase checkpoint by inhibiting cyclin-cdk complexes. The *p14ARF* gene is also located on 9p21 and produces a protein that blocks Mdm2-mediated degradation of p53.[37] Boström et al.[7] used comparative genomic hybridization and microsatellite analysis to show that a complete loss of 9p was found in 38% of anaplastic meningiomas, 18% of atypical meningiomas, and only 5% of benign meningiomas. Furthermore, intact 9p chromosomes containing homozygous deletions of *CDKN2A*, *CDKN2B*, and *p14ARF* were identified in 46% of anaplastic meningiomas and 3% of atypical meningiomas. The authors concluded that inactivation of these particular tumor suppressor genes with subsequent dysregulation of the G_1/S-phase checkpoint was an important feature in the rapid growth and malignant behavior of anaplastic meningiomas. A recent analysis by Goutagny et al.[31] using SNP arrays and gene sequencing showed that although no recurrent chromosomal alterations were identified as meningiomas progressed from Grade I to Grade II, the most frequent genomic alteration upon progression to Grade III was a loss of *CDKN2A*/*CDKN2B* from 9p.

The N-Myc downstream-regulated gene 2 *(NDRG2)* has also been shown to play an important role in the pathogenesis of meningiomas. Using expression profiling with quantitative PCR and immunohistochemistry, Lusis et al.[47] demonstrated that *NDRG2* was consistently downregulated in both anaplastic meningiomas, as well as a subset of atypical meningiomas exhibiting clinically aggressive behavior. Skiriute et al.[85] also showed that *NDRG2* was downregulated in recurrent meningiomas compared with those of primary benign origin in a group of 35 meningiomas.

In addition, several other tumor suppressor candidate genes have been implicated in the development or progression of meningiomas. According to 1 study, *BAM22*, a member of the beta-adaptin gene family, was found to be inactivated in 9 of 71 meningiomas.[72] Although its exact function remains unknown, its role as a potential tumor suppressor may involve intracellular transport of proteins in the trans-Golgi network.[76] By profiling RNA from 6 meningiomas and 4 dural specimens, the deleted in liver cancer 1 gene *(DLC1)* was confirmed to be downregulated as well.[34] Subsequent transfection of *DLC1* complementary DNA into primary cultures of 5 meningiomas resulted in decreased replication in those specimens.

Oncogenes

Oncogenes are genes that are normally responsible for the growth and differentiation of cells. When oncogenes become mutated, however, they lose their ability to be inactivated and become tumor-inducing agents via autonomous stimulation. Mechanisms by which they gain this function include an absolute increase in the oncogene product or the acquisition of new tumorigenic properties. Although they are less likely to result in meningioma tumorigenesis than biallelic tumor suppressor loss, various oncogenes have been demonstrated to play a critical role in the formation of select meningiomas.

The overexpression of *c-sis* has been detected in some meningiomas (Table 2).[41,53,88] Although its exact function in the development of meningiomas has yet to be fully determined, its role in encoding the B-chain of platelet-derived growth factor-B suggests that it may stimulate cell growth and sustain maintenance of those tumors.[53] *C-myc* and *c-fos* are nuclear transcription-regulating genes that are normally under the control of tumor suppressor genes; overexpression of these transcripts may contribute to growth factor autocrine loop signaling.[18,37] The occurrence of the rare *Ha-ras* and *c-mos* alleles was found at a higher incidence in intracranial tumors including meningiomas compared with normal healthy individuals.[9,19,76] Expression of both *TP73* and *bcl-2* has been correlated with higher meningioma grades as well.[1,62]

Recently, the role of *STAT3* was implicated in the pathogenesis of meningiomas.[101] By using reverse transcriptase polymerase chain reaction, Western blot analysis, and immunohistochemistry, Zhang et al.[101] showed that the frequency and expression of *STAT3* was enhanced with increasing tumor grade compared with no expression in normal dural tissue. Constitutively active *STAT3* was significantly associated with expression of vascular endothelial growth factor, a major inducer of tumor angiogenesis.[26]

Signaling Pathways

Cell signaling pathways are networks of signal cascades that control various intracellular processes such as embryogenesis, cell differentiation, and cell proliferation. The mutation of any one gene product within the cascade can affect the signal transduction of the entire pathway, leading to the development of cancers and cancer stem cells.[95] Two signaling pathways that have been heavily implicated in the progression of meningiomas are the Hh

TABLE 2: Meningioma oncogenes*

Gene	Locus	Product	Function	Meningioma Effect
c-sis	22q13.1	B-chain of PDGF-B	growth factor	possible cell growth & maintenance[53]
c-myc	8q24-qter	c-myc protein	transcription factor	cell growth[18,37]
c-fos	14q24.3	c-fos protein	transcription factor	cell growth[18,37]
Ha-ras	11p15.5	p21	cyclin-dependent kinase inhibitor	possible tumorigenesis[9,19,76]
c-mos	8q11	c-mos protein	serine kinase	possible tumorigenesis[19,76]
TP73	1p36.3	p73	apoptosis; blocks proapoptotic function	higher meningioma grade[62]
bcl-2	18q21.33	bcl-2 protein	apoptosis regulator	higher meningioma grade[1]
STAT3	17q21.2	signal transducer & activator of transcription 3	transcription factor	higher meningioma grade[101]

* PDGF = platelet-derived growth factor.

and Wnt signaling pathways (Table 3). Furthermore, the notch, transforming growth factor beta, and insulin receptor signaling pathways have also been associated with meningioma progression.[13,38,68,79,97]

The Hh signaling pathway is intimately involved in cell proliferation and differentiation, angiogenesis, cellular matrix remodeling, and stem cell homeostasis.[44,92] Laurendeau et al.[44] investigated the role of Hh pathway deregulation in 36 meningiomas of varying grades. In comparison with normal tissue, Hh pathway activators including the *SMO*, *GLI* transcription genes (*GLI1*, *GLI2*, *GLIS2*), and *FOXM1* mRNA were found to be overexpressed in both aggressive and benign meningiomas. The *SPP1* and *IGF2* genes, known to be involved in cell proliferation and migration, were found to be overexpressed in the more aggressive WHO Grade II and III tumors. *PTCH1*, an Hh pathway ligand receptor, had previously been described as a tumor suppressor in sporadic meningiomas in patients with basal cell nevus syndrome.[98] Laurendeau et al.[44] found *PTCH1* mRNA levels were lower in Grade I meningiomas compared with their Grade II or III counterparts, suggesting that this gene may be involved in the initial tumorigenesis of meningiomas, but is not likely to play a significant role in the progression to more aggressive lesions.

The Wnt signaling pathway has also been implicated in meningioma progression. The tumor suppressor gene *CDH1* is an important modulator of the Wnt signaling pathway,[52] and has been shown to be downregulated in clinically aggressive meningiomas, including those invading the pia mater and skull.[67,82,102] Intact *CDH1* expression has also been significantly associated with lower rates of postoperative meningioma recurrence.[102] The breakpoint cluster region *(BCR)* gene has been shown to be a negative regulator of the Wnt pathway.[39,78] Recent LOH analysis of the *BCR* gene demonstrated significantly lower expression in 149 meningiomas, suggesting it is likely to be a tumor suppressor candidate involved in meningioma pathogenesis.[96] *SFRP1* is part of the gene family of secreted frizzled-related proteins (SFRPs) that are able to downregulate Wnt signaling. Pérez-Magán et al.[68] used gene expression profiling in 112 original and recurrent meningioma samples to demonstrate evidence of *SFRP1* downregulation in patients with meningioma recurrence compared with primary tumors.

Discussion

Meningiomas are among the most common of all primary intracranial tumors, with approximately 25% arising at the skull base.[6] The management of meningiomas in this location is challenging due to the proximity of critical vasculature and neuronal structures including the circle of Willis, arterial perforators, the brainstem,

TABLE 3: Meningioma cell signaling pathways

Path	Gene	Locus	Product	Function	Meningioma Effect
Hh	*SMO*	7q32.1	smoothened GPCR protein	cellular localization	tumorigenesis[44]
Hh	*GLI1, GLI2, GLIS2*	12q13.3, 2q14.2, 16p13.3	zinc finger proteins	transcription factors	tumorigenesis[44]
Hh	*FOXM1*	12p13.33	forkhead box protein M1	transcription factor	tumorigenesis[44]
Hh	*SPP1*	4q22.1	secreted phosphoprotein 1	cell adhesion	higher meningioma grade[44]
Hh	*IGF2*	11p15.5	insulin-like growth factor 2	hormone	higher meningioma grade[44]
Hh	*PTCH1*	9q22.3	patched protein	sonic hedgehog receptor	early event tumorigenesis[44]
Wnt	*CDH1*	16q22.1	E-cadherin	cell adhesion	meningioma invasion,[67,82,102] meningioma recurrence[102]
Wnt	*BCR*	22q11	bcr protein	serine/threonine kinase, GTPase activator	possible tumorigenesis[96]
Wnt	*SFRP1*	8p11.21	secreted frizzled-related protein 1	secreted extracellular signaling ligand	meningioma recurrence[68]

cranial nerves, and optic pathways. Although gross-total microscopic resection (Simpson Grade I) of meningiomas may predict improved clinical outcomes, aggressive operative resection of locally invasive tumors can lead to significant morbidity and death.[3,12,51,64] A more common treatment paradigm currently relies on aggressive surgical tumor debulking followed by stereotactic radiosurgery to regions of residual tumor. Stereotactic radiosurgery, with or without subtotal resection, has been reported to be an extremely viable primary or secondary option, with long-term tumor control rates ranging from 82% to 98%.[2,36,59,100] On the other hand, adjunctive radiation or radiosurgery has also been associated with a variety of potential complications, including radiation necrosis, peritumoral edema, visual loss, hypopituitarism, and the development secondary neoplasms.[15] Conservative management with clinical observation and serial imaging has been recommended by some authors as well.[12,87,90] In decades to come, more selective and less morbid treatment strategies are likely to complement or replace surgical- and/or radiation-based approaches to cranial base meningiomas. More advanced therapies for refractory meningiomas may, in part, arise from research currently focused on alternate molecular, genetic, and immune-based treatments for meningiomas and are likely to target neoplastic tissue with a higher degree of specificity.

Current Genetics of Meningiomas

Relatively speaking, little work has focused on elucidating the genetic basis of meningioma development and transformation. To date, the most significant genetic finding is that the *NF2* mutation on chromosome 22q12 is a critical initiating event in the formation of approximately half of all meningiomas. Several other candidate genes and pathways have also been suggested to play a role in meningioma formation and progression. Low levels of *TIMP1* and *TIMP3* tumor suppressors were found to be associated with invasive behavior, whereas *NDRG2* was found to be downregulated in a higher percentage of recurrent meningiomas. Loss of chromosome 9p and its *CDKN2A*, *CDKN2B*, and *p14ARF* tumor suppressors has been implicated in the rapid growth and progression of meningiomas. *C-sis*, *c-myc*, *c-fos*, *Ha-ras*, *c-mos*, *TP73*, *bcl-2*, and *STAT3* are oncogenes that have been noted to have a relatively high incidence in meningiomas. The exact effect on tumorigenesis, however, has yet to be elucidated. Due to their critical involvement in cell proliferation and differentiation, dysregulation of the Hh and Wnt cell signaling pathways has been linked to clinically aggressive, higher-grade, and recurrent meningiomas.

Understanding the genetic and molecular mechanisms by which meningiomas develop may provide complementary treatments if curative surgery is not attainable and other adjuvant treatment modalities such as radiation are not viable options. Newer methods using knowledge gleaned from the molecular biology of meningiomas have included biological agents such as interferon,[28,40] endothelin receptor antagonists,[5,80] growth hormone receptor antagonists,[29,55,89] and gene therapy transfection with adenovirus or herpes simplex virus vectors.[10,37] Investigation into these molecular therapeutic targets are advanced by the identification and characterization of selected genes and their respective roles in meningioma formation and progression.

Little information exists as to why a subset of meningiomas become aggressive and/or invasive. To date, only 2 gene expression studies have been performed to address this question. These investigations used old microarray platforms that interrogate few genes, with inconsistent results.[27,97] The following sections address high throughput technologies that can more quickly and accurately analyze whole-genome samples, and therefore potentially identify new genetic associations with meningioma development, progression, and invasiveness.

Genome-Wide Association Studies

The genome-wide association methodology has been made possible with the advent of high-density SNP genotyping arrays and the knowledge acquired from the International HapMap project.[35] The HapMap was designed to create a genome-wide database of patterns of human genetic variation, with the expectation that these patterns would be useful for genetic association studies of common diseases.[48] High-throughput SNP arrays allow the interrogation of hundreds of thousands of SNPs in the human genome, chosen to capture most of the human genetic variation based on the HapMap project, and then identify specific genomic regions or loci where there is a difference of patterns of genetic variation between cases and control subjects.[54] Compared with traditional genetic linkage or candidate gene association studies, GWAS provide a powerful approach to identify common, low-penetrance disease loci by assaying the genome in an unbiased and hypothesis-free manner. As a result, many detected associations provide new insights into pathophysiology, suggesting previously unsuspected etiologic pathways for common diseases that can be of use in identifying new therapeutic targets and developing targeted interventions.

Large-scale GWAS have already been used in a diverse array of common and complex diseases, including various cancers such as breast, prostate, colorectal, and lung, as well as melanoma, leukemia, and neuroblastoma.[22,91] These studies identified more than a few dozen susceptibility loci, confirming that susceptibility to these cancers is polygenic. Additionally, many of these loci were detected at low power, indicating that many additional disease loci are likely to be detected with larger studies. Furthermore, the loci were not previously suspected to be related to carcinogenesis, and some of them point to altogether new disease mechanisms. As of January 2011, meningiomas have not been investigated by GWAS, suggesting that future genomic studies on meningiomas may benefit from this approach. Meningiomas are an interesting candidate for this type of analysis, as most are benign. However, the small subset that display malignant histological phenotypes and aggressive clinical behavior may help elucidate a mechanism of malignant transformation in CNS tumors.

High-Throughput Sequencing

A new generation of sequencing platforms that pro-

duce high-throughput genome or transcriptome sequence data has now made it possible for individual laboratories to generate enormous amounts of sequence data.[57] High-throughput sequencing allows simultaneous examination of complete genomes of the same species, revealing more and more details about how individual genomes as well as individual aspects of their regulation differ from each other. The inclusion of transcriptome sequencing, chromatin-immunoprecipitation sequencing, and epigenetic analysis (DNA methylation or histone modification chromatin immunoprecipitation) adds unprecedented resolution, enabling the detection of even subtle differences such as alternative splicing of individual exons, or base-level binding preferences. There is no doubt that the upcoming mountains of sequencing data will advance functional genomics studies,[60,94] human disease studies,[11] population genetic studies,[21,75] metagenomics,[66,81] clinical diagnosis,[77] as well as other areas of biomedical importance. Furthermore, high-throughput sequencing data may also provides the foundation for new strategies in systems biology and personalized medicine.

Several cancers have been investigated by high-throughput, whole-genome sequencing approaches, and results from these studies provide important insights into the genetics of cancer susceptibility, formation, and progression.[50] For example, by sequencing the genomes of a cancer (primary tumor or cell lines) and a paired lymphoblastoid cell line from the same person, it is possible to infer the comprehensive catalog of somatic mutations from an individual cancer.[73,74] To date, several cancer types have been subject to large-scale whole-genome sequencing.[20,45,49] These initial findings illustrate the potential for next-generation sequencing to provide unprecedented insights into mutational processes, cellular repair pathways, and gene networks associated with cancer.

The Cancer Genome Atlas is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, especially large-scale genome sequencing. TCGA is a joint effort of the National Cancer Institute and the National Human Genome Research Institute, 2 of the 27 Institutes and Centers of the NIH, US Department of Health and Human Services. The first successfully completed pilot project from TCGA involved glioblastoma, which provided new insights into the roles of *ERBB2*, *NF1*, and *TP53*, uncovered frequent mutations of the PI3 kinase regulatory subunit gene *PIK3R1*, and facilitated a network view of the pathways altered in the disease development.[8] Currently, TCGA is expanding its efforts to aggressively study 20 or more additional cancers and yield a comprehensive, rigorous, and publicly accessible data set that will improve our ability to diagnose, treat, and prevent cancer. Among the CNS cancers, however, only glioblastoma was selected to be studied by TCGA. Therefore, although we may glean some general knowledge from TCGA on the genetics of brain tumor development, the results from TCGA will not directly and specifically advance our understanding of meningioma genetics. Additional efforts will be necessary to identify genetic risk factors and oncogenes or tumor suppressors that are specifically activated or inactivated in meningiomas, especially in more clinically aggressive (Grade II/III) subtypes.

Technologies that can quickly and accurately analyze whole-genome samples for genetic variations can be applied to meningioma samples or the serum of patients harboring these tumors. The identification of new genetic associations may help develop diagnostic or prognostic tools that can determine susceptibility to invasive or malignant meningiomas at an early stage, potentially laying the groundwork for customized treatment strategies.

Conclusions

Meningiomas of the cranial base are typically histologically benign tumors but may cause significant treatment challenges due to invasion of critical neurovascular structures, morbidity associated with aggressive resection, local tumor recurrence and/or progression, and toxicity from adjunctive radiation-based treatments. Advances in our understanding of the genetic abnormalities in meningioma pathogenesis have provided substantial insights into the molecular biology of these tumors, and may pave the way for highly selective future therapies with an unprecedented safety profile. Continued work in this area would provide genetic assessment tools to complement current systems for histological and immunochemical grading. Identification of dysregulated genetic targets would also offer data that would serve as a foundation for the development of individualized molecular therapies. The use of genome-wide association studies and high-throughput genomics may be able to rapidly detect additional genetic associations with meningioma growth and development.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Quantitative and qualitative 5-aminolevulinic acid–induced protoporphyrin IX fluorescence in skull base meningiomas

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Object. Complete resection of skull base meningiomas provides patients with the best chance for a cure; however, surgery is frequently difficult given the proximity of lesions to vital structures, such as cranial nerves, major vessels, and venous sinuses. Accurate discrimination between tumor and normal tissue is crucial for optimal tumor resection. Qualitative assessment of protoporphyrin IX (PpIX) fluorescence following the exogenous administration of 5-aminolevulinic acid (ALA) has demonstrated utility in malignant glioma resection but limited use in meningiomas. Here the authors demonstrate the use of ALA-induced PpIX fluorescence guidance in resecting a skull base meningioma and elaborate on the advantages and disadvantages provided by both quantitative and qualitative fluorescence methodologies in skull base meningioma resection.

Methods. A 52-year-old patient with a sphenoid wing WHO Grade I meningioma underwent tumor resection as part of an institutional review board–approved prospective study of fluorescence-guided resection. A surgical microscope modified for fluorescence imaging was used for the qualitative assessment of visible fluorescence, and an intraoperative probe for in situ fluorescence detection was utilized for quantitative measurements of PpIX. The authors assessed the detection capabilities of both the qualitative and quantitative fluorescence approaches.

Results. The patient harboring a sphenoid wing meningioma with intraorbital extension underwent radical resection of the tumor with both visibly and nonvisibly fluorescent regions. The patient underwent a complete resection without any complications. Some areas of the tumor demonstrated visible fluorescence. The quantitative probe detected neoplastic tissue better than the qualitative modified surgical microscope. The intraoperative probe was particularly useful in areas that did not reveal visible fluorescence, and tissue from these areas was confirmed as tumor following histopathological analysis.

Conclusions. Fluorescence-guided resection may be a useful adjunct in the resection of skull base meningiomas. The use of a quantitative intraoperative probe to detect PpIX concentration allows more accurate determination of neoplastic tissue in meningiomas than visible fluorescence and is readily applicable in areas, such as the skull base, where complete resection is critical but difficult because of the vital structures surrounding the pathology.
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Key Words • skull base meningioma • fluorescence-guided resection • protoporphyrin IX • 5-aminolevulinic acid • optical spectroscopy • biophotonics

Skull base meningiomas remain some of the most challenging tumors to treat given their proximity to the origin of major vessels supplying the cerebrum and several cranial nerves crucial to everyday function.[5,21] The involvement of normal structures can render resection difficult, making the need for highlighting the neoplastic tissue imperative.[21] Neuronavigation has significantly improved the precision of dissections but remains impractical for the sharp differentiation of structures, especially when confounded by intraoperative soft tissue shifts.[21] The use of tumor-specific biomarkers for intraoperative guidance appears to be a promising adjuvant therapeutic tool to better address this problem.

In fact, several clinical trials have shown that high-grade gliomas specifically accumulate the endogenous fluorescent biomarker, PpIX, and in concentrations sufficient for visual detection during surgery under blue light exposure following the exogenous administration of ALA.[11,19,20,22,23,25,26,28] Currently, there is little experience and no consensus on the use of this technique for meningiomas.[7,12,17,24] Further, the recent development of quantitative probes[14,26]

Abbreviations used in this paper: ALA = 5-aminolevulinic acid; PpIX = protoporphyrin IX.

that can detect and quantify fluorescence invisible to the naked eye is opening new frontiers for the application of this technique in lower-grade tumors, metastases, and meningiomas. In the current study, we present our experience using both state-of-the art qualitative visible fluorescence imaging and a novel quantitative (detected with a spectroscopic probe) fluorescence detection technology for the resection of a skull base meningioma.[14,26]

Methods

Patient and Study Characteristics

A 52-year-old woman presented with a 2.1-cm right sphenoid wing meningioma that had a small amount of intraorbital extension in the area of the anterior clinoid process. It was incidentally discovered on MR imaging performed for depression. The patient's medical history was otherwise unremarkable.

She was enrolled in an investigational study of fluorescence-guided tumor resection. The study protocol was approved by the institutional review board of the Dartmouth-Hitchcock Medical Center, controlling the participation of human subjects in research, and the patient participated under informed consent. Inclusion criteria for the study have been reviewed in earlier publications.[20] Our patient received an oral dose (20 mg/kg body weight) of ALA (DUSA Pharmaceuticals) dissolved in 100 ml of water approximately 3 hours prior to the induction of anesthesia. Preoperative axial high-resolution, contrast-enhanced T1-weighted MR images were acquired and used for image-guided neuronavigation.

Surgical Procedure

The patient was supine with her head in 3-point fixation and turned to the right side. The head was registered with a StealthStation Treon image-guidance system (Medtronic). A Zeiss OPMI Pentero surgical microscope (Carl Zeis Surgical GmbH) was modified for fluorescence guidance with a 400-nm wavelength source for excitation and a 620- to 710-nm bandpass filter to record fluorescence emissions. The microscope's field of view was coregistered with the surgical field.

The patient underwent a frontotemporal craniotomy for resection of the tumor. To facilitate the approach an anterior clinoidectomy was performed using the ultrasonic bone aspirator. At several points during the operation, the surgeon alternated from white to blue light exposure to reveal fluorescence. Biopsy specimens were collected at several stages of the resection, in both fluorescing and nonfluorescing regions within the preoperatively planned resection volume.

Immediately before obtaining a biopsy specimen, the surgeon placed the probe on the region of the tumor to be biopsied and recorded spectroscopic fluorescence data using the intraoperative probe. Control data were also acquired, in each case consisting of spectroscopic measurements in normal brain (of indiscriminate subtypes) or normal dura mater. Each site was assigned a fluorescence score from 0 to 4 (no [0], minimal [1], moderate [2], high [3], and very high [4] fluorescence) based on the impression of the surgeon, who was blinded to the quantitative results, before biopsy acquisition.

Intraoperative Probe

We used a handheld probe to quantify PpIX concentrations in vivo based on in situ spectroscopic fluorescence measurements.[26] Four optical fibers with a 200-μm-diameter core linearly spaced 260 μm apart were bundled into a stainless steel shaft (1.10-mm-diameter end), and the fibers were connected through a 3-m cable to a data acquisition system. During each measurement, sequential white light (wavelength range 450–720 nm) and fluorescence excitation light (405-nm exposure) through the fiberoptics were used to collect reflectance and fluorescence emission spectra. White light reflectance data provided the necessary information to compute the nonfluorescent optical properties of tested tissue, namely the intrinsic absorption and scattering coefficients. Based on these computed values, light-transport modeling was applied to correct for the distorting effects of intrinsic tissue optical properties on the raw fluorescence spectra and to quantify the absolute PpIX concentrations in tissue to an accuracy of about ± 10%.[14,26]

Pathological Analysis

Neuropathological analysis was done on formalin-fixed, paraffin-embedded biopsy tissue specimens processed for H & E staining. A neuropathologist blinded to the final pathological diagnosis assessed the specimens based on WHO histopathological criteria.[16]

Statistical Analysis

Data processing was performed using MATLAB software (Version R2009b, The Mathworks, Inc.). Wilcoxon rank-sum (Mann-Whitney) tests were used to assess a difference between groups. Two-sided p values < 0.05 were described as statistically significant.

Results

Tumor Fluorescence

Both qualitative visible fluorescence imaging and the quantitative intraoperative probe were used during resection in our patient (Fig. 1). The intraoperative probe detected varying PpIX concentrations in tissue (normal tissue, below the level of quantitation; tumor tissue, mean 4.81 μg/ml, range 0.11–19.15 μg/ml; Fig. 2). Further, the intraoperative probe was able to detect neoplastic tissue more accurately than the state-of-the-art qualitative visible fluorescence approach. In some instances, histologically confirmed tumor tissue showed no visible levels of fluorescence but did accumulate significant PpIX concentrations (> 0.10 μg/ml) above the previously reported optimal cutoff value for meningiomas (< 0.01 μg/ml).[26] For sampled areas of the tumor, visible fluorescence demonstrated 80% sensitivity in detecting pathology, whereas the intraoperative probe was associated with 100% sensitivity. The spatial resolution of the probe was approximately 1 mm^2 (that is, the probe tip that detects the fluorescence of tissue was approximately 1 mm in diameter).

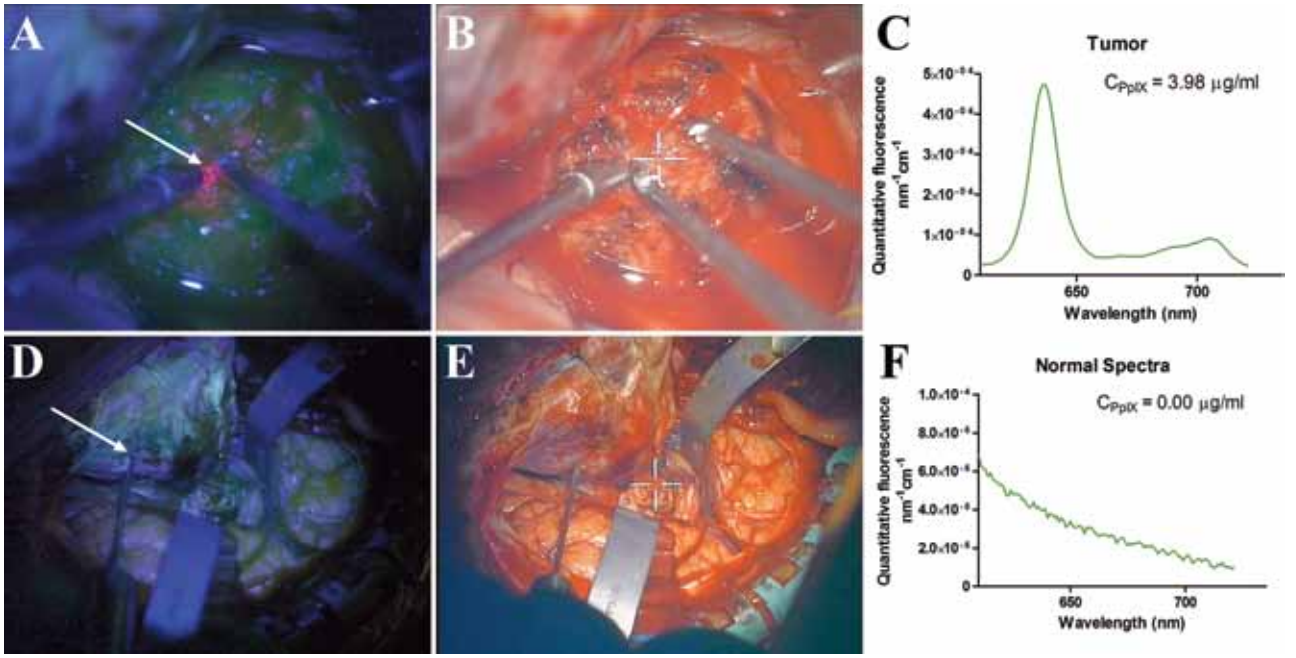

Fig. 1. Qualitative and quantitative ALA-induced PpIX fluorescence–guided resection images. Fluorescence-guided resection of a skull base meningioma showed varying levels of qualitative and quantitative fluorescence. A histologically confirmed tumor region with large amounts of accumulated PpIX showing high levels of visible fluorescence under blue light excitation **(A)** with the corresponding white light image **(B)**, and the quantitative fluorescence spectrum **(C)** showing the distinctive PpIX spectrum. A region of normal dura showed no visible fluorescence under blue light excitation **(D)** with the corresponding white light image **(E)**, and the quantitative fluorescence spectrum **(F)** showed no PpIX peaks, only a distinctive autofluorescence spectrum.

This device can pick up small areas of uncertainty, which can be particularly useful in regions such as the skull base in which the tumors are close to vital neurovascular structures. Complete tumor resection was achieved without any complications or injuries to nearby normal structures. Histological analysis of the tumor revealed a WHO Grade I meningioma.

Discussion

Microsurgical approaches and navigational technology have significantly evolved.[5,21] However, skull base surgery for meningiomas is lacking intraoperative markers for surgical guidance to allow adequate tumor localization and resection, minimize collateral damage, and prevent disruption of normal anatomy. In the current study we demonstrated the combination of qualitative visual fluorescence and quantitative in vivo fluorescence measurements (using an intraoperative probe) based on a light-transport modeling approach, which corrects for the marked distorting effects of variations in tissue optical properties on the fluorescence emission spectrum and intensity and substantially improves the performance of PpIX as an intraoperative imaging tool for a skull base meningioma.

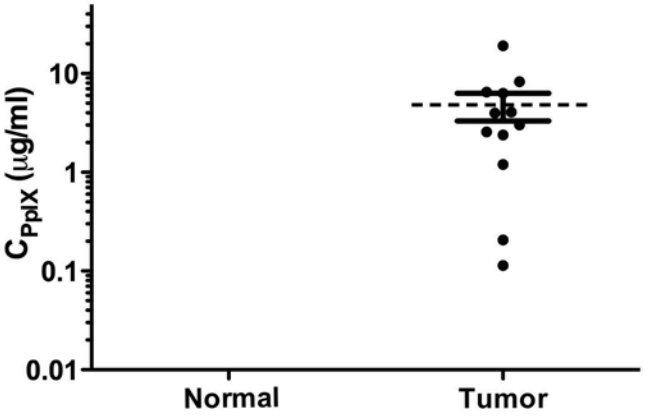

Fig. 2. Protoporphyrin IX concentrations in skull base meningioma. Scatter plot of PpIX concentrations in normal and tumor tissue (mean 4.81 ± 1.49 μg/ml, range 0.11–19.15 μg/ml). Tumor tissue accumulated significantly more PpIX than normal tissue. Concentrations in normal dura were all below the level of quantification and outside the axis limits.

5-Aminolevulinic acid is a natural precursor in the heme biosynthetic pathway. Exogenous administration of ALA leads to significant accumulation of the fluorescent compound PpIX one step prior to the conversion of PpIX to heme by the enzyme ferrochelatase.[7,8] Protoporphyrin IX selectively accumulates in malignant cells as a result of several proposed (and not fully understood) mechanisms, such as reduced activity of ferrochelatase, elevated intracellular ALA uptake, and delayed PpIX secretion from the cell.[6,19] Similar mechanisms have been speculated to be the cause of the increased fluorescence observed in patients with meningiomas.[7]

Previous studies have shown that PpIX accumulates with high specificity and in sufficient concentrations in high-grade glioma to allow visual fluorescence detection of tumor tissue.[19,20,22,23,25,28] Stummer et al.[22,23] showed that the use of ALA approximately doubles the number of patients without residual tumor on postoperative MR imaging and increases 6-month progression-free survival.

Authors of several small series have underscored the

utility of ALA during meningioma surgery.[7,12,17,27] Note that in these studies no relationship was found between the degree of malignancy and tumor fluorescence. Kajimoto et al.[12] reported that the sensitivity and specificity of PpIX fluorescence of the main tumor mass overall were 83% and 100%, respectively. They describe how the information provided by fluorescence led to a modification in their technique and more complete resections. Morofuji et al.[17] demonstrated the use of visible fluorescence to define the areas of bone invasion in a convexity meningioma and successfully correlated the data with histological findings postoperatively. Likewise, Coluccia et al.[7] reported that the overwhelming majority of patients (94%) with meningiomas in their series demonstrated visible fluorescence. All of these authors used a modified surgical microscope to visualize fluorescence as an intraoperative tool to assist skull base and convexity meningioma resection.

In many cases, the use of fluorescence in resecting well-circumscribed tumors, such as meningiomas, is not necessary. The need for a highly sensitive intraoperative tool arises in cases in which the surgeon must identify small areas of invasion and differentiate from normal neurovascular structures in vital areas such as the skull base.[21] In such instances an intraoperative tool, such as fluorescence guidance, would aid the neurosurgeon in identifying tumor tissue. However, as demonstrated in the current study and in accordance with the literature,[7,12,17] ALA-induced PpIX fluorescence does not always display visible levels of fluorescence in meningiomas. We have previously shown the increased diagnostic accuracy of an intraoperative probe in a range of different histologies during intracranial tumor resection. This spectroscopic intraoperative probe takes into account the distortive effects of tissue optical properties on the emitted ALA-induced PpIX fluorescence spectra and quantifies the absolute PpIX concentrations in tissue.[14,26] In the current study, we presented our experience using qualitative and quantitative ALA-induced PpIX fluorescence guidance in the resection of a skull base meningioma.

The use of fluorescence and especially the more elaborate results associated with the application of an intraoperative probe appear to be of increased significance in the treatment of skull base meningiomas. Complete resection decreases the recurrence rate and is related to higher rates of progression-free survival. With the involvement of cranial nerves and blood vessels in the skull base, the chances for total removal decrease and the rates of recurrence and surgical morbidity increase.[1,9] In addition to involving critical functional anatomy, meningioma resection can be complicated by dural involvement, bone involvement, or peritumoral edema.[10,17] Attachments to gliotic brain, major sinuses, and the anterior visual pathways are often left behind and provide foci for recurrence.[1,9,18] Even in patients in whom a Simpson Grade I meningioma resection has been achieved, an 8% 5-year recurrence rate has been reported[2]—and that number only increases with skull base resections.[3,18] Aggressive resection of adjacent dura and gliotic brain has been advocated, with margins of 2–4 cm being proposed in the literature.[4,15,18] Despite the aggressive approach taken in several studies, most of the dural tail apparent on MR imaging has proven to be venous congestion.[13] Morofuji et al.[17] and Kajimoto et al.[12] have shown, with the use of histological analysis, that visible fluorescence can assist in identifying the diseased segment. Quantification of fluorescence with an intraoperative probe could more elaborately map the problematic area and tailor the extent of resection to the true extent of the disease. This strategy can prevent unnecessary morbidity and CSF leaks associated with extensive resections in the skull base. In our patient, complete resection of the intracranial and intraorbital portion of the tumor was achieved, avoiding injury to the adjacent optic nerve and artery.

Although rarely observed, the use of ALA is associated with some adverse effects, which include photosensitivity (primarily in the first 48 hours), transient liver dysfunction, nausea, and vomiting. To manage these effects, we perform serial liver function tests and keep patients in a dark room for 48 hours. Throughout the duration of our prospective study we have not observed any serious adverse effects associated with ALA administration.

Conclusions

Skull base meningiomas are difficult to treat because they involve or are close to the cranial nerves, major blood vessels, and air sinuses. Radical resection of these lesions is imperative to their cure. The use of ALA-induced PpIX fluorescence appears to be a promising tool that can delineate abnormal pathology, demonstrate invasion, and enable tailoring the extent of tumor resection to avoid destruction of normal surrounding tissue. The quantitative approach of intraoperative in vivo measurement of PpIX concentrations opens the door to real-time delineation of these pathologies with much greater accuracy than visible fluorescence. We report on the application of this approach for a skull base meningioma. The intraoperative fluorescence probe could be used as an adjunct to standard white light and qualitative fluorescence image-guided resection, maximizing the therapeutic effect and minimizing complications in the treatment of skull base meningiomas.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Author contributions to the study and manuscript preparation include the following. Conception and design: Roberts, Valdes, Kim, Wilson, Paulsen. Acquisition of data: Bekelis, Valdes, Erkmen, Harris. Analysis and interpretation of data: all authors. Drafting the article: Bekelis. Critically revising the article: Roberts, Bekelis, Valdes, Erkmen, Leblond, Kim, Wilson, Harris, Paulsen. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Valdes. Study supervision: Roberts.

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Predicting postoperative hydrocephalus in 227 patients with skull base meningioma

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Object. Some patients develop communicating hydrocephalus after meningioma surgery, and this can develop into a serious clinical condition. However, this has rarely been addressed in the literature. Therefore, the authors sought to determine predictive patient variables for the occurrence of postoperative hydrocephalus following skull base meningioma surgery.

Methods. For this purpose, the authors retrospectively analyzed all patients who underwent resection of intracranial meningiomas between 1998 and 2009 at the Department of Neurosurgery, University Hospital Zurich, Switzerland. Of 594 patients with meningioma, 227 (38%) had a lesion located at the skull base, and thus were included for analysis. The following patient variables were examined: demographic data (age and sex); tumor number (solitary vs multiple); tumor side and localization within the skull base region (anterior, medial, posterior); infiltration of the cavernous sinus; compression of the optic channel/optic nerve; tumor volume; preoperative embolization (yes/no); duration of surgery; Simpson grade of resection; histopathological features (WHO grade); number of surgeries (single vs multiple); preoperative embolization; duration of hospital stay; tumor recurrence; use of an artificial dural substitute; postoperative infection rate; and clinical outcome (Glasgow Outcome Scale score at discharge and at 3 months, and vital status at last follow-up). Hierarchical clustering, factor analysis, and stepwise regression models revealed a ranking list for the top predictive variables for the occurrence of postoperative hydrocephalus.

Results. A total of 35 patients (5.9%) of the cohort of 594 developed communicating postoperative hydrocephalus, with no patient manifesting obstructive hydrocephalus. Of these 35 patients, 18 had a meningioma located at the skull base (18 [7.9%] of 227), in contrast to 17 patients with meningiomas in other locations (17 [4.6%] of 367). The following patient variables correlated with the occurrence of hydrocephalus, as defined by factor analysis: age, duration of surgery, duration of hospital stay, tumor volume, postoperative infection, and preoperative embolization. A stepwise regression analysis of the latter variables identified 2 variables as significantly predictive: age ($p = 0.0012$) and duration of surgery ($p = 0.0013$).

Conclusions. In this study, the incidence of communicating postoperative hydrocephalus was almost twice as high in patients with skull base lesions as in patients with meningiomas in other locations. Patient age, duration of surgery, duration of hospital stay, tumor volume, postoperative infection, and preoperative embolization were associated with the occurrence of hydrocephalus. In the statistical prediction model, patient age and duration of surgery were the most significant predictors of postoperative hydrocephalus after skull base meningioma surgery.
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Key Words • skull base meningioma • hydrocephalus • neurosurgery • predictive variable

The mean incidence of intracranial meningiomas among all primary brain tumors in adults is 20% in hospital-based studies, and 30% in population-based studies.[5] They occur in 30% of cases near the skull base.[8,11,13,15] The incidence rate is described to be 1.8 for men and 4.2 for women per 100,000 in the US and Europe, and varies with age. In the US, approximately 170,000 individuals are currently affected by this tumor type.[10,22]

The occurrence of hydrocephalus in patients afflicted by benign brain tumors (such as meningiomas) is well known, although systematic studies on de novo or postoperative hydrocephalus are sparse. The incidence of hydrocephalus in surgically treated patients with meningioma has been described to range from 2% to 13% in the

Abbreviation used in this paper: GOS = Glasgow Outcome Scale.

* Drs. Burkhardt and Zinn contributed equally to this work.

literature, but most of the studies did not specify whether hydrocephalus existed before surgery.[3,4,6,12,14,15,19] True postoperative hydrocephalus needs to be distinguished from the occurrence of transient obstructive hydrocephalus, which is most frequently due to the mass effect of the meningioma present before surgery.[6] Although causes and factors influencing the occurrence of true postoperative hydrocephalus are still unknown, our data demonstrate that this disorder is more likely to occur after meningioma extirpation in the skull base region compared with other locations, as has been suggested by others.[6,11] One theory argues that intraoperative spillage of blood into cisterns and subarachnoid space during surgery may lead to a malresorptive hydrocephalus.[6] The more complex nature of the surgical treatment of skull base meningiomas, showing extensive infiltration of the connective and osseous tissues of the skull base, support this hypothesis.[11] Furthermore, it has been shown in patients with subarachnoid hemorrhage that malresorptive hydrocephalus may be caused by blood products clogging the arachnoid villi.[9,18]

In this study, we sought to determine patient variables predicting the occurrence of true postoperative hydrocephalus.

Methods

General Patient Data

In this retrospective analysis of operations performed in a single tertiary center, we reviewed the data obtained in all patients who underwent surgery for intracranial meningiomas at the Department of Neurosurgery, University Hospital Zurich, Switzerland, between January 1998 and January 2009. A total of 594 patients coded with ICD-9 225.2 (benign neoplasm of cerebral meninges) were identified. Of those, 227 meningiomas were located in the skull base region and were selected for analysis. All patients underwent primary surgical treatment via an expert cranial base approach, which varied depending on localization of the tumor. A pterional craniotomy with or without an anterior clinoidectomy was the most frequently used approach, but also orbitozygomatic and subfrontal as well as subtemporal or retrosigmoid approaches were performed. None of the analyzed patients showed evidence of hydrocephalus in any of the preoperative MR imaging or CT studies or at the time of their clinical examination. In cases of recurrence or secondary surgery, patients were not double counted as an additional case in this study, but were entered into the study at the time of their index surgery. The median postoperative follow-up time for patients in the cohort was 2.5 years (range 7 days–10.5 years); the GOS was used to assess the patient's clinical outcome. All patients with de novo postoperative hydrocephalus were treated with ventriculoperitoneal shunt placement at the time of symptomatic presentation (Fig. 1).

Patient Variables

Based on the literature, 21 pertinent patient variables

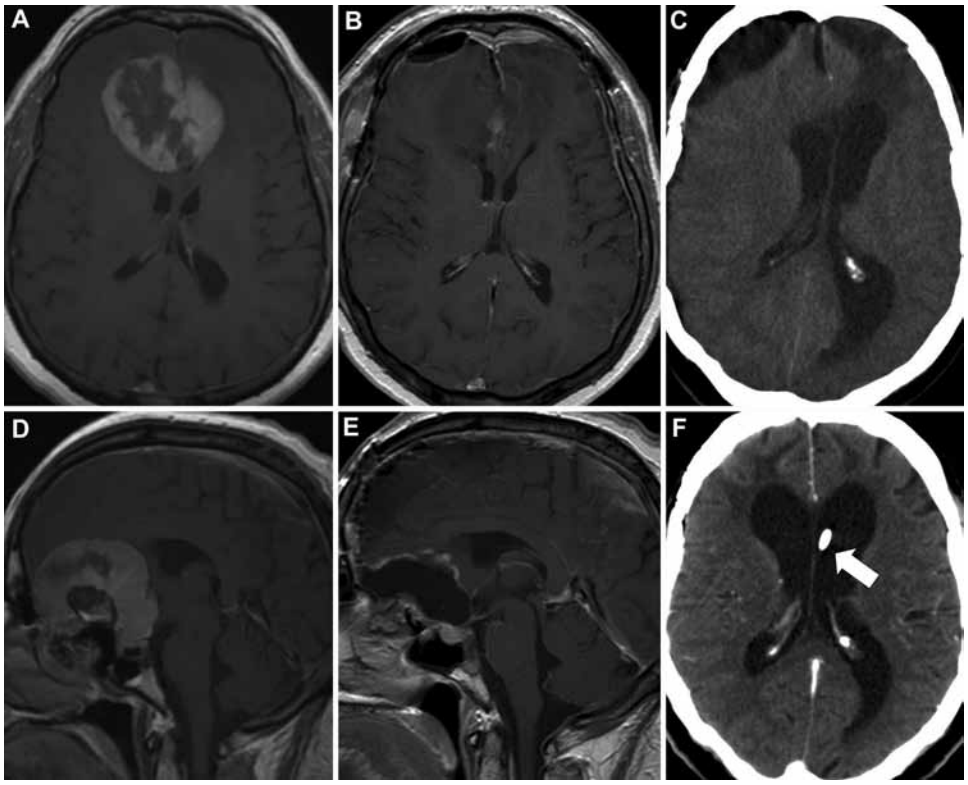


Fig. 1. Axial and sagittal contrast-enhanced MR images obtained in a 66-year-old woman showing an extraaxial mass located in the right anterior part of the skull base **(A and D)**. After endovascular embolization, the tumor was removed successfully via an anterior subfrontal approach **(B and E)**, and the diagnosis of a meningioma (WHO Grade I) was made. Postoperatively, the patient showed clinical signs of hydrocephalus 10 days after surgery, and CT scans revealed radiological signs of hydrocephalus **(C)**. On Day 14 after primary meningioma surgery, a ventriculoperitoneal shunt *(arrow)* was implanted **(F)**.

that may influence the incidence of postoperative hydrocephalus were analyzed: duration of hospital stay; Simpson grade; number of operations; sex; age; WHO grade; multiple meningiomas; tumor volume; tumor side; postoperative infection; preoperative embolization; duration of surgery; GOS score after discharge and after 3-month follow-up; vital status at last follow-up; infiltration of cavernous sinus; compression of the optic channel/optic nerve; recurrence; localization within the skull base region (anterior, medial, posterior); and use of artificial dural substitute at closure.

Hydrocephalus Subgroups

Regarding the onset of de novo postoperative hydrocephalus, two different subgroups of patients were defined: an early-onset group, which showed clinical and/or radiographic signs of hydrocephalus during the initial hospital stay after index surgery (9 patients, mean time of occurrence 15.6 days); and a late-onset group diagnosed after the initial hospital stay for meningioma surgery (9 patients, mean time of occurrence 2.7 months).

Statistical Analysis

The statistical analysis was performed using the following software packages: Microsoft Excel 2010, SAS JMP 9 (SAS Institute, Inc.) and dChip (http://www.dchip.org). Hierarchical clustering and factor analysis were used to identify variables correlated with hydrocephalus, and stepwise regression models were used to rank the correlated variables according to their predictive significance for the occurrence of postoperative hydrocephalus. The ANOVA and Tukey-Kramer testing was performed to compare outcomes of the hydrocephalus versus the nonhydrocephalus group; p values < 0.05 were considered to be significant.

Results

Incidence of Hydrocephalus

Initially 594 patients were identified with ICD-9 code 225.2 and entered into this study. A total of 227 (38%) of those 594 patients harbored a meningioma located in the skull base region. Within this group, patients were further classified according to tumor localization, with 197 cases (86.8%) in the anterior, 12 cases (5.3%) in the medial, and 18 cases (7.9%) in the posterior part of the skull base (Table 1). Of 594 patients with meningioma, de novo postoperative hydrocephalus was diagnosed in 35 (5.9%). Of these, 18 (7.9%) of 227 patients with a meningioma located in the skull base region developed hydrocephalus, which contrasts with only 17 (4.6%) of 367 patients in the group without meningiomas in the skull base. Of the 18 patients with hydrocephalus in the skull base tumor group, 15 (83.3%) of the tumors were located in the anterior part (1 tuberculum sellae, 3 planum sphenoidale, and 11 sphenoid wing meningiomas). The other 3 (16.6%) were in the posterior part of the skull base (including 1 cerebellopontine and 2 petroclival meningiomas).

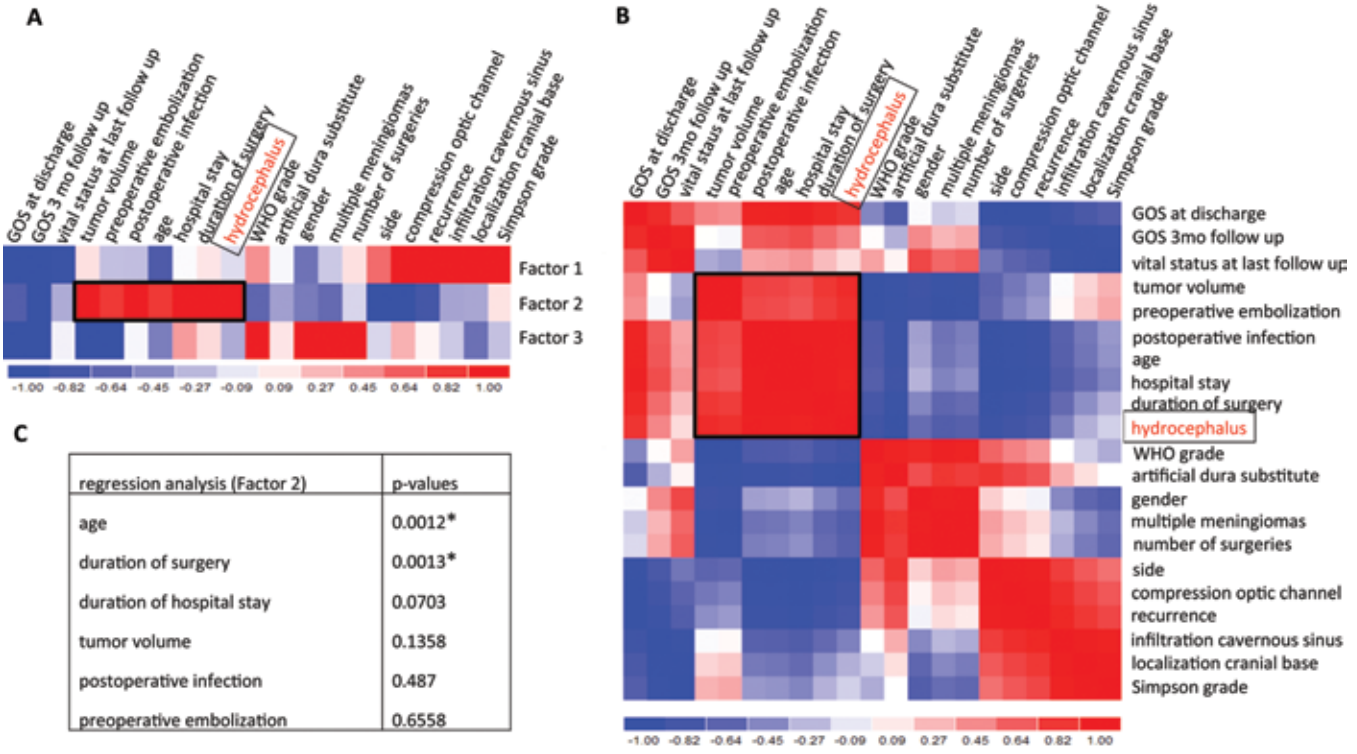
Factor Analysis and Regression Model

Factor analysis of the 21 patient variables charted in the 227 patients in the skull base group revealed 3 distinct clusters of correlating variables (3 factors). The occurrence of hydrocephalus appeared in the second factor (Fig. 2A), together with the following: age, duration of surgery, duration of hospital stay, tumor volume, postoperative infection, and preoperative embolization. A sample correlation matrix reveals the hydrocephalus factor as the most prominent among the examined variable clusters (Fig. 2B). A stepwise regression analysis of this cluster (Factor 2) identified 2 significant variables, age ($p = 0.0012$) and duration of surgery ($p = 0.0013$), as predictors. Duration of hospital stay ($p = 0.0703$) showed a strong trend for prediction, whereas tumor volume ($p = 0.1358$), postoperative infection ($p = 0.487$), and preoperative embolization ($p = 0.6558$) were ranked as less predictive when compared with the previous variables. However, all these variables from Factor 2 are correlated with the occurrence of postoperative hydrocephalus (Fig. 2C).

TABLE 1: Clinical characteristics in 227 patients with skull base meningiomas*

Characteristic	No. (%) w/o Hydrocephalus	No. (%) w/ Hydrocephalus
total no. of patients	209	18
mean age in yrs, ± SD	57 ± 13	73 ± 10
mean postop FU in mos, ± SD	51 ± 35	49 ± 32
mean LOS in days, ± SD	14 ± 7	25.5 ± 17
sex distribution; female	130 (62.2)	13 (72.2)
localization in skull base		
anterior part	182 (87.1)	15 (83.3)
medial part	12 (5.7)	0 (0.0)
posterior part	15 (7.2)	3 (16.6)
WHO grade		
I	173 (82.8)	13 (72.2)
II	31 (14.8)	5 (27.8)
III	5 (2.4)	0 (0.0)
infiltration/compression of optic canal/nerve	84 (40.2)	3 (16.6)
infiltration of cavernous sinus	54 (25.8)	8 (44.4)
preop tumor embolization	76 (36.4)	10 (55.5)
recurrence rate	36 (17.2)	2 (11.1)
mean GOS score		
at discharge		
5	104 (49.7)	4 (22.2)
4	91 (43.5)	11 (61.1)
3	12 (5.7)	3 (16.7)
2	2 (1.0)	0 (0.0)
1	0 (0.0)	0 (0.0)
at 3-mo FU		
5	128 (61.2)	10 (55.5)
4	74 (35.4)	7 (38.9)
3	5 (2.4)	1 (5.6)
2	2 (1.0)	0 (0.0)
1	0 (0.0)	0 (0.0)

* FU = follow-up; LOS = length of hospital stay.



C

regression analysis (Factor 2)	p-values
age	0.0012*
duration of surgery	0.0013*
duration of hospital stay	0.0703
tumor volume	0.1358
postoperative infection	0.487
preoperative embolization	0.6558

Fig. 2. Factor analysis and regression model. **A:** Color heat map representation of the 3-factor analysis. Of note, hydrocephalus, the focus of our study, clusters into the second factor, and thus is closely associated with other variables occurring in this factor. The hydrocephalus cluster is marked with a *black outline*. **B:** Factor rotation matrix highlighting strongly correlated variables in *dark red*. The hydrocephalus cluster is marked with a *black outline*. **C:** Stepwise regression analysis and predictive rank model of variables in the hydrocephalus factor (Factor 2). The top 2 variables, age and duration of surgery, are significantly predictive for the occurrence of hydrocephalus (see p values marked with *asterisk*).

Patient Outcome

Overall tumor recurrence was 16.7% (11.1% in the hydrocephalus group and 17.2% in the nonhydrocephalus group). Patients with hydrocephalus had a significantly longer meningioma surgery than did patients who did not develop hydrocephalus (8.25 vs 4.2 hours; p = 0.0001). Cases of postoperative infection were also associated with a longer surgery time, regardless of the occurrence of hydrocephalus (9.55 vs 4.3 hours; p = 0.0004). The postoperative infection rate was found to be 4.4% in our patient series (10 of 226 patients), which is in concordance with the literature.[19] One of our patients died in the 1st week postsurgery, and therefore was not included in the total for infection rate. Four of the 10 patients with infection were among the 18 individuals in the skull base meningioma hydrocephalus group (22.2%), with 3 (33.3%) of 9 showing early onset and 1 of 9 in the late-onset hydrocephalus subgroup (11.1%).

As expected, a higher Simpson grade significantly correlated with the incidence of meningioma recurrence in this series (p = 0.0045). Overall, 4 patients in our series died during the follow-up period (after 7, 68, 566, and 665 days), but none of these suffered from hydrocephalus. One death was most likely causally associated with the hospitalization for meningioma surgery; a fatal pulmonary embolism occurred in the 1st week after surgery. Using the GOS measure, the patients' condition improved significantly postsurgery at 3-month follow-up, both in the nonhydrocephalus and hydrocephalus groups (Table 1 and Fig. 3A). Only 8 of 227 patients were still categorized with a GOS score of 3 or worse at 3 months. Meningioma localization also influenced the GOS score significantly at patient discharge and at the 3-month follow-up, and patients with tumors located in the anterior part of the skull base scored significantly higher than patients with tumors located posteriorly (p = 0.0002 and p = 0.0011, respectively; Fig. 3B).

Discussion

Available data on the incidence of de novo postoperative hydrocephalus after meningioma surgery are scarce and incomplete. To remedy this, we conducted an analysis of variables influencing the occurrence of postoperative hydrocephalus in patients undergoing surgery for skull base lesions. In this study, we report a nearly 2-fold increase of postoperative hydrocephalus in cases of surgically treated skull base meningiomas versus meningiomas in other intracranial locations (7.9% vs 4.6%). Our overall incidence of hydrocephalus, at 5.9%, is in concordance with other studies showing incidence rates ranging from 2% to 13%.[3,6,12,21] The wide range reported in the literature thus far is most likely due to the different localizations of the meningiomas included in these studies. For instance, Duong et al.[6] showed a postoperative hydrocephalus incidence rate of 8% for meningiomas located

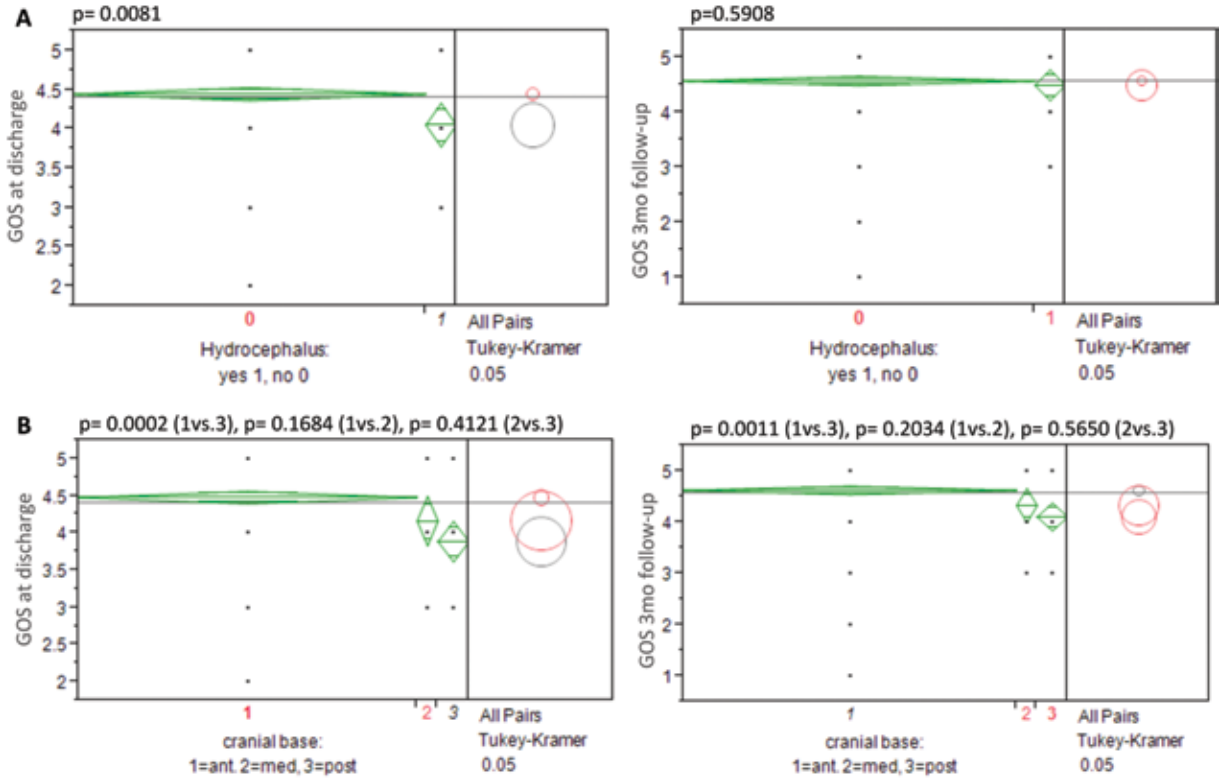


Fig. 3. Results of ANOVA and Tukey-Kramer testing to compare patient outcomes. **A:** The GOS score after discharge was significantly better in the nonhydrocephalus compared with the hydrocephalus group. At the 3-month follow-up, the GOS score was similar in both groups. **B:** With regard to the localization within the skull base, patients with a surgically treated meningioma in the anterior part had a significantly better GOS score at discharge and at 3-month follow-up than patients with a meningioma located in the posterior part of the skull base. ant = anterior; med = medial; post = posterior.

in the skull base region, and Boviatsis et al.[3] described a rate of 6.9% for supratentorial meningiomas. In contrast, Tahara et al.[21] reported a higher hydrocephalus incidence rate of 13.3% for petroclival meningiomas, which is confirmed by our results (16.6%) in patients with meningiomas located in the posterior part of the skull base.

In this study, we identified age and duration of surgery as the two most predictive and statistically significant variables for the occurrence of de novo postoperative hydrocephalus in skull base meningiomas. Age in general is known to be a variable prolonging or complicating the postoperative clinical course after intracerebral tumor surgery, and not only in meningiomas.[1,7] Not surprisingly, this was corroborated by our analysis. However, this factor is not under the surgeon's control. In contrast, duration of surgery is partially dependent on the approach chosen. In this study we showed that patients who developed postoperative hydrocephalus had undergone an operation of significantly longer duration than patients who did not develop postoperative hydrocephalus ($p = 0.0001$). Cases of postoperative infection were also associated with a longer surgery time, regardless of the occurrence of hydrocephalus in these cases ($p = 0.0004$). It is likely, though, that tumor characteristics (such as size, location, and pathological features of the meningioma) as well as patient characteristics (for example, age and comorbidities such as diabetes) are reflected in the duration of surgery, which certainly influences the infection rate to some extent.[17] The latter variables may then result in the occurrence of postoperative hydrocephalus, whereas in our study the most relevant predictive variables were age and duration of surgery. Other studies analyzing the association of surgical time with postoperative hydrocephalus are rare.

Nevertheless, the correlation between incidence of postoperative infection and hydrocephalus has been shown, and indirectly supports our observation. Patir et al.[17] showed that a surgical time of more than 4 hours was significantly associated with higher postoperative infection rates.

Regarding the onset of postoperative hydrocephalus, we found two different subgroups (early vs late) with an equal number of cases (Table 2). Obviously, patients included in the early-onset group showed a longer duration of hospital stay (mean 32 days) compared with patients with delayed-onset hydrocephalus (mean 21 days) and patients without hydrocephalus (mean 14 days). In contrast to our observations, Duong et al.[6] reported postoperative hydrocephalus in their patient series only within the first 2 months after surgery, and argued that postoperative hydrocephalus occurs in the acute postoperative period. We hypothesize that one reason for having two rather distinct groups in our patient cohort may be found in the fact that patients included in the late-onset group had a slower onset and delayed time course in the development of hydrocephalus, and were therefore only identified during prolonged follow-up. However, it remains a question whether the late-onset group is associated with meningioma sur-

TABLE 2: De novo postoperative hydrocephalus in 18 patients with skull base meningiomas

Characteristic	No. (%) w/ Early Onset	No. (%) w/ Late Onset
total no. of patients	9	9
mean age in yrs, ± SD	73 ± 9	66 ± 10
mean postop FU in mos, ± SD	50 ± 23	40 ± 20
mean LOS in days, ± SD	32 ± 12	21 ± 20
sex distribution; female	6 (66.6)	7 (77.8)
localization of skull base		
anterior part	9 (100)	6 (66.6)
medial part	0 (0.0)	0 (0.0)
posterior part	0 (0.0)	3 (33.3)
infiltration/compression of optic canal/nerve	2 (22.2)	1 (11.1)
infiltration of cavernous sinus	4 (44.4)	4 (44.4)
preop tumor embolization	4 (44.4)	6 (66.6)
mean GOS score		
at discharge		
5	2 (22.2)	2 (22.2)
4	5 (55.5)	6 (66.6)
3	2 (22.2)	1 (11.1)
2	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)
at 3-mo FU		
5	6 (66.6)	4 (44.4)
4	3 (33.3)	4 (44.4)
3	0 (0.0)	1 (11.1)
2	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)

gery only, or if communicating hydrocephalus may have occurred in these patients for other reasons. Hydrocephalus in patients who have not undergone brain surgery has a population-based incidence of 5.5 per 100,000 and a prevalence of 21.9 per 100,000 for normal-pressure hydrocephalus. In patients between 60 and 65 years of age, the prevalence increases to 49.3 per 100,000.[20] We observed 9 of 10 patients with hydrocephalus (with a mean age of 66 years) in our 227-patient skull base meningioma cohort, and they were identified in our late-onset group. Given the extremely low incidence of spontaneous hydrocephalus in the general population, we assume that the occurrence of hydrocephalus in these patients is related to meningioma surgery. The correlation of prolonged hospital stay and occurrence of hydrocephalus is certainly influenced by the early-onset group, in which patients had a longer hospital stay due to hydrocephalus. This correlation is much lower in the late-onset group; thus we concluded that the strong predictive trend of the duration of hospital stay for the occurrence of hydrocephalus is mainly attributable to the early-onset group and not to the longer hospital stay of the patients per se.

Postoperative infection was also found to be correlated with the occurrence of postoperative malresorptive hydrocephalus in our study. Since our overall infection rate of 4.4% was comparable with previous studies,[2,19,21] we noticed that a significantly higher number of individuals in the hydrocephalus group had had a postoperative infection (22.2%). Especially in the early-onset hydrocephalus subgroup, a postoperative infection was diagnosed in one-third of the patients with hydrocephalus. These findings reflect other studies showing that postoperative infection is associated with malresorptive hydrocephalus after tumor removal or treatment of intracerebral aneurysms.[6,16,18] In our study, the use of artificial dura mater was not associated with a higher occurrence of infection in the hydrocephalus group (affecting 1 of 9 patients), but the numbers may be too low to establish a correlation.

Outcome analysis indicates that the patients included in our study cohort had a favorable outcome after skull base meningioma surgery, and most of the patients significantly improved in their GOS score at 3-month follow-up. This observation holds true for patients both with and without hydrocephalus. With regard to the meningioma localization, patients in whom surgery was performed in the anterior part of the skull base had a significantly better GOS score than patients who were treated in the posterior part of the skull base (Fig. 3).

Our results suggest that some predictive variables (such as patient age and tumor volume as well as preoperative embolization, which depends on the size and location of the tumor) have a varying influence on the risk of postoperative hydrocephalus, but none of these are under the surgeon's immediate control. However, duration of surgery, infection rate, and duration of hospital stay are somewhat dependent on the surgeon. Interestingly, in our study the Simpson grade was not well correlated with the incidence of postoperative hydrocephalus, whereas duration of surgery was. However, a higher Simpson grade is associated with a significantly higher rate of meningioma recurrence ($p = 0.0045$). Therefore, our results reinforce the goal that surgery should be as short as possible, but the extent of resection should also be as complete as possible to prevent a postoperative hydrocephalus.

Conclusions

In our case series, the incidence of communicating postoperative hydrocephalus was nearly twice as high in patients in the skull base group, when compared with patients with meningiomas that were not in skull base locations. Patient age, duration of surgery, duration of hospital stay, tumor volume, postoperative infection, and preoperative embolization were associated with the occurrence of hydrocephalus after meningioma surgery; of these, patient age and duration of surgery were the most significant predictors. We conclude that to prevent postoperative hydrocephalus, patients should be treated surgically as early as possible: the patient is younger, meningiomas are comparably smaller, and tumor embolization less frequently indicated. However, surgery and its alternatives (such as conservative observation) need to be accurately discussed with the patients on an individual basis, because patients may not like to undergo surgery for many reasons. The duration of surgery should be kept at a minimum that ideally still achieves the best possible Simpson grades,

which contributes to minimizing infection rates and tumor recurrence. If early-onset postoperative hydrocephalus is diagnosed, then standard shunting procedures prove successful in achieving improved 3-month postoperative GOS scores, which are comparable to those in the nonhydrocephalus group. However, ventriculoperitoneal shunt placement carries its own short- and long-term risks, and therefore it is crucial to prevent hydrocephalus to minimize the need for shunting.

Here we demonstrate that postoperative hydrocephalus occurs in a significant number of patients undergoing skull base surgery for meningioma. Elderly patients and those with long surgical interventions are at highest risk to develop this condition, and proper attention is needed for identification of its early and delayed manifestations to assure the best possible clinical outcome.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Burkhardt, Zinn, Krayenbühl. Acquisition of data: Burkhardt, Zinn, Graenicher. Analysis and interpretation of data: all authors. Drafting the article: Burkhardt, Zinn, Santillan, Kasper. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Burkhardt, Zinn. Study supervision: Krayenbühl.

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Hemangiopericytomas of the skull base

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Object. Intracranial hemangiopericytomas are frequently located along the dural sinuses along the skull base and represent rare, aggressive CNS neoplasms that are difficult to distinguish from meningiomas based on both imaging and gross characteristics. The authors of this study describe 3 patients with these lesions and review the pertinent literature.

Methods. Two men and 1 woman, whose median age at the time of the initial presentation was 37 years (range 20–53 years), constitute this series. They underwent multimodal treatment consisting of resection, embolization, radiation therapy, and in 1 case chemotherapy.

Results. Two of the 3 patients treated were alive after a mean follow-up of 93 months (range 4–217 months). One patient died 217 months after the initial diagnosis. The longest tumor progression–free interval after the initial or secondary resection was 43 months (range 4–84 months).

Conclusions. Hemangiopericytomas have been reclassified as mesenchymal nonmeningothelial tumors. They have an inevitable tendency to recur locally and metastasize distally. The mainstay of therapy remains an aggressive attempt to achieve gross-total resection at the initial surgery. Postoperative adjuvant radiotherapy should be offered to all patients, regardless of the degree of resection achieved. Diligent long-term follow-up is paramount as local recurrences and distal metastases can develop sometimes years after the initial treatment.
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Key Words • **hemangiopericytoma** • **skull base** • **stereotactic radiosurgery**

Primary meningeal HPCs are rare, aggressive, dura-based tumors thought to originate from Zimmermann pericytes, which are contractile spindle cells surrounding capillaries and postcapillary venules. These tumors are composed of spindle cells with a rich vascular network, which apparently arises from pericytes, cells of smooth muscle origin that lie around small vessels. The clinical, radiographic, and gross characteristics of these lesions often render them indistinguishable from meningiomas.[30] Such characteristics contributed to their early misclassification by Cushing and Eisenhardt[2] as an angioblastic variant of meningioma. Benign and malignant HPCs exist, and the rarity of these lesions in general has led to considerable confusion in distinguishing between the benign and malignant variants.

In 1954 Begg and Garret[3] reported on the first documented case of a primary intracranial HPC, but meningeal HPCs were not classified as a distinct entity by the WHO until 1993, despite their demonstration of a unique immunohistochemical profile.[10] Observing that peripheral soft-tissue tumors share histopathological features identical with meningeal HPCs ultimately led to the latter's more accurate classification as "mesenchymal nonmeningothelial tumors," which can arise from multiple organ systems.[15,17,28] Moreover, the long-term biological and/or clinical behavior of an HPC differs from that of a meningioma, with its local recurrence rates as high as 91% and a 15-year risk of distant metastasis approaching 70% after surgery alone.[8]

We describe 3 patients with HPCs of the skull base. Neurosurgeons have treated these lesions as meningioma variants for a long time, and certain commonalities in their surgical management apply. Hemangiopericytomas have an aggressive nature, and a different philosophy is used in their optimal treatment. Thus, it is imperative that the surgeon include HPC as part of the differential diagnosis when evaluating patients with dura-based extra-axial lesions of the skull base.

Methods

From the senior author's (C.B.H.) prospectively maintained database, we found 3 cases of skull base HPCs. The 2 men and 1 woman in these cases had a median age of 37 years (range 20–53 years) at the time of their initial presentations. None of these patients has been reported on previously.

Abbreviations used in this paper: GTR = gross-total resection; HPC = hemangiopericytoma; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy.

Two patients had previously undergone resection and had neuropathological confirmation of the diagnosis, whereas 1 patient (Case 3) was a new presentation (Fig. 1). The average number of craniotomies per patient was 2 (range 1–3). Two additional craniotomies were performed for tumor recurrence. Endovascular embolization was used twice (Cases 1 and 3; Fig. 1C–E). In 1 patient (Case 2) a diagnostic angiogram did not reveal a suitable embolization target.

One patient (Case 1) received chemotherapy concurrent with fractionated radiotherapy, 1 patient underwent Gamma Knife surgery after a secondary resection, and 1 patient underwent fractionated radiotherapy after the initial resection. Two patients had intracranial recurrences adjacent to the initial resection site; the most recent recurrence in the patient in Case 1 was unresectable (Table 1). Variations in the presenting symptoms correlated with the location of the lesion in this series of cases.

On follow-up, patients were monitored for changes in their neurological condition and the development of recurrent tumors or metastases. Follow-up neurological assessments were performed at our institution by the senior author (C.B.H.). Follow-up imaging was typically performed 6 months after the initial treatment. After obtaining a number of unchanged scans in any patient, the interval between imaging studies was extended slightly, up to yearly intervals. Clinical evaluations were performed around the time of scheduled follow-up imaging assessments.

Results

Two of the 3 patients treated in this series remained alive after a mean follow-up of 93 months (range 4–181 months; Table 1). The patient in Case 1 was last seen by us 181 months after surgery, and then she was monitored by local physicians, for a total follow-up of 217 months before she ultimately succumbed to her disease. The follow-up interval was approximately 5 years in another patient (Case 2). Before presenting to us with a recurrence, 1 patient (Case 2) suffered from homonymous hemianopia after an initial resection (Fig. 2). A hemorrhage from residual tumor in the surrounding occipital lobe caused a clinical deterioration with complete loss of vision. After decompression and resection, the patient was able to recover some useful vision. In the patient in Case 1 right trigeminal neuropathy

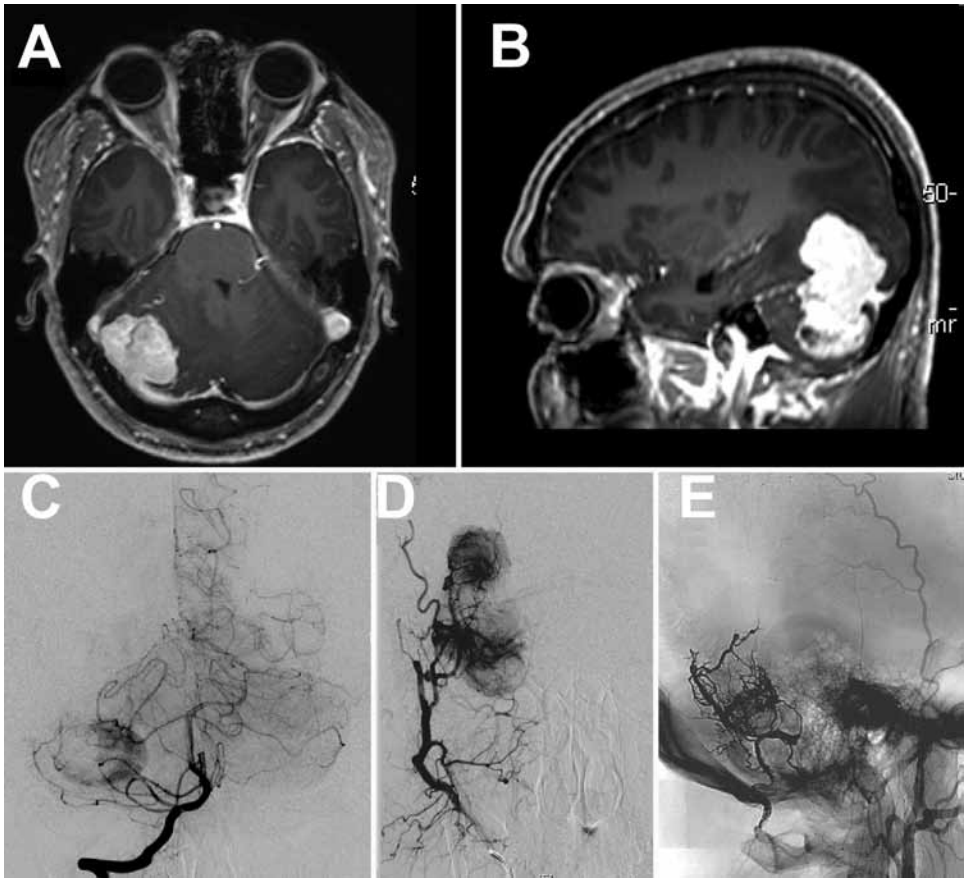

Fig. 1. Case 3. Preoperative axial **(A)** and sagittal **(B)** post-Gd T1-weighted MR images demonstrating a homogeneously enhancing lesion near the right transverse sinus, extending into the supratentorial space and the posterior fossa. Selective right vertebral artery injection angiogram **(C),** posterior-anterior projection, demonstrating tumor blush with feeders from the superior cerebellar artery and anterior inferior cerebellar artery enhancing the posterior fossa component of the tumor. External carotid artery injection angiogram **(D),** posterior-anterior projection, showing feeders and tumor blush from the occipital artery. External carotid artery angiogram **(E),** lateral projection, demonstrating the liquid embolic material used to embolize feeders arising from the occipital artery.

TABLE 1: Summary of demographic and clinical data in 3 patients with HPCs*

Parameter	Case 1	Case 2	Case 3
age (yrs)	20	53	39
sex	F	M	M
initial clinical presentation	headaches, nausea, vomiting, visual field defect, seizures (lt arm)	altered mental status, rt visual field defect	dizziness, disequilibrium
primary location of tumor	rt sphenoid wing, cavernous sinus & middle fossa floor	lt occipital falcotentorial junction	rt tentorial posterior fossa & supratentorial
follow-up (mos)	181	58	4
longest progression-free period (mos)	84	41	4
no. of resections (craniotomies)	3	2	1
reason for repeat craniotomy	2nd: residual tumor; 3rd: recurrence	2nd: recurrence	NA
endovascular embolization	yes	no	yes
chemotherapy	adriamycin	none	none
radiotherapy treatment	fractionated intensity-modulated therapy; total dose 60 Gy	GKS; 16 Gy to 50% isodose line	fractionated intensity-modulated therapy; 33 fractions, total dose 180 Gy

* GKS = Gamma Knife surgery; NA = not applicable.

developed, with abnormal and dysesthetic sensation on the right side of the face due to involvement of the right cavernous sinus by recurring disease.

The longest mean tumor progression–free interval following the initial or secondary resection was 43 months (range 4–84 months).

Discussion

Pathological Features and Presentation

Hemangiopericytomas are rare, aggressive neoplasms that most often involve the musculoskeletal system and skin.[14,15] Intracranial HPCs represent less than 1% of all intracranial tumors and approximately 2%–4% of all meningeal tumors.[1,17,26,28,29] They almost always present as solitary, supratentorial (62%) dura-based lesions often arising from the falx, tentorium, dural sinuses, and skull base. Histopathologically, they are characterized by spindle cells with a rich vascular network, with large, dilated, "staghorn" vascular channels (Fig. 3). Their relative vascularity coupled with their frequent association with vital neural structures often makes GTR challenging.[22,30]

In contrast to meningiomas, whose incidence in female patients predominates, HPCs tend to occur more often in males, with a male/female ratio approaching 2:1.[14,15,29]

Imaging Features

Radiological differentiation of an HPC from a meningioma is important for preoperative planning and subsequent management. Knowing that the differential diagnosis favors HPC has significant influence on the surgical approach, mainly because of the greater risks of severe bleeding and local recurrence that are associated with this tumor as compared with those for a meningioma. Imaging similarities between the 2 tumor types are profound and distinguishing between the two can be difficult. Nevertheless, the combination of characteristic features, such as the presence of internal signal voids, heterogeneous enhancement, and adjacent bony erosion, suggest HPC as a likely diagnosis. Hemangiopericytoma margins are often lobulated, with frequent internal serpentine signal voids and absent calcifications, as compared with meningiomas, in which margins are usually smooth, flow voids are rare, and calcifications occur in 20%–25% of cases.[27] Hemangiopericytomas display a relative paucity of peritumoral edema and have a common angioarchitectural pattern that can be used to distinguish them from meningiomas. The angioarchitecture includes a dual supply from the internal carotid or vertebral and external carotid arteries, with the dominant supply coming from the internal carotid artery branches rather than the primarily external carotid supply seen with meningiomas, numerous corkscrew vessels arising from a main feeder within the tumor, a dense, fluffy, long-lasting tumor stain rather than the sunburst pattern of meningiomas, and no early draining veins.[20]

Multimodal Management

Surgery. Hemangiopericytomas are neoplasms with an aggressive natural history. The optimal method of treatment consists of GTR followed by postoperative radiotherapy. Surgery not only offers immediate relief of mass effect but also allows tissue confirmation of the histopathological diagnosis to differentiate HPCs from other meningiomas. Because of the high vascularity of the lesions, preoperative embolization can sometimes be advantageous. Soyuer et al.[29] reported a superior 5-year local control rate in patients treated with GTR (84%) as compared with the rate in patients treated using subtotal resection (38%).

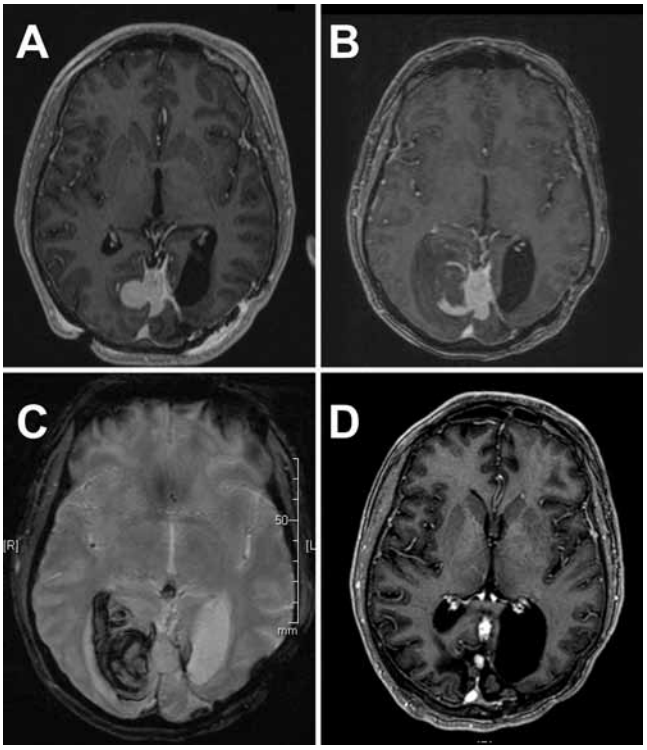

Fig. 2. Case 2. Axial post-Gd T1-weighted MR image **(A)** obtained 3 months after an initial resection, demonstrating a homogeneously enhancing nodular tumor arising from the occipital falx near the falcotentorial junction. Follow-up image **(B)** obtained after 1 year showing recurrent tumor growth and hemorrhage into the adjacent occipital lobe, better seen on a gradient-echo weighted sequence **(C)**. Follow-up image obtained after 58 months, demonstrating a local small nodular recurrence **(D)**.

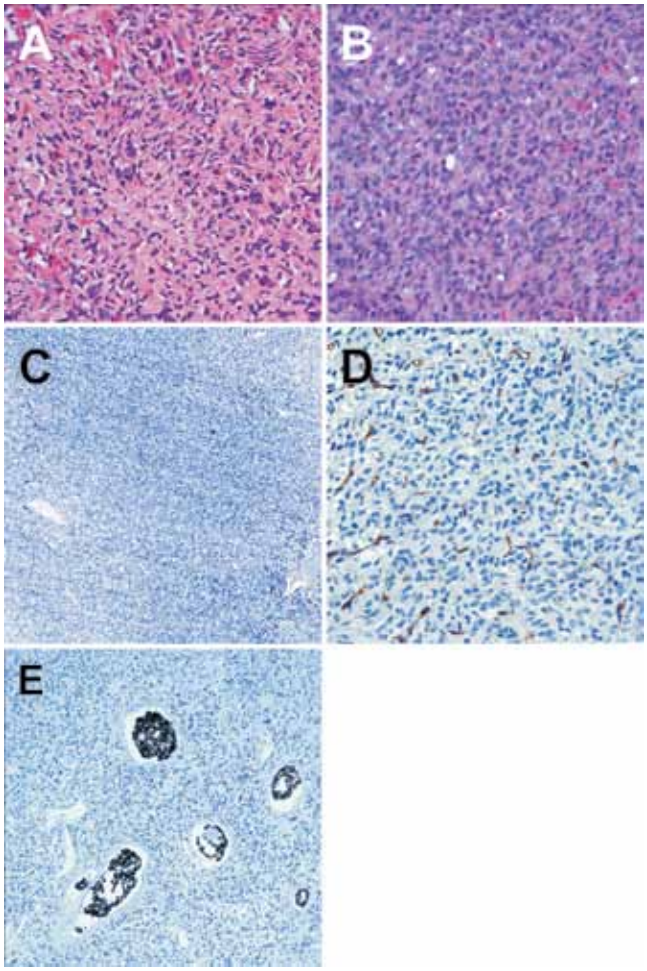

Fig. 3. Case 3. Photomicrographs demonstrating the histopathology of HPCs. These lesions **(A and B)** are composed of elongated spindle- to carrot-shaped cells with pleomorphic nuclei and eosinophilic cytoplasm. Original magnification × 30. Immunohistochemical markers for meningiomas are mainly negative in this tumor: epithelial membrane antigen **(C)** and CD34 **(D)**. Hemangiopericytoma is characterized by large dilated "staghorn" vascular channels **(E)**, shown here after embolization with liquid embolic material. H & E **(E)**. Original magnification × 30 **(A, B, and D)**, × 10 **(C)**, and × 20 **(E)**.

Radiotherapy. The propensity of HPCs to arise from the skull base or in close association with the dural sinuses can often preclude GTR. Consequently, postoperative radiotherapy has gained increasing acceptance in the initial management of these tumors. Two groups reported that radiotherapy after an initial resection extended the mean time to local recurrence from 34 to 75 months and extended overall survival from 62 to 92 months.[6,12] Dufour et al.[7] reported in their series that HPCs recurred after an average interval of 74 months if they were subjected to irradiation after the first surgical treatment, as compared with an average of 29 months if they were not treated with radiotherapy after initial resection.

Radiotherapy in addition to the quality of resection and the duration of follow-up affects local recurrence following the resection of HPCs.[7,11–13,21,25] The response of HPCs to radiotherapy is dose dependent, with overall treatment doses of 45 Gy or higher resulting in superior local control.[6] The current SRT treatment plan used in most centers delivers 46–52 Gy fractionated over 25–35 sessions. In recent years, SRT has emerged as a viable salvage strategy for the treatment of recurrent intracranial HPCs, ideally less than 3 cm in their greatest dimension. A focal fractionated radiation dose of 50 Gy is recommended as a standard to prevent recurrence.[7,12,23]

Stereotactic Radiosurgery. Gamma knife radiation has occasionally been used as an upfront therapy for the treatment of HPC, and the literature supports a role for this treatment in recurrent lesions, as disease-free survival tends to be higher in cases of newly diagnosed HPCs treated with a combination of resection and adjuvant postoperative SRT.[6,12] Sheehan et al.[26] demonstrated in a series of 14 patients with 15 HPCs treated with radiosurgery, 7 of which had been subjected to radiotherapy, an 80% local control rate for recurrent intracranial HPCs using Gamma Knife surgery, with a median time to local recurrence of 21 months. Authors of this study also demonstrated Kaplan-Meier survival rates of 76% and 100% 5 years after Gamma Knife surgery but reported remote metastases in 29% of the patients, and thus concluded that local tumor control afforded by radiosurgery provided seemingly little protection from distant metastases.[26] In a later paper the Virginia group reported on a series of patients with an 81% 5-year survival rate after radiosurgery

but a tumor control rate of only 29% at the 5-year mark.[23] Prior fractionated irradiation or a radiosurgical prescription dose did not correlate with tumor control. In 4 (19%) of 21 patients, extracranial metastases developed. Stereotactic radiosurgery is most effective for treating tumors < 8 cm^3 (< 2 cm in diameter) in volume with radiation doses of 15 Gy or higher at the 50% isodose line.[28] Recurrent lesions ≥ 3 cm in their greatest diameter are best treated by reresection followed by postoperative SRS, whereas recurrent lesions < 3 cm in their greatest diameter can be successfully controlled by SRS alone. Unfortunately, although the addition of either SRT or SRS seems to confer superior local control over surgery alone, these therapies do not appear to provide any significant protection against the development of distant metastases.[6,26] In patients with advanced, symptomatic extracranial HPC, radiotherapy may also play an important palliative role. Based on the data summarized in Olson et al.[23] it appears that a higher margin dose of at least 18–20 Gy should be recommended to avoid early recurrence.

Chemotherapy. The role of chemotherapy in the treatment of systemic HPC is unclear, and the collective experience documented in the literature is limited. Hemangiopericytoma can be considered a soft-tissue sarcoma, and progress in the chemotherapeutic treatment of this entity has been unexceptional.[5] Anthracycline and ifosfamide have been established as the most active agents for metastatic sarcoma, with ongoing debate about the advantage of combination versus single-agent chemotherapy in the treatment of soft-tissue sarcoma. However, both a meta-analysis and a recent randomized phase III trial suggest that single-agent doxorubicin is the treatment of choice for advanced soft-tissue sarcomas.[4,19] Other chemotherapeutic agents used include doxorubicin and dacarbazine, both with equally poor results.[9] There have been some attempts to treat HPC with interferon immunomodulatory therapy,[16,18] as α-interferon appears to have antiangiogenic activity by slowing endothelial proliferation and migration and by suppressing the production of 2 proangiogenic factors, interleukin-8 and basic fibroblast growth factor. The investigation of other antiangiogenic agents, for example, bevacizumab or sunitinib, could be considered as well.[5] Another report describes monotherapy utilizing dasatinib as a molecular therapy targeting the Src gene–related tyrosine kinases, which led to a stable tumor after multiple recurrences in 1 case.[24]

Even most HPCs treated with GTR and adjuvant SRT tend to locally recur by 6 years after treatment.[6,12] However, cases of local recurrence and distal metastases have been reported more than 20 years out from the initial diagnosis. Therefore, long-term follow-up with annual serial imaging is suggested for optimal management. Screening should not be limited to the intracranial compartment, as extracranial metastases tend to represent a relatively common occurrence in the natural history of HPC.

Conclusions

Intracranial HPCs, frequently located along the dural sinuses along the skull base, are rare, aggressive CNS neoplasms that are difficult to distinguish from meningiomas based on both imaging and gross characteristics. Once thought to be histopathologically related to meningiomas, these lesions have been reclassified as mesenchymal nonmeningothelial tumors. Hemangiopericytomas seem to have an inevitable tendency to recur locally and metastasize distally. The mainstay of therapy remains aggressive GTR at the initial surgery. Postoperative adjuvant radiotherapy should be offered to all patients, regardless of the degree of resection achieved. Chemotherapy can be considered, but no clear data exist regarding its efficacy, and consensus about the appropriate agent or timing of therapy is lacking. Frequent imaging follow-up is necessary to discover recurrences early, and a follow-up interval of 6 months is recommended in most cases.

Recurrent intracranial disease management must be tailored to the size and location of the local recurrence and the overall systemic disease burden. Postoperative radiation treatment does not confer any significant protection against the development of distant metastases, making long-term clinical and radiographic follow-up in these patients necessary.

Local recurrences and distal metastases may develop long after the initial treatment, sometimes after several years, underlining the need for long-term follow-up.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: Schirmer. Drafting the article: Schirmer. Critically revising the article: both authors. Reviewed final version of the manuscript and approved it for submission: both authors. Study supervision: Heilman.

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Treatment of unresectable skull base meningiomas with somatostatin analogs

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Object. The standard surgical treatment for meningiomas is total resection, but the complete removal of skull base meningiomas can be difficult for several reasons. Thus, the management of certain meningiomas of the skull base—for example, those involving basal vessels and cranial nerves—remains a challenge. In recent reports it has been suggested that somatostatin (SST) administration can cause growth inhibition of unresectable and recurrent meningiomas. The application of SST and its analogs is not routinely integrated into standard treatment strategies for meningiomas, and clinical studies proving growth-inhibiting effects do not exist. The authors report on their experience using octreotide in patients with recurrent or unresectable meningiomas of the skull base.

Methods. Between January 1996 and December 2010, 13 patients harboring a progressive residual meningioma (as indicated by MR imaging criteria) following operative therapy were treated with a monthly injection of the SST analog octreotide (Sandostatin LAR [long-acting repeatable] 30 mg, Novartis). Eight of 13 patients had a meningioma of the skull base and were analyzed in the present study. Postoperative tumor enlargement was documented in all patients on MR images obtained before the initiation of SST therapy. All tumors were benign. No patient received radiation or chemotherapy before treatment with SST. The growth of residual tumor was monitored by MR imaging every 12 months.

Results. Three of the 8 patients had undergone surgical treatment once; 3, 2 times; and 2, 3 times. The mean time after the last meningioma operation (before starting SST treatment) and tumor enlargement as indicated by MR imaging criteria was 24 months. A total of 643 monthly cycles of Sandostatin LAR were administered. Five of the 8 patients were on SST continuously and stabilized disease was documented on MR images obtained in these patients during treatment (median 115 months, range 48–180 months). Three of the 8 patients interrupted treatment: after 60 months in 1 case because of tumor progression, after 36 months in 1 case because of side effects, and after 36 months in 1 case because the health insurance company denied cost absorption.

Conclusions. Although no case of tumor regression was detected on MR imaging, the study results indicated that SST analogs can arrest the progression of unresectable or recurrent benign meningiomas of the skull base in some patients. It remains to be determined whether a controlled prospective clinical trial would be useful.
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Key Words • **meningioma** • **skull base** • **somatostatin** • **hormone therapy**

Meningiomas represent around 20% of all intracranial tumors and have a 10-year recurrence rate of 20%–50% despite aggressive surgery and irradiation.[14] The standard surgical treatment for meningiomas is total resection. However, many tumors are not amenable to surgery given their deep location or proximity to delicate structures.[25] The complete removal of skull base meningiomas can be especially difficult when basal vessels and cranial nerves are involved. For inaccessible tumors and those with aggressive histological or clinical features, radiation therapy is another important treatment option. Most authors recommend using standard external beam radiation therapy, whereas radiosurgical techniques may also be appropriate in selected patients.[1,8] Additionally, chemotherapy is being explored as another treatment option for unresectable or growth-progressive residual meningiomas.[4,32] In recent reports it has been suggested that SST administration can cause growth inhibition of unresectable and recurrent meningiomas;[3,11] however, the application of SST and its analogs has not been routinely integrated into standard treatment strategies for meningiomas. Clinical studies clearly proving growth-inhibiting effects do not exist to date. We report on our experience using Sandostatin LAR in 8 patients with recurrent meningiomas of the skull base.

Abbreviations used in this paper: DTPA = diethylenetriamine pentaacetic acid; LAR = long-acting repeatable; PFI = progression-free interval; PFS = progression-free survival; SST = somatostatin; SSTR = SST receptor.

Methods

Between January 1996 and December 2010, 13 patients harboring progressive residual meningiomas (according to MR imaging criteria) following operative ther-

apy were treated with a monthly injection of the SST analog octreotide (Sandostatin LAR 30 mg, Novartis). Eight of the 13 patients had a meningioma of the skull base and were analyzed for this study. Postoperative tumor enlargement was documented in all patients on MR images obtained before the initiation of SST therapy. The term "growth progressive" in this study is used for tumors that have shown progression of growth according to MR imaging criteria. The PFI before SST treatment was defined as the time range from the last surgery to tumor enlargement visible on MR imaging and was not defined clinically; PFI during SST treatment was defined as the time from the onset of SST treatment to tumor progression according to MR imaging. All patients had actively growing residual tumors according to MR imaging at the onset of SST therapy. Informed consent was obtained from all treated patients before the application of SST. To decide which patients were suitable for treatment SST scintigraphy using ^{111}I-labelled DTPA-octreotide (according to Hildebrandt et al.[9]) was performed in all patients, showing a high uptake. Tumor growth during SST therapy was monitored by serial MR imaging every 12 months. The PFI after the onset of SST therapy was defined as the time range from the first SST injection to tumor enlargement according to MR imaging and not clinical changes.

Results

A summary of the cases is featured in Table 1. The mean age of our cohort at the beginning of SST therapy was 50.5 years (median 52 years). Seven of the 8 patients were women. Three patients underwent surgery 1 time; 3 patients, 2 times; and 2 patients, 3 times (mean number of surgeries 1.875). The mean time from the initial diagnosis to the onset of SST therapy was 5.5 years (median 3 years, range 0.5–21 years). The most common tumor location was the sphenoid wing (5 of 8 patients). Histological verification of a meningioma by resection or biopsy was performed in all patients. All tumors were benign (WHO Grade I), and no patient received radiation or chemotherapy either before or during SST treatment. The mean time from the last meningioma operation to tumor enlargement on MR imaging was 24 months. Six hundred forty-three monthly cycles of SST were administered. Two of 8 patients interrupted treatment without signs of tumor progression, after 36 months in 1 case because of side effects and after 36 months in 1 case because the health insurance company denied cost absorption. Six of 8 patients were continuously on SST. Five of these 6 patients had stabilized disease documented on MR images obtained during treatment to date (median 115 months, mean 102 months, range 48–180 months). One of 6 patients showed tumor growth on MR imaging after 60 months of therapy. No case of tumor regression was detected on MR imaging, and no case showed clinical improvement during SST treatment. Sandostatin LAR was reasonably well tolerated, except in 1 patient who experienced psychiatric side effects.

Discussion

It is important that more effective medical therapy is developed for growth-progressive residual or recurrent meningiomas. There is a subgroup of patients that has persistent recurrences despite multiple resections and/or progress through radiotherapy. The use of chemotherapy might obviate the need for further surgical procedures in certain patients and offer another treatment option in patients with tumor progression through surgery and irradiation.[30] Although early attempts at chemotherapy with traditional antineoplastic agents and hormonal approaches have been disappointing, treatment with hydroxyurea may prove to be efficacious.[15,32]

In the current study, we used an alternative method of hormone therapy by using the SST analog octreotide (Sandostatin LAR). Somatostatin is a natural peptide hormone secreted in various parts of the human body. The biological effects of SST are mediated through its specific receptors (SSTRs 1–5).[19,20] Endogenous SST's short half-life in circulation (1–3 minutes) makes it difficult to use continuously and has resulted in the development of synthetic analogs. The cyclic octapeptide octreotide is more resistant to peptidases, and its half-life and hence its biological activity is substantially longer than for native SST (1.5–2 hours vs 1–2 minutes). The development of a depot formulation of octreotide, Sandostatin LAR, which was

TABLE 1: Summary of data in 8 patients with skull base meningiomas*

Case No.	Age (yrs), Sex	Lesion Location	No. of Ops Since Initial Dx	Time From Dx to Last Op (yrs)	PFI After Last Op (mos)	PFI on SST (mos)	Status
1	63, M	spw	3	21	70	180	stable disease
2	53, F	spw	2	5	24	120	stable disease
3	52, F	spw	3	8	36	115	stable disease
4	55, F	spw	1	3	36	48	stable disease
5	37, F	spw	2	3	24	48	stable disease
6	52, F	optic nerve	1	0.5	6	36	stable disease†
7	46, F	petroclival	1	1.25	15	36	stable disease†
8	46, F	petroclival	2	2	16	60	progression after 60 mos

* spw = sphenoid wing.

† Interruption of SST therapy without tumor enlargement.

administered up to 30–60 mg once every 4 weeks, has to a large extent eliminated the need for daily injections.[31] There are 5 different G-protein–coupled SSTR subtypes (SSTRs 1–5), and the majority of meningioma cells show positivity for at least 1 of the 5 SSTR subtypes.[18–20,23,24]

One cell proliferation study evaluating a possible role of blocked SSTR in the control of human meningioma cell growth showed a significant inhibition of DNA synthesis in 4 of 5 tissue cultures, and the authors suggested promising effects against meningiomas.[2] In contrast, another analysis showed no direct growth-inhibiting action on cultured human meningioma cells. Rather, there was a slight but significant stimulation of growth in the presence of SST. The authors concluded that therapeutic trials in patients with recurrent or inoperable meningiomas with somatostatin analogs must be performed with caution.[13] The first case reports concerning the obvious effect of SST on meningioma have been published since 1989.[7,26,27] One report showed rapid clinical improvement in patients on octreotide, although no radiological signs of tumor regression were detected.[10] In contrast, De Menis et al.[5] documented the growth of a meningioma during treatment with octreotide for acromegaly. Octreotide effectively suppressed growth hormone secretion but could have stimulated the growth of the tentorium meningioma since SST did not significantly influence the in vitro proliferation of the patient's cultured tumor cells. The results of our study are similar to those of Chamberlain and colleagues,[3] who also used Sandostatin LAR in 16 patients with recurrent intracranial meningiomas. Ten of the 16 patients responded to or stabilized on SST (median 27 weeks, range 5–39 weeks), while disease in the other 6 patients progressed. Five of our 6 patients remained stable on SST (median 115 months, range 48–180 months), and disease progressed in only 1 patient after 60 months of treatment. The overall PFS was 44% (7 of 16 patients) at 6 months in the Chamberlain and colleagues series. The PFS in our study was 100% at 48 months and 83.3% (5 of 6 patients) at a median of 87.5 months, resulting in a median PFI of 87.5 months during SST treatment (compared with a median PFI of 30 months in these patients before SST therapy). The more extended follow-up of responsive patients in our study, as compared with that in the study of Chamberlain et al. (median 115 vs 5 months), verifies that stabilization of disease with SST in responsive patients can be quite durable. In contrast to the collective sample of Chamberlain et al., none of our patients had radio- or chemotherapy after surgery (denied by either the radiooncologists or the patients themselves). In their study, 14 of 16 patients underwent surgery, 13 of 16 had radiation therapy, and 12 of 16 had chemotherapy before beginning SST therapy. They treated 8 of 16 patients with malignant meningiomas, whereas we treated exclusively benign tumors. Chamberlain and colleagues' patients received 2–15 cycles of SST (total 92 cycles, median 4.5 cycles) with minimal toxicity. In our patients, 36–180 cycles (total 643 cycles, median 54 cycles) were administered, and we documented 1 patient with newly diagnosed depression during SST treatment. This patient wished to interrupt the treatment after 36 cycles, although this side effect is not described as a typical one and no tumor progression was detected.

Our results suggest that Sandostatin LAR might have modest activity in patients with unresectable or progressive meningiomas of the skull base. The strength of our data is weakened because of the low number of treated patients. In addition, the natural history of meningiomas is such that unpredictable intervals of slow growth or no growth can occur in some patients. Zeidman et al.[33] found 2 of 21 patients without tumor growth during a mean postoperative interval of 3.64 years (range 2.08–10.83 years). One study examining 33 patients with meningiomas showed a median relative growth rate of 14.18% per year, and the median tumor doubling time was 5.228 years.[16] Another study of 41 patients with meningiomas treated conservatively showed a comparable mean annual growth rate (14.6%, range 0.48%–72.8%), and the mean tumor doubling time was 21.6 years.[17] The median postoperative time to tumor enlargement on MR imaging among 38 patients with subtotally resected residual petroclival meningiomas was 66 months (87.5 months in our report), and the 5-year PFS rate (indicated by MR imaging criteria) was 60% (75% in our study).[12]

Therapeutic costs for Sandostatin LAR are around US $2000/month for each injection. Compared with stereotactic radiosurgery (around US $6500 for a single-fraction treatment or US $3500 + US $1000 for every 2 additional fractions in hypofractionated therapy), the SST therapy is more costly after 4–6 months of treatment (according to the table of charges for physicians in Germany). Note, however, that radiotherapy after postoperative tumor enlargement on MR imaging was not performed in our 8 patients with skull base meningiomas (denied in 2 cases by the radiooncologists and in 6 cases by the patients themselves).

Somatostatin analogs like octreotide (Sandostatin LAR) are traditionally used to treat acromegaly and neuroendocrine tumors of the gastrointestinal tract.[5,22] About 88% of the meningiomas analyzed (37 of 42 lesions) were positive for at least 1 of the 5 SSTR subtypes, displaying a variable pattern of mRNA expression of the different SSTR subtypes.[2] Messenger RNA from SSTRs 1 and 2 was the most frequently detected, and in half of the meningioma cells 3 or more SSTRs were detected.[2,6] Especially the binding of SST on SSTR2 decreases the production of vascular endothelial growth factor with a reduction in peritumoral edema and is perhaps one factor inhibiting meningioma growth.[6,21,29] The different receptor subtype binding affinities seem to result in different biological and clinical activities. The effects of the SST analogs are mainly mediated by interaction with SSTRs 2 and 5, while the new SST analog pasireotide (SOM230) shows higher binding capacity toward SSTRs 1, 2, 3, and 5 with no agonist activity at SSTR4.[28] As a consequence, this substance might have a higher growth-inhibiting potential on meningioma cells than Sandostatin LAR.

Conclusions

Data suggest that SST analogs might have modest activity against recurrent and inoperable skull base meningiomas and could induce long-term stabilization of tumor growth in some patients. Although no case of tumor regression was detected in our study, the results indicate

that Sandostatin LAR may arrest the progression of unresectable or recurrent benign meningiomas of the skull base. Further clinical trials (prospective and randomized) with larger patient cohorts and longer follow-up periods will be necessary to confirm the activity of SST analogs against meningiomas.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Schulz. Acquisition of data: Mathieu. Analysis and interpretation of data: Schulz. Critically revising the article: Mauer. Reviewed final version of the manuscript and approved it for submission: Mauer. Study supervision: Kunz.

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Meningiomas involving the optic canal: pattern of involvement and implications for surgical technique

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Object. Juxtasellar meningiomas frequently extend into the optic canal. Removing these meningiomas from the optic canal is crucial for favorable visual outcome.

Methods. The authors performed a retrospective analysis of 45 patients with anterior and middle fossa meningiomas with involvement of the optic pathway in whom surgery was performed by the senior author (O.A.M.) during the period from 1993 to 2007. Extent of resection and recurrence rates were determined by pre- and postoperative MR imaging studies. Visual outcomes were evaluated with full ophthalmological examinations performed before and after surgery.

Results. Forty-five patients (31 women and 14 men) were involved in this study; their mean age was 51.6 years. Patients were followed for a mean of 29.8 months (range 6–108 months). No surgery-related death occurred. The average tumor size was 3.1 cm. Total resection of the tumor (Simpson Grade I) was achieved in 32 patients (71.1%). Gross-total resection (Simpson Grades II and III) was achieved in 13 patients (28.9%). Only 1 patient harboring a left cavernous sinus meningioma had tumor recurrence and underwent repeat resection. Meningiomas extended into 58 optic canals in these cases; 13 patients showed extension into both optic canals. Visual disturbance was the main presenting symptom in 37 patients (82.2%); 8 patients had normal vision initially. Visual improvement after surgery was seen in 21 (57%) of 37 patients and in 27 (34.6%) of 78 affected eyes. Vision remained unchanged in 48 (61.5%) of 78 eyes. Transient postoperative visual deterioration occurred in 2 eyes (2.6%), with recovery to baseline over time. Only 1 (1.3%) of 78 eyes had permanent visual deterioration after surgery. The visual outcome was affected mainly by the tumor size, the preoperative visual status, and the duration of symptoms.

Conclusions. Involvement of the optic canal in meningiomas is frequent. It occurs in a wide variety of anterior skull base meningiomas and it can be bilateral. It is a prominent factor that affects the preoperative visual status and postoperative recovery. Decompression of the optic canal and removal of the tumor inside is a crucial step in the surgical management of these tumors to optimize visual recovery and prevent tumor recurrence.
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Key Words • **meningioma** • **surgical technique** • **optic canal** • **optic pathway** • **brain tumor surgery**

Visual disturbance due to optic nerve compression is the initial presentation for many patients with anterior and middle fossa meningiomas. Optic nerve compression is variable depending on the size and the location of the tumor; bilateral optic nerve involvement and optic chiasm compression further add to the complexity of the surgical decision-making process.[2,4,9,19,25,26,28,31] Optic canal involvement by these tumors is not rare, and reports have described unilateral or bilateral optic canal extension.[2–4,32] The primary goal of surgery is total removal of the tumor, with improvement or preservation of the preoperative visual status.[1–3,24,26,28] In this setting, complete nontraumatic decompression of the optic pathway is of paramount concern, with particular attention paid to the full preservation of the attendant delicate blood supply of the optic nerve and chiasm.[2,3,8,21,24,27]

Several reports have addressed the prognostic criteria for visual recovery in patients with these tumors, with series documenting a 25% to 80% chance of visual improvement depending on tumor size, location, extension, preoperative visual status, duration of symptoms, and the surgical technique.[1,2,4,5,7,19,25,26,29,30] Optic canal decompression is an important step to optimize visual recovery and

Abbreviations used in this paper: ACA = anterior cerebral artery; CA = carotid artery; COZ = cranioorbitozygomatic; ICA = internal carotid artery; MCA = middle cerebral artery; OphA = ophthalmic artery; SHA = superior hypophyseal artery.

extent of tumor resection. It can be achieved extradurally, intradurally, or with a combined approach often requiring anterior clinoidectomy.[1,2,4,24,29] Further surgical maneuvers include opening of the bony canal, sectioning the falciform ligament, and opening of the optic nerve sheath. In this study we review 45 patients with meningiomas extending into the optic canal, and we discuss the pattern of involvement of the canal and implications for method of decompression as well as the outcome.

Methods

Between 1993 and 2007, 45 patients (31 women and 14 men) with meningiomas involving the optic canal underwent surgery performed by the senior author. Patients ranged from 30 to 79 years of age (mean 51.6 years). Clinical characteristics of the patients are presented in Table 1. Meningiomas involving the optic canals are summarized in Table 2. Thirteen patients showed bilateral optic canal involvement, and 7 cases were recurrent tumors previously operated on elsewhere. Patients with optic canal decompression with no tumor inside the canal were excluded from the study.

Preoperative imaging studies (MR and CT studies of the brain) were retrospectively analyzed to define tumor size, extent and pattern of optic canal involvement (correlated with operative notes), and the origin and extension of the tumor (Fig. 1). Full ophthalmological assessment was done preoperatively, in the early postoperative evaluation, and through the follow-up examinations. It included visual acuity, visual field testing, ocular motility, and fundoscopy. The WHO criteria to evaluate vision were applied (Table 3).[6] Data regarding the presence of a dissection plane between the tumor and optic pathway, the degree of optic canal involvement, timing of intraoperative optic canal decompression (early extradural or late intradural), and extent of tumor resection were collected from the operative reports. Early postoperative CT and MR imaging were done for all patients to determine the extent of tumor resection. All patients were followed up with serial clinical and MR imaging examinations (mean follow-up 29.8 months, range 6–108 months).

TABLE 1: Clinical characteristics of 45 patients with meningiomas*

Characteristic	Value
sex (no.of pts)	
M	14
F	31
age range	30–79 yrs (mean 51.6 yrs)
follow-up range	6–108 mos (mean 29.8 mos)
no. of pts w/ main presenting Sx	
visual disturbances	37
headache	2
migraine	1
vertigo	1
epilepsy	2
trigeminal neuralgia	1
duration of Sx	1 mo–5 yrs (mean 17.3 mos)

* pts = patients.

TABLE 2: Tumor location and involvement of optic canal

Feature	Value
tumor size	0.5–6 cm (mean 3.1 cm)
origin of meningioma	
clinoidal	11 pts (3 recurrent cases); Type III in 3 pts (2 recurrent cases)
tuberculum sellae	13 pts
planum sphenoidale	5 pts (1 recurrent case)
diaphragma sellae	2 pts
sphenoid wing	7 pts (3 recurrent cases)
cavernous sinus	4 pts
sphenopetroclival	2 pts
en-plaque tumor of anterior skull base	1 pt
optic canal involvement	
unilat meningioma	58 canals
rt side	32 pts
lt side	12 pts
bilat meningiomas	20 pts
tuberculum sellae	13 pts
planum sphenoidale	7 pts
diaphragma sellae	2 pts
clinoidal	2 pts
partial involvement	47 canals
complete involvement	11 canals
optic nerve compression	78 optic nerves
unilat	12 pts
bilat	33 pts

Technical Considerations

The Approach. The COZ approach was used for meningiomas originating lateral to the optic nerve, and was tailored to the size and extension of the tumor. In our experience, this approach facilitates dissection in spaces between the optic nerve and the CA, lateral to the CA in the cavernous sinus, and between both optic nerves, and allows for both extradural and intradural dissection. It was used in 24 patients with meningiomas of the anterior clinoid, sphenoid wing, cavernous sinus, or sphenopetroclival region. We prefer the supraorbital approach for meningiomas located in the midline. The craniotomy in this approach incorporates the orbital rim, the anterior portion of the orbital roof, and the adjacent frontal bone.[18] The supraorbital approach was used in 21 patients harboring meningiomas of the tuberculum sellae, planum sphenoidale, diaphragma sellae, or an en-plaque meningioma.

Optic Canal Unroofing and Clinoidectomy. Anterior clinoidectomy and removal of the bony optic canal was performed either extradurally, intradurally, or as a com-

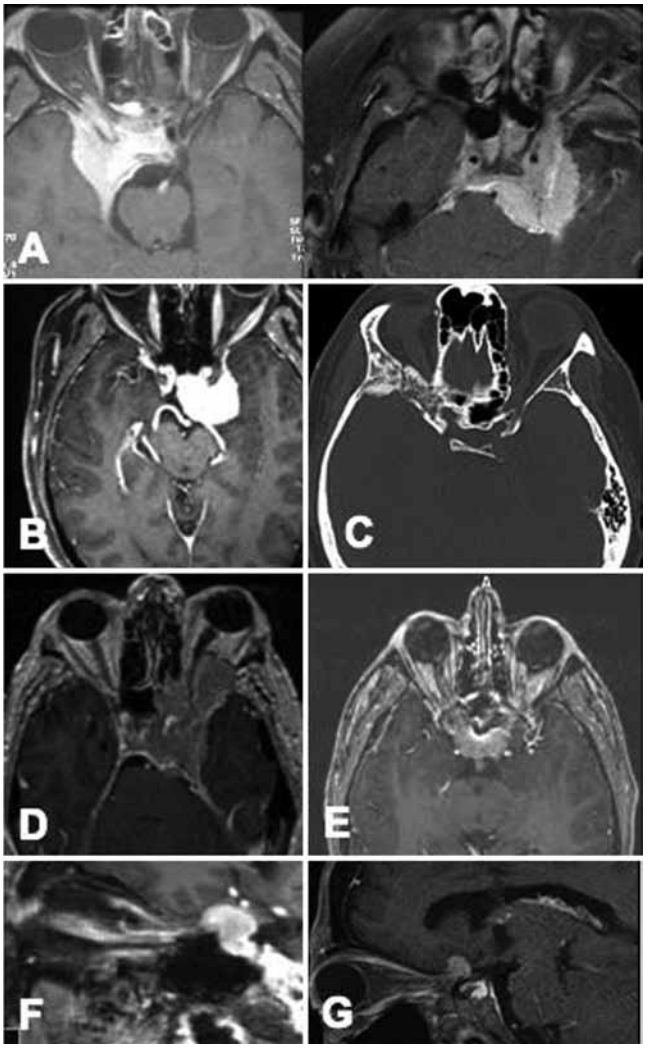

Fig. 1. Preoperative neuroimages showing optic canal involvement by different tumors. **A:** Axial MR images of 2 examples of sphenopetroclival meningioma with involvement of the optic canal. **B:** Axial MR image of a clinoidal meningioma involving the optic canal both medial and lateral to the optic nerve. **C:** Axial CT scan of a right sphenoid wing meningioma with bony involvement of the right optic canal. **D:** Axial MR image of a cavernous sinus meningioma extending into the orbit along the optic canal and superior orbital fissure. **E:** Axial MR image of a tuberculum sellae meningioma with bilateral involvement of the canal. **F:** Oblique MR image demonstrating a tuberculum sellae meningioma with extension into the canal. **G:** Oblique MR image of a recurrent clinoidal meningioma involving the optic canal.

bination of both. After the COZ osteotomy is completed, the microscope is introduced and the remainder of the sphenoid ridge is drilled away, opening the superior orbital fissure. Drilling is continued extradurally to unroof the optic canal and disconnect the optic strut, allowing the anterior clinoid process to be removed extradurally. A diamond drill is used for unroofing of the optic canal, with copious irrigation to prevent thermal injury of the optic nerve. Tumors invading the bone, extending into the cavernous sinus, and or into the orbit can be resected extradurally. The release of a limited amount (30–40 ml) of CSF through a preoperatively placed lumber drain eliminates the need for brain retraction at this stage. Intradural unroofing of the optic canal follows the same principles and is preferred for meningiomas that are located medial to the optic nerve and resected through the supraorbital approach. In some circumstances when there is marked hyperostosis due to bone invasion by meningioma, anterior clinoid removal is started extradurally and completed once the dura mater is opened.

Dissection and Decompression of the Optic Apparatus. The initial steps of intradural dissection include tumor exposure, devascularization, internal debulking, and resection. Brain retraction can be avoided with adequate brain relaxation, which is achieved by partial drainage of CSF through a lumbar catheter or through an opening made in the arachnoid cisterns. Only the small amount of CSF required for brain relaxation should be removed, because the presence of fluid in the arachnoid cisterns facilitates their dissection. Dissection of the tumor from the optic pathway, the CA, the pituitary stalk, and the hypothalamus should follow these arachnoid planes.

The optic nerve may be displaced in several ways. Common patterns of displacement include inferior and medial compression, or elevation by tumor located between the CA and the optic nerve. The nerve may be totally encased by tumor; however, under high microscopic magnification an arachnoid plane can often be established, allowing dissection between the tumor and the optic nerve. In these cases of optic nerve encasement, it is easier to begin dissection from the chiasm and continue toward the optic canal. Removing the tumor inside the optic canal requires drilling the bony canal, opening the falciform ligament, and opening the optic nerve sheath (Fig. 2). Intraorbital extension of the tumor can be removed by following the tumor through the canal into the orbit. Postoperative visual loss generally results from compromise of the vascular supply to the chiasm or the nerve. Particular attention should be directed to preservation of all blood vessels encountered, because the vascular supply to the optic system may course within or around the tumor. The inferior group of vessels arising from the CA is the sole blood supply to the inferior decussating fibers of the chiasm.[8]

Results

Optic Canal Involvement

Tumor extension into the optic canal was seen in 45 patients with anterior and middle fossa meningiomas. In 13 patients there was tumor extension bilaterally, for a total of 58 involved optic canals. Tumor was involving the entire length of the optic canal in 11 sides, and there was direct extension of tumor to the intraorbital compartment in 4.

Twenty sides showed optic nerve compression, but without optic canal involvement, for a total of 78 optic nerves/eyes with tumor compression.

Tumor Location, Approach Selection, and Extent of Resection

The average tumor size was 3.1 cm, with a range of 0.5–6 cm. The origins of the meningiomas involving the canal are summarized in Table 2.

TABLE 3: Criteria for visual changes*

WHO Category	Degree of Vision Changes	Visual Acuity w/ Correction	Definition
normal vision	none	≥20/25	range of normal vision
	slight	<20/25	near-normal vision
low vision	moderate	<20/70	moderate/low vision
	severe	<20/200	severe low vision; FC at ≤6 m
blindness (1 or both eyes)	profound	<20/400	profound low vision or moderate blindness; FC at ≤3 m
	near-total	<3/200	severe or near-total blindness or FC at ≤1 m, or HM at ≤5 m
	total	NLP	total blindness, including absence of eye

* Classifications based on the system of Govsa et al. Abbreviations: FC = finger counting; HM = hand motion; NLP = no light perception.

The COZ approach was used in 24 patients harboring clinoidal, sphenoid wing, cavernous sinus, and sphenopetroclival meningiomas. Extradural anterior clinoidectomy and opening of the bony optic canal was done in 22 patients, whereas in 2 patients the anterior clinoidectomy was performed extradurally and opening of the bony canal was done intradurally. In 2 cases (Type III clinoidal meningioma, cavernous sinus meningioma), tumor within the optic canal was resected extradurally.

The supraorbital approach was used in 21 patients harboring diaphragma sellae, tuberculum sellae, planum sphenoidale, and en-plaque anterior skull base meningiomas, with 2 of these patients undergoing bifrontal craniotomies. In 2 cases of tuberculum sellae meningioma, resection of the part of the tumor inside the optic canal was achieved without drilling the bony canal. A good arachnoid plane of dissection could be achieved in most cases and the tumor could be safely dissected from the optic apparatus, the CA and its branches and perforating vessels (especially those supplying the optic chiasm), the pituitary stalk, and in some instances from the hypothalamus.

Early postoperative CT and MR imaging studies of the brain were used to confirm the extent of tumor resection. Simpson Grade I tumor resections were achieved in 32 patients (71.1%). Gross-total resections (Simpson Grades II and III) were achieved in 13 patients (28.9%). Among 7 patients with recurrent meningiomas, total resection was achieved in 4 cases, whereas gross-total resection was achieved in the other 3 cases. In 3 cases with recurrent meningioma, the cause of recurrence was thought likely to be a result of failure to remove the portion of tumor extending into the optic canal. Postoperatively, there were no recurrences in cases in which radical tumor resection was performed. Tumor recurred in 1 patient with residual tumor in the left cavernous sinus, and reexcision of the tumor was performed 4 years later.

Ophthalmological Presentation and Outcome

Visual disturbances were the main presenting symptom in 37 patients (82%). Tables 4 and 5 summarize the preoperative and the postoperative visual status. Visual outcomes in the 58 optic canals with tumor involvement were variable based on preoperative visual symptoms. Preoperative vision was intact in 3 eyes, and remained the same postoperatively. There was slight visual loss preoperatively in 23 eyes. Of these, 6 improved to normal vision, 14 remained stable, 2 showed transient worsening,

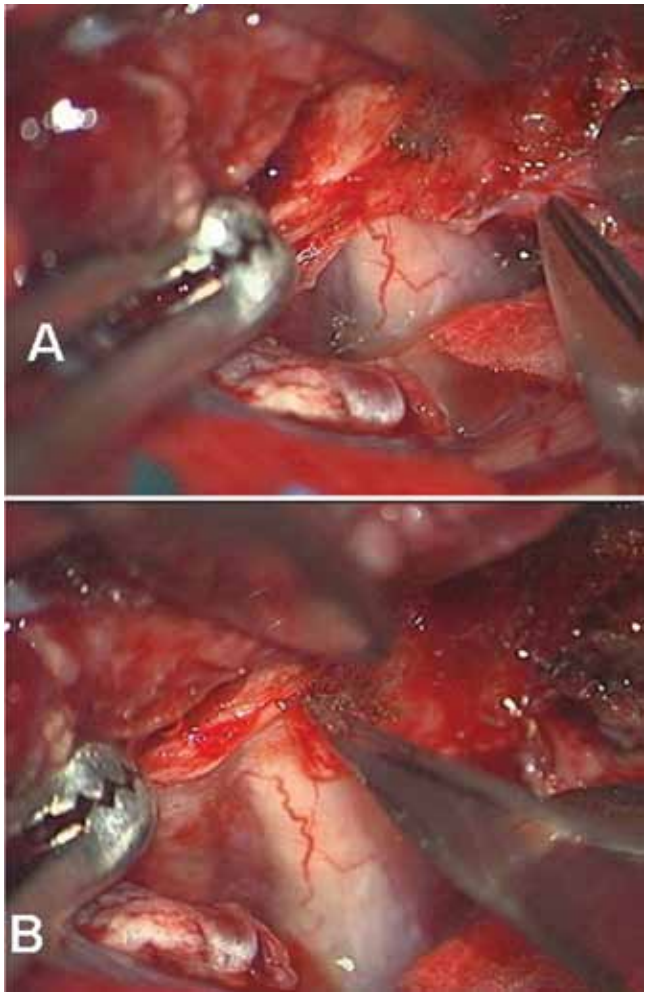

Fig. 2. Intraoperative photographs. **A:** Opening the falciform ligament, showing tumor inside the optic canal. **B:** Opening the falciform ligament and optic nerve sheath to ensure adequate optic nerve decompression.

TABLE 4: Visual outcome in 58 eyes affected with tumor involving the optic canal*

WHO Category	Degree of Vision Impairment on Preop Evaluation	No. of Eyes	Postop Outcome
normal vision	none (≥20/25)	3	3 remained the same
	slight loss (<20/25, near-normal vision)	23	6 improved
			14 remained the same
			1 w/ transient worsening to light perception, then improvement
			1 w/ transient worsening to 20/70, then improvement
			1 w/ permanent worsening to NLP, w/ slight improvement to FC
low vision	moderate loss (<20/70, moderate/low vision)	10	6 improved
			4 remained the same
	severe loss (<20/200, FC at ≤6 m)	7	3 w/ good improvement
			2 w/ mild improvement
			2 remained the same
blindness	profound loss (<20/400, moderate blindness; FC at ≤3 m)	4	1 w/ good improvement
			1 w/ mild improvement
			2 remained stable
	near-total loss (<3/200, near-total blindness; FC at ≤1 m or HM at ≤5 m)	7	3 w/ good improvement
			3 w/ mild improvement
			1 remained the same
	total (NLP, total blindness)	4	1 w/ mild improvement
			3 remained stable

* Optic nerve compression with optic canal involvement (58 canals).

and 1 had rapid deterioration with some recovery. Moderate visual loss was seen preoperatively in 10 eyes, with postoperative improvement in 6 and stable findings in 4. A total of 7 eyes had severe loss preoperatively, with only 3 improving to near-normal vision postoperatively, whereas only 1 of 4 eyes with profound visual loss improved to near-normal vision. Among 11 eyes with near-total and total visual loss, good improvement to near-normal vision was achieved in 3 eyes only. Although some improvement was seen in others, it was not to a functional level.

In one of the cases of transient worsening after resection of tuberculum sellae meningioma, the visual acuity dropped to light perception, then improved gradually to the preoperative visual status over 9 months. In the second case of transient worsening, a right clinoidal meningioma was resected, with postoperative visual acuity worsening to 20/70 (moderate visual loss), which improved to the preoperative status over the course of weeks. In the only case of permanent postoperative visual deterioration, the patient had undergone resection of tuberculum sellae meningioma, with rapid visual loss in his right eye over 36 hours postoperatively to no light perception (total visual loss), which improved slightly to finger counting (near-total visual loss) over the next few weeks.

TABLE 5: Visual outcome in 20 eyes with optic nerve compression without involvement of the optic canal

WHO Category	Preop Evaluation		Postop Outcome
	Vision Impairment	No. of Eyes	
normal vision	none	5	same in 5
	slight	11	same in 11
low vision	moderate	3	1 improved
			2 remained the same
	severe	1	1 remained the same
blindness	profound	0	
	near-total	0	
	total	0	

Twenty sides demonstrating optic nerve compression without direct optic canal involvement had better vision both pre- and postoperatively (Table 5). Of these, 5 sides showed normal preoperative vision and 11 sides showed slight visual loss; all of them remained the same after surgery. Three sides presented with moderate preoperative visual loss, of which 1 improved to normal and 2 remained stable. Only 1 side showed severe preoperative visual loss, which remained stable on postoperative examination. No profound visual loss, near-total loss, or total loss was encountered in any side.

In all cases, there was an overall visual improvement in 21 (57%) of 37 patients who presented with visual disturbance. However, the improvement in 8 eyes was in-

sufficient for functioning visual acuity. Postoperative improvement was related to tumor size and the duration of preoperative symptoms. The tumor size was less than 2.5 cm in 17 of 21 patients who showed postoperative improvement. Patients with postoperative visual improvement had a shorter duration of visual symptoms (median 12 months) when compared with those patients who failed to show improvement (median 21 months). Age was not related to visual outcome in most cases, although the only patient to suffer permanent visual deterioration was 71 years old. Optic canal involvement resulted in worse visual outcomes, although surprisingly, there appeared to be no relationship between the extent of optic canal involvement and visual outcome.

A significant fraction of patients harboring each tumor subtype presented with visual field deficits (Table 6), and surgery led to improvement in at least half of the patients in each group. Patients with clinoidal, sphenoid wing, and cavernous sinus meningiomas presented predominantly with unilateral visual field deficits, whereas patients with diaphragma sellae, tuberculum sellae, and planum sphenoidale lesions in this series often presented with bilateral involvement.

Postoperative Complications

There were no surgery-related deaths. All patients were endocrinologically intact on preoperative assessment. One case of a recurrent sphenoid wing meningioma that had been treated with radiotherapy and Gamma Knife radiosurgery demonstrated panhypopituitarism and complete third nerve palsy postoperatively. Three other patients demonstrated postoperative transient third nerve palsy that recovered over the course of weeks. Two patients developed postoperative deep vein thrombosis that required inferior vena cava filter placement.

Discussion

Optic Canal Involvement in Basal Meningioma

Unilateral or bilateral involvement of the optic canal has been described in many reports of tuberculum sellae meningioma management.[4,9,23–26,28,31] However, optic canal involvement can occur in a wide variety of anterior and middle fossa skull base meningiomas, including those of the planum sphenoidale, diaphragma sellae, clinoid, sphenoid wing, sphenopetroclival, and cavernous sinus regions.[1–3,24] Extension of the tumor inside the canal represents another way in which these tumors may threaten the visual apparatus and worsen the preoperative visual status.[4,24,26,31] In our study, 22 (37.9%) of 58 eyes showed poor preoperative vision due to optic canal involvement. In comparison, 1 (5%) of 20 eyes showed poor preoperative vision due to optic nerve compression without canal involvement. Thus, the overall surgical outcome is guided not only by the extent of tumor resection but also by the extent of optic nerve decompression through unroofing of the optic canal.[4,24–26,28]

TABLE 6: Visual field deficits and their improvement after decompression in tumor subsets

	Presentation w/ Visual Field Deficits	
Tumor Origin	No. of Pts	No. w/ Improvement After Decompression
clinoidal	7 of 11	4 of 7
tuberculum sellae	13 of 13	10 of 13
diaphragma sellae	2 of 2	1 of 2
planum sphenoidale	5 of 5	3 of 5
sphenoid wing	4 of 7	2 of 4
cavernous sinus	3 of 4	3 of 3
sphenopetroclival	1 of 2	1 of 1
en plaque	1 of 1	1 of 1

Optic Canal Decompression and Prevention of Optic Nerve Ischemia

Timing and the manner of optic canal decompression is still a subject of debate.[24–26,28] Many recent reports advocate extradural anterior clinoidectomy and optic canal decompression early in the operation as the best way to achieve a favorable visual outcome, with good surgical results in support.[24–26,28] The claim is that early release of the optic nerve allows its safe manipulation and handling during dissection of the tumor. Also, extradural anterior clinoidectomy has the added advantage of increasing the surgical corridor through the opticocarotid angle.[17,28] This is especially valuable in large tumors with lateral extension to the optic nerve and that involve the cavernous sinus. The additional exposure provides the surgeon with multiple vantage points to the tumor and good visualization of the CA branches. Others have emphasized the need to remove the tumor in the medial aspect of the optic canal to achieve the best long-term visual results, and that this part cannot be addressed by an extradural approach alone.[7,18,19,29]

In the senior author's experience,[1–4] no single method of decompressing the optic canal can be universally applied. First, the location of the tumor in relation to the optic nerve, and hence the pattern of optic canal involvement, play an important role in decision making. Laterally located tumors (53.3% in this series) such as clinoidal, sphenoid wing, cavernous sinus, and sphenopetroclival meningiomas usually compress the optic nerve from a lateral to medial direction, and invade the canal lateral to the nerve. Those tumors are best addressed via a COZ approach with extradural anterior clinoidectomy and decompression of the optic canal. However, anatomical variability[20,22] in such complex areas may alter the approach. In 2 cases in this study complete extradural decompression of the optic canal was difficult, and intradural decompression of the bony canal was achieved after subtotal extradural anterior clinoidectomy. Meningiomas located medial to the optic nerve (46.6% in this series), like those of the tuberculum sellae, planum sphenoidale, and diaphragma sellae, are usually addressed by a unilateral or bifrontal supraorbital approach. They usually extend to the optic canal medial to the optic nerve, with more chance of bilateral canal involvement. Indeed, these tumors accounted for 84.6% of cases with bilateral involvement in this series. Intradural decompression of the optic canal can be used to obtain

good decompression of the medial wall of the bony canal, which cannot be performed extradurally. Also, extradural anterior clinoidectomy has become a routine technique, which can be performed rapidly and safely.[12,14] Generous irrigation during drilling is crucial to prevent thermal injury to these neurovascular structures.[4,19,24,25,31]

Optic canal decompression requires opening of the bony canal, the falciform ligament (which is the most common site of compression injury of the nerve), and, in some cases (Type III clinoidal meningioma), opening of the optic nerve sheath. Achieving all of these steps is necessary for good visual outcome. Extradural optic canal decompression may not suffice as the sole means of optic nerve decompression in some cases, and intradural decompression may be required.[29] The timing of intradural decompression is guided by the tumor size, the relationship between the tumor and the optic nerve, and the feasibility of achieving a plane of dissection between the tumor and the optic nerve. Early dissection of the tumor out of the optic nerve at the canal without establishing a plane of dissection may compromise the blood supply of the nerve and cause ischemic damage to it.[2,4,19,28,33] In most of our cases, it was easier to begin dissection from the chiasm and continue forward toward the optic canal. This allowed easy dissection of the optic nerve by using the identified arachnoid planes, and also early identification and preservation of the blood supply to the optic nerve and chiasm.

The optic pathway has a delicate blood supply. The intradural portion of the optic nerve and the optic chiasm receive their blood supply from perforating vessels coursing from the ICA directly or from the SHA. These perforating vessels arising directly from the CA represent the sole blood supply to the inferior decussating fibers of the chiasm.[8]

The extradural portion and intracanalicular part receive their blood supply from the OphA, either directly or from its small branches. This delicate blood supply is vulnerable to either direct surgical trauma or delayed vasospasm from manipulation. In 1 patient in our study, postoperative visual deterioration 36 hours after surgery may have been a result of a vascular insult to the nerve, possibly from vasospasm related to manipulation around the optic nerve. Establishing a plane of dissection between the tumor and the ICA and its branches (especially the ACA and MCA and their perforators) is essential to achieving successful total tumor resection with minimal morbidity. Encasement of the ICA is commonly seen on preoperative imaging studies; however, it is often not difficult to establish a plane of dissection between the tumor and those vessels at the time of surgery.[2,4,10,19,24,28,33]

Approach Selection is Important to Optimize Optic Canal Decompression

The choice of the approach for removing such lesions depends on many factors, including the origin of the meningioma; size of the tumor; relationship to important structures, including the optic pathway, CA and its branches; extension into the cavernous sinus; and extent of bone involvement.[1–5,19,24,31] Some surgeons advocate the use of a limited pterional approach to address such tumors,[18,21,34] whereas others have suggested that such approaches may require undue brain retraction and result in difficult resection of the tumor, with its dural and osseous involvement.[1–5,24] A modified pterional approach has been shown to be safe and effective for resection of these tumors.[13,15,16] In our experience, skull base approaches, including COZ and supraorbital approaches, can be safely performed without any significant added morbidity. The principal advantages of skull base approaches include the additional exposure obtained while minimizing the need for brain retraction. These approaches provide several corridors to access the tumor and may increase the likelihood of total resection of the tumor with its dural and osseous extensions. Even with tumors totally encasing the optic nerve, total excision is still achievable provided that there is an intact arachnoid plane.[2,4,11,19,24,25,28,31] In this series, total tumor resection (Simpson Grade I) was achieved in 32 patients (71.1%), whereas gross-total resection (Simpson Grades II and III) was achieved in 13 patients (28.9%).

Factors Affecting the Visual Recovery

Optic canal decompression and removal of tumor within the optic canal play prominent roles in both optimizing visual outcomes and preventing tumor recurrence.[24,26,27,31,32] Many authors attribute tumor recurrence in such cases to incomplete resection of the part of the tumor within the optic canal.[5,7,25,26] Residual tumor within the optic canal after an initial operation was probably the cause for tumor regrowth in 3 cases in our series. In addition, in the rare cases of tumor recurrence after optic canal decompression, visual deterioration may be delayed because the optic nerve is already decompressed from the surrounding falciform ligament and optic canal.[24,28] Although many reports conclude that extension of the tumor inside the canal is an indicator of a poor prognosis due to the possibility of nerve ischemia,[24,26] this series demonstrates that adequate optic canal decompression is effective in preserving preoperative visual status in 23 patients (51%), while improving the visual outcome in 21 patients (46.6%). Other factors affecting visual outcome include the age of the patient, tumor size, preoperative visual status, and duration of symptoms.[1,3–5,9,19,24–27,29–31] Large tumors cause more stretching of the adjacent nerves and vessels, and consequently result in more difficult resection. Visual recovery is more favorable in patients with relatively good preoperative vision. Our study showed that the best visual outcome was achieved in patients whose tumors were 2.5 cm or less and with patients presenting with milder visual symptoms.

Although the follow-up period only averaged 29.8 months, there were no recurrences in this series in patients with Simpson Grade I or II resection. Only 1 recurrence occurred 4 years after Simpson Grade III resection of a left cavernous sinus meningioma that necessitated repeat operation. Minimal morbidity due to the operative approaches was observed, despite aggressive resection with extensive bone drilling.[1,3,4,24,26,28]

Conclusions

The unilateral or bilateral extension of juxtasellar meningiomas into the optic canal strongly influences the

preoperative visual status and postoperative recovery. Decompression of the optic canal and removal of tumor extending into the canal are crucial steps in the surgical treatment of these lesions to optimize the patient's visual recovery and to prevent tumor recurrence.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Al-Mefty, Erkmen, Pravdenkova.

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Pneumosinus dilitans and meningioma: a case series and review of the literature

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Pneumosinus dilitans (PSD) is enlargement of the sinuses of the skull base and is frequently seen with meningiomas. Identifying PSD on imaging can assist with operative planning and preparation. Meningiomas associated with PSD are not more commonly high grade, and complete resection is frequently possible.
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Key Words • pneumosinus dilitans • meningioma • sphenoid sinus • planum sphenoidale • tuberculum sella

Pneumosinus dilitans is the abnormal expansion of the paranasal air sinuses, most often the frontal sinus, without an associated mass in the sinus.[6] This condition can affect any of the paranasal sinuses, but the frontal sinus is most often affected.[6] Accurately identifying a mass on preoperative imaging is helpful for planning the operative procedure, discussing with patients and families the outcomes of and expectations from surgery, and planning for postoperative treatment and recovery. The differential diagnosis for lesions adjacent to the sinuses is vast, and being able to narrow this differential is essential for operative planning. In cases in which there are imaging findings of PSD, the likelihood of an intracranial mass being a meningioma should be raised. We report on 10 cases of PSD associated with meningiomas.

Methods

We conducted a retrospective review of 8 patients with histologically verified meningiomas associated with PSD who underwent resection at the Maine Medical Center and Tufts Medical Center between 1995 and 2010. Another 2 patients did not undergo surgery: 1 patient opted for no resection, and PSD in the other was incidentally found during the workup for a pontine stroke. The patient population consisted of 6 women and 4 men, ranging in age from 32 to 63 years (mean 47.3 years). Patient demographics, tumor locations, and presenting symptoms are listed in Table 1. All patients had significant evidence of PSD on preoperative imaging studies. Eight cases (80%) were associated with enlargement of the sphenoid sinus, and 2 cases (20%) involved both the frontal and the sphenoid sinuses. The tumors ranged in size from a few centimeters to very large with significant associated intracranial edema (Fig. 1).

Surgical Treatment

Three operative approaches to the tumors (in addition to unilateral and bilateral approaches) were performed (Table 2).

Radiological Studies

In all cases the patients had preoperative CT and/or MR imaging with and without contrast, with a clear demonstration of enlargement in at least one of the paranasal sinuses. Eighty percent of the patients had expansion of the sphenoid sinus, and 20% had involvement of the sphenoid and frontal sinuses (Figs. 2 and 3).

Abbreviation used in this paper: PSD = pneumosinus dilatans.

TABLE 1: Summary of characteristics in 10 patients with PSD

Case No.	Age (yrs), Sex	Tumor Location	Presenting Symptom
1	32, F	planum sphenoidale	visual loss
2	32, F	tuberculum/olfactory groove	visual loss
3	33, F	planum sphenoidale	visual loss
4	39, F	tuberculum sellae	headache
5	43, M	planum sphenoidale	visual loss, abulia
6	55, F	planum sphenoidale	anosmia
7	60, M	planum sphenoidale	headache, visual loss
8	63, F	olfactory groove	headache
9	63, M	planum sphenoidale	visual loss
10	53, M	planum sphenoidale	none*

* Incidental finding during stroke workup.

Results

The initial surgery resulted in a Simpson Grade 1 resection in 100% of the patients who underwent surgery and in whom the resection grade was known. The pathology of the resected meningiomas was WHO Grade I in all cases. Postoperatively, 7 of 8 patients had stabilization of vision or improvement in visual symptoms. There were 2 complications in this series, one related to the surgical procedure and one postoperative complication. One patient had an infected bone flap, which resulted in return trips to the operating room for bone removal and debridement of the surgical site. In the 7 patients with known follow-up, there has been no tumor recurrence. One patient had worsening right optic neuropathy with presumed tumor recurrence but no visible recurrence on MR imaging and was referred for fractionated radiotherapy (Table 2).

Discussion

Pneumosinus dilatans, first described by Meyers in 1889, is the abnormal expansion of the paranasal sinuses.[4] The term "pneumosinus dilatans" was introduced by Benjamin in 1918.[3,6] In PSD there is enlargement of the paranasal sinuses, with expansion of the surrounding bone, without bony thinning or evidence of mucosal abnormality. Expansion can involve all of a sinus or just a portion;[6] this contrasts with pneumoceles, which have a loss of integrity of part or all of the bony sinus wall.[1] In previous studies, the frontal sinus has been described as being affected most often, followed by the sphenoid, maxillary, and ethmoid sinuses. In our series the most frequently affected sinus was the sphenoid sinus. The most common locations of meningiomas in this series were the planum sphenoidale and tuberculum sellae. This finding may represent a selection bias, as practitioners without expertise in skull base tumor resection often refer patients with planum sphenoidale and tuberculum sella meningiomas to our centers for evaluation and treatment.

Patients will frequently present with symptoms of

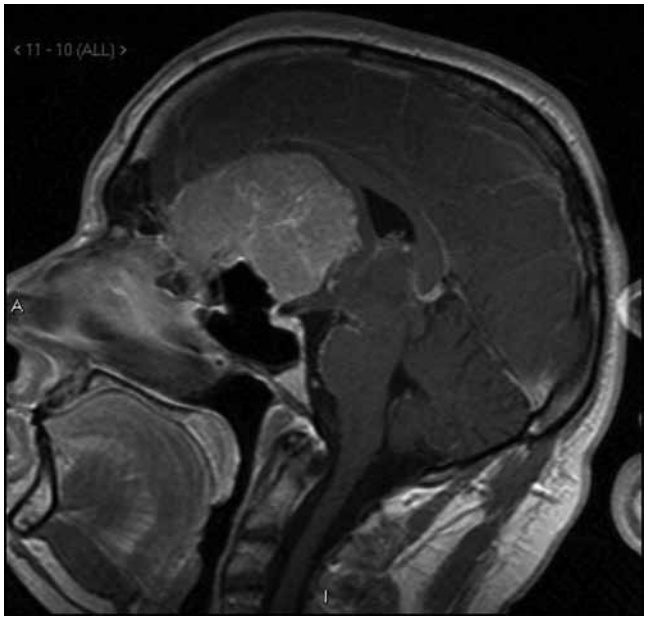

Fig. 2. Case 5. Sagittal contrast-enhanced T1-weighted MR image showing a large planum sphenoidale meningioma, mostly homogeneous enhancement, expansion of the sphenoid sinus with normal thickness, and surrounding bone.

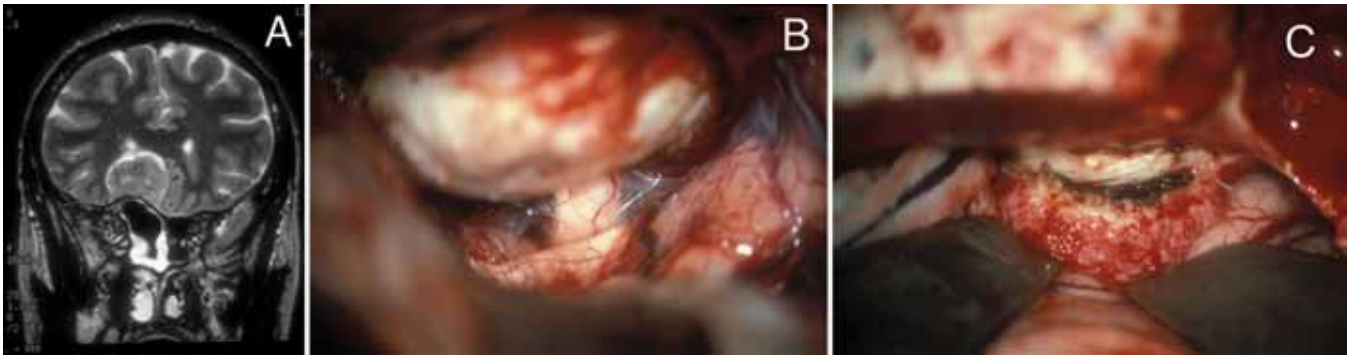

Fig. 1. Case 3. **A:** Coronal T2-weighted MR image demonstrating an extraaxial mass associated with asymmetrical enlargement of the sphenoid sinus. The mass is heterogenous and somewhat hyperintense to surrounding brain. **B:** Intraoperative photograph showing two retractor blades elevating the right frontal lobe. The olfactory tract can be seen at the tip of the retractor blade. A thin veil of arachnoid is deeper, and behind that is the right optic nerve. The planum sphenoidale and right orbital roof appear at the top of the image, bowed upwards. **C:** Intraoperative photograph showing the meningioma, separated from the dura and exposing the underlying planum sphenoidale and right orbital roof with the frontal lobes retracted.

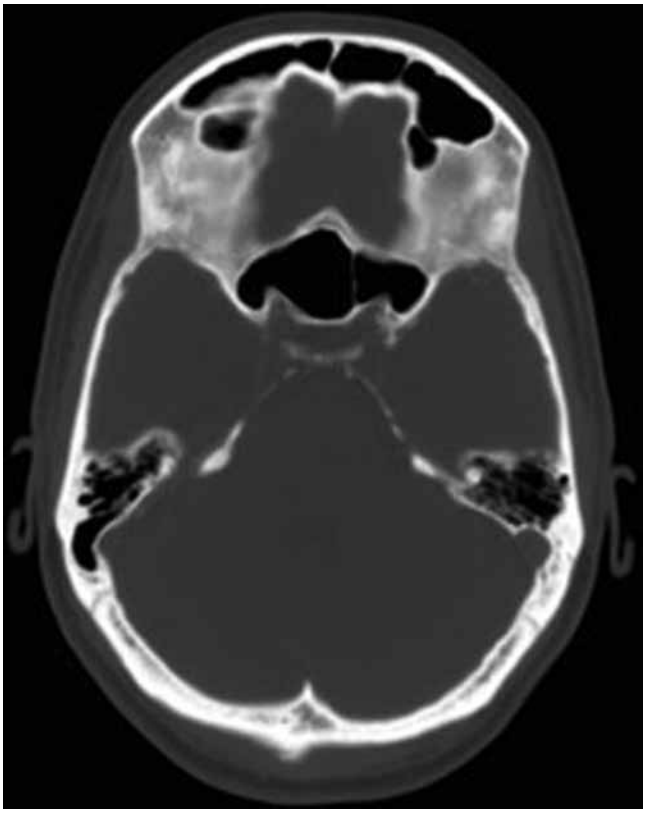

Fig. 3. Case 1. Axial bone window CT scan showing enlargement of the sphenoid sinus with normal bone thickness.

changes in facial contours, pain in the affected area, diplopia, visual loss, headache, or symptoms of local pressure. Examination can reveal frontal bossing, orbital roof elevation, displacement of the globe, ptosis, and anosmia.[1,2,5] The etiology of PSD is not completely understood. Pneumosinus dilitans has been associated with fibroosseous disease, arachnoid cysts, and intracranial meningiomas. One proposed mechanism in the formation of PSD includes a ball-valve mechanism of the sinus ostia leading to sinus expansion. However, this theory has been challenged given the fact that there are many cases with normal sinus ostia intraoperatively.[6] Other mechanisms that have been proposed include chronic air trapping or chronic inflammation. Note, however, that frequently there is no evidence of inflammation intraoperatively. In our cases series no patients were found to have chronic inflammation or mucosal abnormalities of the sinuses. In all cases the presence of a meningioma was thought to be the cause of enlargement of the sinus.

Conclusions

From this series we hope to raise awareness of the association between PSD and meningioma. Prior to the wide availability of contrast-enhanced MR images, PSD on other imaging modalities was an important diagnostic indicator. In our opinion, the presence of PSD of the sphenoid sinus essentially guarantees that an overlying tumor is a meningioma. Pneumosinus dilitans never occurs with pituitary adenomas, malignant tumors, or suprasellar masses other than meningiomas. Although previous papers have indicated that the frontal sinus is most often involved in PSD, in this series the sphenoid sinus was far more commonly affected. Recognizing that the anatomy of the sinuses can be distorted in patients with skull base meningiomas, especially those with associated PSD, is important to avoid complications such as CSF leakage. Surgical removal of the meningioma resulted in stabilization or improvement in visual symptoms in nearly all patients with preoperative visual symptoms. The presence of PSD was not associated with a higher histological grade (atypical/malignant) of the meningioma removed. Surgical removal of meningiomas along with PSD has a low complication rate in this series, and complete resection with no need for further treatment is likely to be achieved.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Gibbons, Florman, Heilman. Acquisition of data: Gibbons, Miele, Florman, Heilman. Analysis and interpretation of data: Gibbons, Miele, Florman.

TABLE 2: Summary of operative and postoperative characteristics in 10 patients treated for PSD*

Case No.	Surgical Approach	Lumbar Drain	Simpson Resection Grade	Complication
1	bifrontal craniotomy	yes	1	none
2	lt orbitofrontal craniotomy	no	1	none
3	rt frontal craniotomy	no	1	none
4	rt pterional craniotomy	no	1	none
5	biorbitofrontal craniotomy	no	unknown	infected bone flap
6	rt orbitofrontal craniotomy	no	1	DVT
7	no surgery	NA	NA	NA
8	bilat orbitofrontal craniotomy	no	1	none
9	bilat orbitofrontal craniotomy	no	1	none
10	no surgery	NA	NA	NA

* DVT = deep vein thrombosis; NA = not applicable.

Drafting the article: Gibbons, Miele. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Gibbons, Miele, Florman, Heilman, Horgan.

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Decision making for the surgical approach of posterior petrous bone meningiomas

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Object. The authors undertook this study to examine the surgical approaches used to treat posterior petrous bone meningiomas at a single institution and retrospectively evaluate their surgical strategy based on a previously published classification.

Methods. Cases in which craniotomies were performed to treat posterior petrous bone meningiomas between 2002 and 2010 were retrospectively reviewed. Data were examined from 57 patients who were treated for 59 tumors. The tumors were classified into 3 types according to the location of their primary dural attachment: Type A, located around the porus trigeminus (33 tumors); Type M, located at the level of the porus of the internal auditory canal (IAC) (12 tumors); and Type P, located laterally to the IAC (14 tumors). The median tumor diameter was 34 mm (range 20–67 mm).

Results. The choice of the approach was based on tumor location, as the displacement of vascular structures and cranial nerves was primarily determined by the site of dural attachment on the posterior petrous bone. An anterior petrosectomy was performed in 82% of Type A meningiomas, and a retrosigmoid approach was used in 86% of Type P meningiomas. The spectrum of approaches was less uniform for Type M meningiomas. Overall, total resection was obtained in 39% of all cases, and in 18%, 50%, and 86% of Type A, Type M, and Type P tumors, respectively. The postoperative mortality rate was 8.8% (5 deaths among 57 patients), and all 5 patients who died during the early postoperative period had large Type A tumors. At last follow-up, the functional preservation of the facial nerve was excellent in 49 (94%) of the 52 surviving patients.

Conclusions. The authors believe that proper selection of the approach favorably impacts functional outcome in patients undergoing surgery for the treatment of skull base tumors. In the authors' case series of posterior petrous bone meningiomas, Type P and most Type M tumors were safely managed through a regular retrosigmoid approach, whereas Type A tumors were optimally treated via an epidural anterior petrosectomy.
(DOI: 10.3171/2011.2.FOCUS1119)

Key Words • **meningioma** • **skull base** • **petrous bone** • **posterior fossa**

Posterior petrous bone meningiomas account for 50% of posterior fossa meningiomas. Although these lesions share the characteristic of critical relationships with neurovascular structures of the posterior fossa, they encompass a wide spectrum of distinct clinical and radiological situations linked to distinct prognoses.

In addition to the regular retrosigmoid approach, several skull base approaches have been used for the resection of these meningiomas.[2,4,8,14] Criteria for the selection of these approaches have not been addressed. The goal of this short paper is to clarify the roles of these approaches for the various subtypes of posterior petrous bone meningiomas.

Abbreviations used in this paper: CPA = cerebellopontine angle; IAC = internal auditory canal.

Methods

Patient Population

Between 2002 and 2010, a total of 160 consecutive skull base meningiomas were surgically treated at the Université de la Méditerrannée by the senior author (P.H.R.). All data regarding surgery were integrated into an Excel data base (Microsoft Corp.). For this retrospective study, we selected from this database 71 cases of posterior fossa meningioma. Jugular foramen, clivus, tentorium, and foramen magnum meningiomas were excluded, leaving 59 cases of posterior petrous bone meningiomas for inclusion in the study. The institutional review board of the Université de la Méditerrannée at Marseille Nord approved this retrospective study.

Preoperative Neuroradiological Evaluation

Posterior petrous bone meningiomas were classified into 3 types following the Desgeorges classification,[6] which is based on the tumor's dural attachment to the posterior petrous bone surface: Type A (anterior) meningiomas originate from the petrous apex, Type M (middle) meningiomas originate at the level of the internal auditory meatus, and Type P (posterior) meningiomas develop from the posterior part of the petrous bone, between the posterior wall of the IAC and the groove of the sigmoid sinus (Fig. 1).

Computed tomography scans and MR images, including contrast-enhanced images, had been obtained in all patients. High-resolution CT scans of the petrous bone had been obtained in selected cases involving patients who had previously undergone surgery in other centers, but neither cerebral angiography nor preoperative embolization was performed in the cases included in this study. Illustrative cases are shown in Fig. 2. The measure of tumor size used in this study is the largest cross-sectional tumor diameter on CT scans or MR images.

Approaches and Surgical Technique

The standard retrosigmoid approach has been detailed in key papers on CPA tumors and was used routinely in this series.[11] In many cases, and depending on the location of the tumor, its size, and the patient's preoperative hearing level, we also used various transpetrous approaches. Anterior petrosectomy, combined petrosectomy, translabyrinthine, and retrolabyrinthine approaches have been extensively described in key papers and by our group in previous reports.[7,11,12] To clarify the systematization of the drilling zone corresponding to each approach, a model of the petrous bone segmentation according to Pellet[11] is shown in Fig. 3.

Basically, we selected the approach that could offer both the best chance of optimal resection and the safest dissection of the tumor within the environment of the neurovascular structures and cranial nerves. To do so, the type of tumor according to the "A-M-P" Desgeorges classification was carefully determined. An injected specimen with the lateral skull base exposed on the left side is shown in Fig. 4: a combined petrosectomy was performed, and the exposure shows the critical neural structures delineating the different regions we considered.

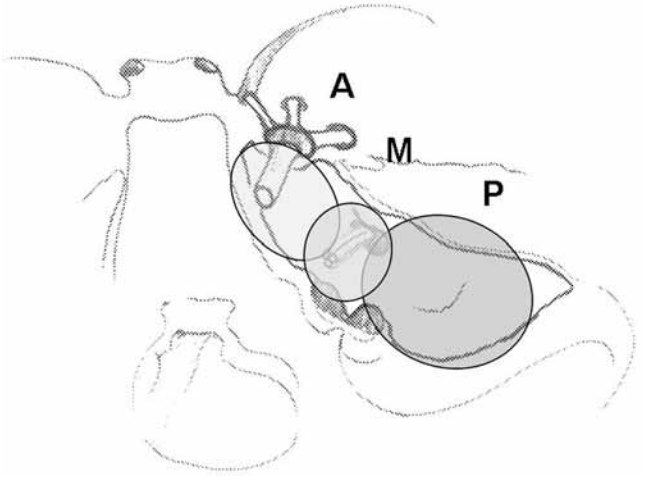

Fig. 1. Schematic illustration of the classification used in this study, adapted from Desgeorges. The posterior petrous bone meningiomas are classified according to their main dural attachment: Type A (anterior), attachment around the porus trigeminus; Type M (middle), at the level of the porus of the IAC; and Type P (posterior), lateral to the IAC.

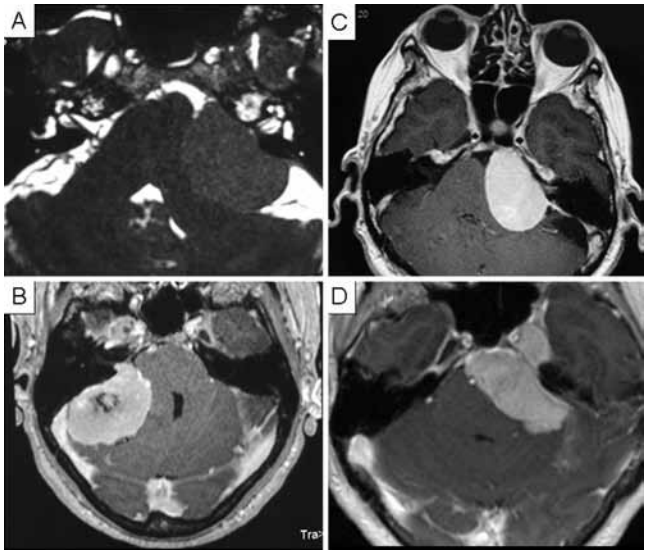

Fig. 2. Axial MR images showing the radiological classification of posterior petrous bone meningiomas. **A:** Left-side Type M meningioma. **B:** Right-side Type P meningioma with extension into the IAC. **C:** Type A meningioma with extension into the IAC. **D:** Type A meningioma with multiple extensions into the clivus and Meckel cave.

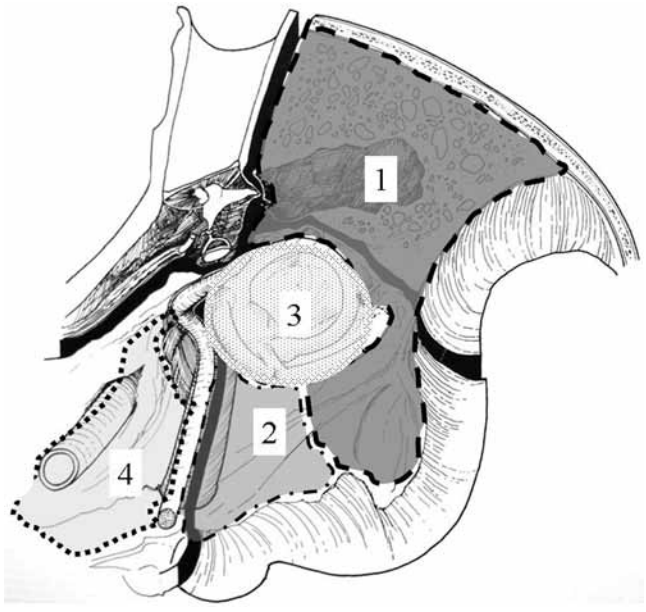

Fig. 3. Schematic illustration of the drilling regions on a right petrous bone. This sketch represents the segmentation of a right petrous bone shown from above. The retrolabyrinthine approach is performed by drilling of Segment 1 (the mastoid segment) and Segment 2 (the retromeatal segment), the translabyrinthine approach by the additional drilling of Segment 3 (the labyrinthine segment), and the anterior petrosectomy by resection of Segment 4 (the carotid segment) also. Combined petrosectomy is achieved by resection of Segments 1, 2, and 4.

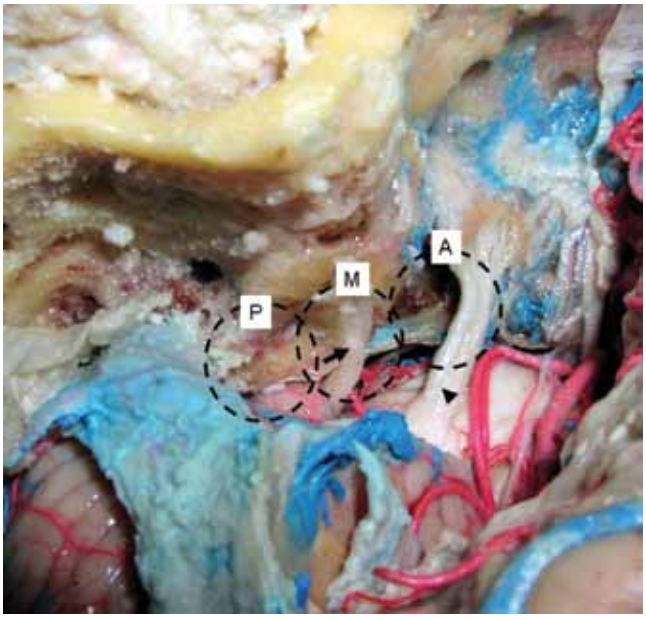

Fig. 4. Exposure of the regions of interest on the left posterior petrous bone in an injected specimen. A combined petrosectomy has been performed, revealing the acousticofacial bundle *(black arrow)* in the internal auditory meatus and the trigemeninal nerve from the Meckel cave to the pons *(black arrowhead)*. The *circle* labeled P represents the area of attachment of posterior meningiomas. The acousticofacial bundle is shifted anteriorly in patients with Type P lesions. The *circle* labeled M indicates the zone of attachment of meningiomas with relationship to the IAC; the exact position of cranial nerves VII and VIII may be less predictable in this group. The *circle* labeled A indicates the area of attachment of petrous apex meningiomas and their relationship to the trigeminal porus, Meckel cave, and pons. Cranial nerves VII and VIII are displaced backward and usually downward in patients with Type A lesions.

We gave special attention to the location of the tumor's main insertion site, the involvement of the adjacent areas (as illustrated in Fig. 2D), and the tumor size. Prediction of nerve displacement, with special attention to the acousticofacial bundle, was a key factor in the decision. The patient's preoperative hearing status was considered, with both sides being taken into account. The amount of tumor resection planned (complete removal vs subtotal resection) may also modify the choice of the approach.

Whichever approach we used, cranial nerve function was monitored intraoperatively. Transpetrosal approaches allowed control and resection of the osteodural insertion of the meningioma, with significant coagulation of the tumor's feeding vessel being obtained at the early stage of the procedure. Once the dura was resected or opened, the next step was to undertake optimal internal debulking followed by peripheral dissection, with special attention to the identification and protection of the neurovascular structures and cranial nerves. We did not perform systematic radical resection when we estimated that the tumor could not be safely dissected from the brainstem, the vessels, or the preoperatively intact cranial nerves.[1,9] Radical resection was not generally our main goal, since remnant tumor could be treated by stereotactic radiosurgery in a second stage.[13]

Extent of Tumor Resection

The extent of tumor resection was defined by the intraoperative findings using the Simpson criteria. These findings had to be confirmed by postoperative MR imaging performed 3 months after surgery. In this study, Simpson Grade 1 or 2 resection and no residual tumor on postoperative MR images corresponds to a total resection; Simpson Grade 3 or 4 resection and/or presence of residual tumor on postoperative MR images corresponds to a nontotal resection.

Patient Follow-Up

Systematic clinical examination and postoperative MR imaging were performed at 3 months, 1 year, 2 years, 3 years, and 5 years after surgery, and every 3 years thereafter. The decision to administer adjuvant stereotactic radiosurgery or any other modality of radiation therapy was decided in a multidisciplinary conference, depending on the size of the remnant tumor and the clinical condition of the patient at the time of the examination. Hence, stereotactic radiosurgery was delayed when the patient had any transient postoperative cranial nerve deficit.

Results

Patients

The patient population consisted of 13 men and 44 women (mean age 55.9 years) harboring 59 tumors. Preoperative symptoms depended on the location of the meningiomas. Trigeminal signs and gait ataxia were mainly present in patients with Type A meningiomas, whereas vestibular and hearing symptoms predominantly occurred in association with Type M and Type P meningiomas. Histological examination revealed a WHO Grade I meningioma in 55 cases and a WHO Grade II meningioma in 4 cases. The median duration of follow-up in this series is 30 months (range 6–124 months).

Tumor Size and A-M-P Classification

The mean cross-sectional diameter of the nodular part of the meningiomas was 36.4 mm, and the median cross-sectional diameter was 34 mm (range 20–67 mm).

The classification data are shown in Table 1. Various types of extensions were observed depending on the primary dural attachment of the tumor. The involvement of the middle fossa was not infrequently observed in Type A meningiomas, and Meckel cave involvement was observed in 64% of Type A tumors in this series.

Extent of Resection

Total resection was obtained in 23 (39%) of 59 tumors; resection was classified as Simpson Grade 3 or 4 in the remaining 61% of cases. There was a clear correlation between the site attachment of the meningiomas and the extent of resection, as shown in Table 2.

Morbidity and Mortality

Five patients (8.8%) died in the first 45 days after surgery. In one case, death was due to a myocardial infarction 3 days after surgery. Another patient died from neurogen-

TABLE 1: Selection of approaches in 59 cases stratified by meningioma type and subtype*

Type & Subtype	Total No. of Cases	Anterior Petrosectomy	Combined Petrosectomy	Translabyrinthine	Retrolabyrinthine	Retrosigmoid
Type A	33					
A	4	4				
A-Mc	13	13				
A-Mc-M	8	6	2			
AM	6	4	2			
AMP	2		2			
Type M	12					
M	8			3		5
MA	2	2				
MP	2			1	1	
Type P	14					
P	10				2	8
PM	4					4

* The meniogiomas are classified according to type (based on area of dural attachment) and subtype. Abbreviations: A = anterior; M = middle; Mc = Meckel cave involvement; P = posterior.

ic pulmonary edema 6 days postoperatively, although surgery was uneventful and findings on postoperative MR imaging were considered normal. An 80-year-old patient died of general complications 3 days after surgery. Two patients died of ischemic arterial complications. All 5 of these cases involved large Type A meningiomas with clival extension. Four of the patients had previously undergone surgical treatment of the lesion in another center either once or twice.

Four cases of bacterial meningitis were suspected and treated by intravenous antibiotic therapy, but only 2 of these cases were confirmed by CSF analysis. (Lumbar puncture was performed in 4 cases, but bacteria causing meningitis were identified in only 2.)

TABLE 2: Extent of resection stratified by meningioma type and subtype

Type & Subtype	Total No. of Cases	Extent of Resection*	
		Total	Nontotal
Type A	33	6 (18)	27 (82)
A	4	2	2
A-Mc	13	0	13
A-Mc-M	8	1	7
AM	6	3	3
AMP	2	0	2
Type M	12	6 (50)	6 (50)
M	8	5	3
MA	2	0	2
MP	2	1	1
Type P	14	12 (86)	2 (14)
P	10	9	1
PM	4	3	1

* Values represent numbers of cases (%).

One case of pneumonia was noted.

Cerebrospinal fluid leaks were documented in 3 patients. One resolved with lumboperitoneal shunt placement, whereas 2 required reoperation for closure of the fistula. In these last 2 cases, high-resolution contrast-enhanced CT cisternography was performed to better identify the site of the CSF leak. Surgical repair was then performed: we reopened the skin and elevated the superficial layers to expose the patent air cells and plug them with abundant fat and fibrin glue. Lumbar drainage was maintained for 72 hours after surgery.

Cerebral arterial and cranial nerve complications occurred in several patients and are detailed in Table 3. All the vascular complications we noted were permanent.

TABLE 3: Summary of vascular and cranial nerve complications*

Type of Complication & Involved Structure	Complications	
	Early Postop	Present at Last FU
stroke		
internal carotid artery	1	1
anterior choroidal artery	1	1
anterior inferior cerebellar artery	2	2
cranial nerve deficit†		
CN III	2	0
CN IV	6	4
CN V	9	8
CN VI	15	6
CN VII	5	3
CN VIII	4	3
lower CNs (IX–XI)	3	2

* CN = cranial nerve; FU = follow-up.

† New deficit or worsening of a preoperative deficit.

Among the patients who had postoperative oculomotor deficits, 67% had recovered at last follow-up; these deficits occurred primarily in patients harboring Type A tumors. We found that 5% of patients had permanent hypacusia and 5% of patients had permanent facial nerve deficits; most of these patients harbored Type M tumors. We found that 13.5% of patients had trigeminal nerve numbness, including 2 with anesthesia dolorosa; Type A tumors with Meckel cave involvement were mostly responsible for these symptoms.

Patient Follow-Up and Treatment Failure

Of the 36 patients in whom residual tumor was present after microsurgery, 25 patients were eligible for radiosurgery. In all these cases, Gamma Knife surgery was performed during the first 6–18 months after resection. Those patients in whom resection was graded Simpson 3 or 4 with small remnants had Gamma Knife surgery. A dose of 12 Gy was delivered.

One patient with a larger remnant underwent stereotactic fractioned radiation therapy. No patient experienced permanent side effects after these radiation treatments.

At last follow-up, 3 cases of tumor regrowth had been observed; in all 3 cases, the lesions were initially WHO Grade II tumors. Radiological regrowth was diagnosed in these 3 cases at 6, 7, and 54 months.

Overall, tumor control was obtained in 49 (94%) of 52 of cases.

Discussion

We report our 8-year experience treating posterior petrous bone meningiomas and provide easy criteria based on the Desgeorges classification to use in choosing the surgical approach. Posterior petrous bone meningiomas are lesions that develop in an area delineated by the superior petrosal sinus, the inferior petrosal sinus, and the sigmoid sinus. Despite early contact of the cranial nerves V, VII, and VIII with the meningioma, these nerves often remain protected in their own arachnoid sheath even in cases of large tumors. Therefore, if care is taken to avoid damaging these nerves during surgery, they can be preserved with excellent functional results. Before surgery is initiated, it is essential to predict the direction of displacement, which depends on the meningioma's attachment site.

About Tumor Classifications

There is a lack of consensus on the definition of posterior petrous meningiomas, and these cases were initially all referred to as CPA meningiomas. Bricolo et al.[3] divided posterior petrous meningiomas into tumors anterior to the IAC and tumors posterior to the IAC. Desgeorges et al.[6] refined this description when they introduced the A-M-P classification, the one we adopted in this paper. In Type M meningiomas, the area of dural attachment is around the porus of the IAC. While displacement of the acousticofacial bundle is predictable in Type A and Type P tumors, the situation is more varied in Type M lesions and depends on the exact growth of the tumor from the margin of the porus (pre-, post-, supra-, or inframeatal meningiomas). Whatever the classification used, large broad-based meningiomas involve more than one segment of the posterior petrous bone and it becomes harder to predict the exact shifting of the cranial nerves around the tumor capsule. Type A meningiomas usually involve the middle fossa (Meckel cave, petroclinoid fold) and the IAC. Large Type P meningiomas extend toward the Type M zone.

About the Approaches

The retrosigmoid approach was initially used primarily for the management of CPA schwannomas and was subsequently applied to resection of posterior petrous bone meningiomas.[3,10,15] The retrosigmoid approach is quick, straightforward, offers wide exposure of the CPA, and involves well-known anatomy. However. it does not allow for early control of the tumor feeding vessels and easy Simpson Grade 1 resection in Type A tumors because the dura and bony insertion cannot be extensively resected. Therefore, this approach is reserved for Type P and some Type M meningiomas because the posterior tumor capsule is then in close proximity to the surgeon and nerves stay protected in their arachnoid sheath at the ventral part of the tumor capsule. In Type A meningiomas, the acousticofacial bundle is usually displaced posteriorly and interposed in the operative field. Repeated maneuvers of resection and coagulation put these nerves at risk during the operative procedure.

On the other hand, transpetrous approaches allow early resection of involved bone and dura, control of the feeders, and limited retraction of the brain.[4,5] They offer shorter distances and better orientation toward the ventral brainstem. Nevertheless, they require special training and knowledge of the complex anatomy of the petrous bone. Moreover, the intrapetrous otoneurological structures are at risk for damage during the approach. We considered the anterior petrosectomy the most logical approach for Type A meningiomas. Once the Kawase triangle is resected,[8] the surgical corridor offers direct access to the porus trigeminus where these meningiomas are located. Opening of the Meckel cave is allowed by the approach, as well as resection of the tentorium and petroclinoid fold; exposure of the lower pons and the area behind the IAC is, however, limited. While gaining greater experience, we have gradually simplified our paradigm of approaches, and we have switched from the use of the whole panel of lateral skull base approaches to the routine use of 2 approaches: the retrosigmoid approach and the Kawase approach. However, for giant A-M-P tumors involving the petroclival area and the middle fossa, we still consider that combined petrosectomy offers the best exposure for a one-stage surgery.[12]

About Complications

In this series, we present the results of microsurgically managed large and extra-large posterior fossa meningiomas. To summarize, quality of resection and functional results are excellent in patients with Type P or Type M meningiomas and less favorable in those with Type A meningiomas.

Major life-threatening complications were of vascular origin. They were observed when resection was undertaken for the largest tumors, which originated from the petrous apex with extensions to the clivus and middle fossa. These complications were due to direct manipulation of the vessels involved in the tumor capsule. Those patients who had undergone surgery previously were also at greater risk of complications, probably because of more adhesions and fibrous scar tissue.

As a rule, cranial nerves are not involved by the tumor but are in a vulnerable position at the point where they enter their own dural sheath. The cranial nerve IV is usually identified in its perimesencephalic course even in very large tumors, but attempting tumor resection at the level of the petroclinoid fold usually results in permanent deficit. As for the cranial nerve V, the risk is greater at the level of the porus trigeminus and inside the Meckel cave, where the pars triangularis is usually infiltrated by the meningioma. In cases of pure Type A meningiomas, there is no reason to damage the cranial nerve VI because it runs medially and caudally to the tumor. However, the area of dural attachment may extend toward the groove of the inferior petrosal sinus and to the porus of the Dorello canal where the nerve is under tension. Attempting tumor resection or coagulation at this location may cause permanent damage. Taking this point into account, in most cases of Type A meningiomas, we intentionally opted for subtotal resection followed by stereotactic radiosurgery to treat the remnant tumor instead of performing radical resection.

Conclusions

Careful analysis of preoperative CT and MR images of posterior petrous bone meningiomas allows reliable identification of the site of dural attachment and demonstrates the neurovascular displacement. In our current practice, these parameters guide the selection of surgical approach. For all but Type P meningiomas, attempting radical resection places the patient at greater risk of morbidity. Moreover, subtotal resection can be safely and effectively combined with stereotactic radiosurgery. Therefore, our current policy is moving toward less use of complex and aggressive skull base approaches. In such a paradigm, the retrosigmoid approach appears to be the best choice for Type P and most Type M cases, whereas most Type A meningiomas are adequately managed with an epidural anterior petrosectomy.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Roche, Lubrano. Acquisition of data: Roche, Régis. Analysis and interpretation of data: Roche, Lubrano, Régis. Drafting the article: all authors. Critically revising the article: Lubrano. Reviewed final version of the manuscript and approved it for submission: Roche, Lubrano, Noudel, Melot. Study supervision: Roche.

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Expanded endonasal endoscopic resection of anterior fossa meningiomas: report of 13 cases and meta-analysis of the literature

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Object. Transnasal endoscopic (TNE) approaches have been proposed for the resection of anterior cranial base meningiomas. The purpose of this article was to evaluate the results of endoscopic resection of anterior cranial fossa meningiomas by reviewing available published data in addition to the authors' experience with 13 cases.

Methods. The literature was searched via OVID to identify all available disaggregate data pertaining to anterior fossa meningiomas treated primarily by TNE. In addition, the authors reviewed the records of a personal series of 13 patients who underwent TNE removal of parasellar meningiomas through a pure TNE approach.

Results. Meta-analysis from studies included a total of 69 patients with adequate disaggregated data to summarize. Mean age (± SD) at surgery was 53.3 ± 13.0 years (range 27–80 years); 78% of the patients were women. Tumor size was skewed toward smaller lesions, with a mean volume of 24.4 ± 2.9 cm^3. Intraoperative impressions were of gross-total resection in 76% of cases. The most common complication reported was CSF leakage, occurring in 32% of the cases (22 of 69). The rate of CSF leakage was not affected by size ($p = 0.52$), location of tumor ($p = 0.9$), or age ($p = 0.56$). There was 1 death overall. The mean duration of follow-up was 21 ± 18 months.

Conclusions. Transnasal endoscopic resection of anterior cranial base meningiomas is feasible in selected cases. Reported resection rates are adequate, although the follow-up in the reported series is too short (mean 21 months) to make definitive conclusions regarding the long-term effectiveness. Cerebrospinal fluid leakage is a common complication, although it appears not to be associated with additional morbidity except for the need for reoperation. Long-term results are necessary before considering TNE resection as a valid alternative, in selected cases, to the more established transcranial techniques. *(DOI: 10.3171/2011.1.FOCUS118)*

Key Words • **meningioma** • **endoscopic approach** • **endonasal approach** • **neurosurgery**

Midline anterior fossa meningiomas, such as olfactory groove and parasellar (including both tuberculum sellae and planum sphenoidale) tumors constitute approximately 12%–20% of all intracranial meningiomas.[23] Treatment for anterior fossa meningiomas typically entails resection. Standard transcranial surgery includes unilateral frontotemporal, or subfrontal and bifrontal approaches.[23] Newer approaches include minimally invasive supraorbital keyhole craniotomies with endoscopic assistance.[9,10]

In the past 10 years, there has been an explosion of interest in the application of TNE therapy for sellar and anterior cranial fossa lesions. With increased experience, surgeons have tackled more formidable pathologies such as larger and more technically difficult anterior fossa meningiomas.[2] Advantages of TNE over transcranial approaches include minimization of brain retraction and optic apparatus manipulation, earlier identification of the pituitary gland, and a cosmetically appealing postoperative result with no visible scar. Endoscopic transnasal surgery is also appealing to patients because it is perceived as being less invasive than the more traditional transcranial route.[25] However, despite several small single-center series, the potential role of TNE resection for anterior cranial base meningiomas is not defined, and to date there has been no critical evaluation of the literature regarding its effectiveness. In this report, we systematically analyze the available literature regarding TNE surgery for anterior skull base meningiomas. We also include a personal series of patients surgically treated by 2 of the authors (G.F. and E.P.).

Abbreviation used in this paper: TNE = transnasal endoscopic.

Methods

Chart Review

The records of 13 consecutive patients who underwent TNE removal of parasellar meningiomas through a pure TNE approach performed by 2 of the authors (G.F. and E.P.) were retrospectively reviewed. Standard extended

endoscopic transtuberculum approaches were performed (Video 1).

Video 1. Case 2. An edited recording of the removal of a parasellar meningioma, demonstrating representative portions of the approach and resection and, at the end of the video clip, the closure with fascia lata. Click here to view with Windows Media Player. Click here to view with Quicktime.

Literature Search

Unique articles were identified by means of Ovid MEDLINE using the following MeSH headings: "endonasal," "endoscopic," "extended transphenoidal," "meningioma," "sellar," "transnasal," "olfactory groove," "tuberculum sellae," "planum," alone and in combination. We then searched all references in these manuscripts. The inclusion criteria for this set of articles were as follows: 1) individual patient data were reported in a disaggregated fashion, 2) the primary treatment modality was clearly reported and limited to endonasal endoscopic surgery, and 3) outcome data were reported, including follow-up duration and/or time until death.

Data Extraction

Data from individual reports and case series were extracted. Manuscripts reporting only sum-aggregate results were not used, as these data did not permit meaningful analysis; however, these articles are included in our discussion. Tumors with posterior fossa extension were excluded due to unknown origin; this applied to the case series reported by Gardner et al.,[14] from which 7 tumors were excluded as being possibly petroclival. Follow-up duration was tabulated in months. Disease status, mortality, and cause of death were extracted and coded for as of death or the termination of follow-up. There was inadequate follow-up to permit survival analysis. We did not distinguish between tuberculum sellae and planum sphenoidale tumors, we simply included this as one group, labeled PS (parasellar). This was done because the difference between these two locations was often not clearly defined in the original manuscripts, and also the largest series on this topic did not distinguish these tumors, recognizing the difficulty in separating them.[14]

Statistical Analysis

The Pearson chi-square test was used to analyze for differences in preoperative categorical factors. The results of statistical tests were considered significant at $p < 0.05$. Continuous variables are presented with the SE unless otherwise noted. Differences in age were tested for significance using the independent-sample t-test after demonstrating normality of the data. All descriptive and statistical analysis was performed using JMP 8.0.

Results

Patient Series

Thirteen patients were treated by 2 of the authors (G.F. and E.P.) for meningioma using a TNE approach between 2003 and 2010. There were 11 women and 2 men with a mean age of 62 ± 15 years (range 31–77 years, median 67 years). Two patients (15%) had undergone prior resection via a craniotomy. The maximum diameter of tumors ranged from 13 to 35 mm, with an average of 24.3 ± 6.6 mm. Figure 1 shows the lesions in the first 8 consecutive cases as examples of the spectrum of pathology treated. Twelve of the 13 patients presented with visual deficit and 1 had persistent headaches (Table 1). At surgery, tumors were judged to be soft in 3 cases, firm in 5, fibrotic in 3, and calcified in 2. Of the 12 patients with documented postoperative visual examinations, vision was found to have improved in 8, remained unchanged in 4, and worsened in none. Postoperative imaging confirmed complete tumor resection in 7 of 13 cases; in 6 cases there were small remnants. In these last 6 cases, 3 patients had undergone TNE resection with the only goal being decompression of the optic apparatus. Therefore, of the 10 cases in which radical resection was the goal, it was achieved in 7. Figure 2 demonstrates a typical postoperative appearance after TNE resection. Significant postoperative complications occurred in 1 patient, who suffered a postoperative left anterior cerebral artery stroke causing right leg weakness. There were no episodes of postoperative CSF leakage in this series. Follow-up data were available in 10 patients (mean duration of follow-up 13 months, median 8 months). All but 1 of these 10 patients were alive at the time of this writing (December 2010); in the single patient who died, the cause of death was not related to the tumor or the surgery.

Meta-Analysis

On the basis of the literature search, we identified a total of 69 patients with adequate disaggregated data to summarize. There were 50 parasellar and 19 olfactory groove tumors.[3,5,6,10,14,18,24] Patient age was parametrically distributed with a mean (± SD) of 53.3 ± 13.0 years (range 27–80 years) at the time of surgery. There were 50 women (78%) and 14 men (21%). Tumor size was significantly skewed toward smaller lesions with minimum, first quartile, median, third quartile, and maximum values of 1.4, 8.6, 20, 26, and 109 cm^3, respectively. Average maximum diameter was 27.5 mm. In 27% of cases, the patients had prior treatment either by a transsphenoidal or transcranial approach. Of the 69 resections, 76% were qualified as gross total; there were equal proportions of those declared subtotal (12%) or near total (12%). Overall, the CSF leakage rate was 32% (with CSF leak occurring in 22 of 69 cases). The CSF leakage rates for olfactory groove and parasellar tumors were 26% (5 of 19) and 34% (17 of 50), respectively; this difference was not significant ($p = 0.9$). The CSF leakage rate was not affected by tumor size ($p = 0.5$) or patient age ($p = 0.6$). There was 1 death overall. The mean (± SD) duration of follow-up was 21 ± 18 months.

Discussion

Midline anterior fossa meningiomas, specifically olfactory groove and parasellar meningiomas, have conventionally been removed via various transcranial subfrontal approaches. In the modern era of microneurosurgery, the first report of extended transnasal removal of a meningi-

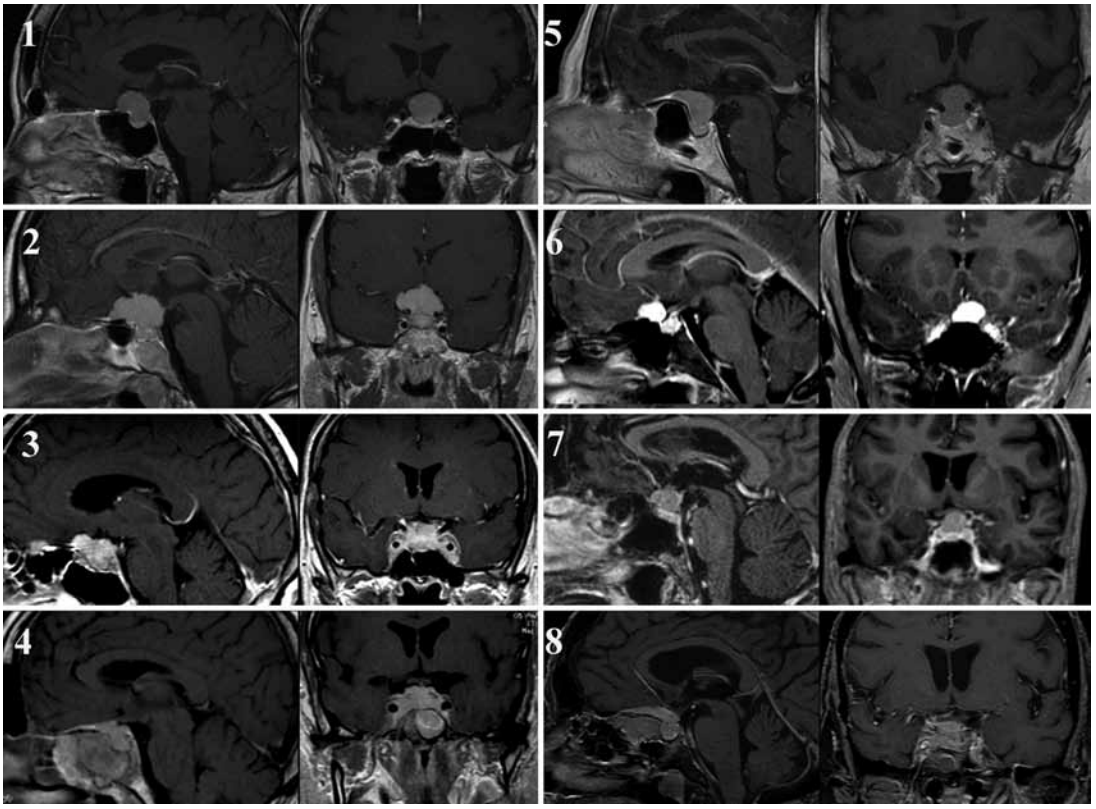

Fig. 1. Preoperative sagittal **(left)** and coronal **(right)** contrast-enhanced T1-weighted MR images obtained in the first 8 cases (as numbered) in the senior authors' series of 13, demonstrating typical lesions treated with TNE resection. In general these lesions are midline, do not extend outside the carotid arteries, and are relatively small.

oma is credited to Weiss and coworkers in 1987.[3] Following the pioneering work of Jho and others, TNE resection has been applied to a variety of lesions of the cranial base including anterior cranial fossa meningiomas.[15,16] Transnasal endoscopic surgery allows a window to the anterior skull base of the approximately 15–20 mm left to right by 25–30 mm anterior to posterior.[2] The approach is relatively straightforward. However, it has been suggested that resection of complex tumors such as meningiomas through a TNE approach is for the "virtuosos only."[11,12]

TABLE 1: Clinical and demographic characteristics in 13 patients who underwent TNE resection of parasellar meningiomas*

Case No.	Age (yrs), Sex	Tumor Size (mm)	Previous Treatment	Presenting Symptoms	Postop Vision	Postop MRI	FU (mos)	Complication
1	70, F	22 × 16	none	BTHA	normal	negative	20	none
2	31, F	26 × 18	none	BTHA & rt AD	improved	negative	11	none
3	59, M	25 × 14	craniotomy	lt blindness & rt AD	stable	remnant	65	none
4	68, M	28 × 27	none	rt AD	improved	remnant	8	none
5	77, F	30 × 25	none	lt AD & rt AD	stable	remnant	3	stroke†
6	32, F	13 × 10	none	headache	normal	negative	3	none
7	72, F	14 × 12	craniotomy	lt blindness	improved	remnant	8	none
8	76, F	31 × 18	none	rt blindness & lt AD	stable	remnant	13	none
9	67, F	17 × 22	none	lt AD & rt AD	improved	negative	3	none
10	69, F	25 × 12	none	BTHA	NA	negative	NA	none
11	57, F	NA	none	BTHA & AD	improved	negative	NA	none
12	64, F	20 × 18	none	BTHA	normal	negative	0	none
13	62, F	30 × 35	none	lt blindness & rt AD	stable	remnant	NA	none

* AD = acuity deficit; BTHA = bitemporal hemianopia; FU = follow-up; NA = data not available.
† Left anterior cerebral artery ischemia, right lower-extremity hemiparesis.

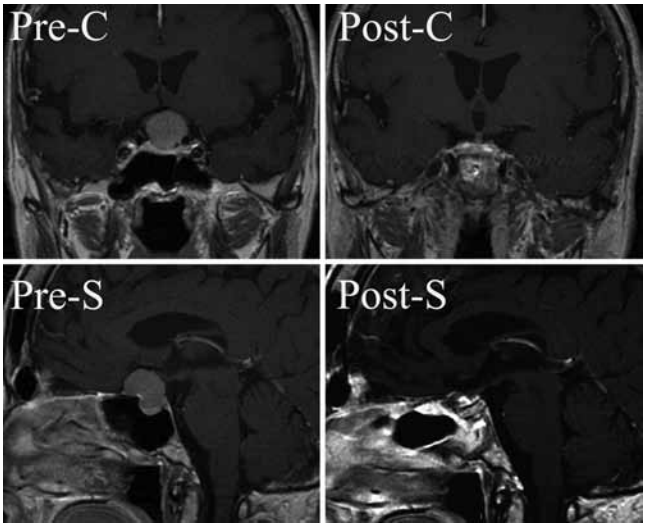

Fig. 2. Case 1. Preoperative **(left)** and postoperative **(right)** T1-weighted contrast-enhanced coronal **(upper)** and sagittal **(lower)** MR images demonstrating a complete resection and the typical postoperative appearance.

We report a meta-analysis of various studies that includes a total of 69 cases of anterior fossa meningiomas treated with TNE therapy and for which enough information was available to allow for a disaggregate analysis. Overall, there were 50 parasellar and 19 olfactory groove meningiomas in addition to the 13 from our series.[3,5,6,10,14,24] As one would expect, there was a large proportion of women in this series, which is concordant with other large meningioma series.[1,13] The major shortcoming of evaluating a series of TNE resections of anterior fossa meningiomas at this time is the lack of adequate long-term data. Most currently available reports are relatively limited, as they are series that report the direct surgical accomplishments of the technique and do not focus on appropriate outcome assessment for meningiomas. Most of these studies have 6–24 months of follow-up (mean 21 ± 18 months).[24] Therefore, no conclusions can be made about the effectiveness of this surgical strategy.

Direct comparison within one institution between TNE and TC surgery for anterior cranial fossa meningiomas suggested that the amount of resection is similar in the 2 approaches (86.4% gross-total resection with TNE treatment and 83.3% gross-total resection with transcranial surgery).[5] However, removal is most typically reported as gross total in TNE series and is not gradable in the Simpson grading system, therefore making direct comparison difficult.[9,10] Overall, the reported gross-total resection rates for TNE surgery are 50%–84%, whereas total resection rates vary between 70% and 100% with trancranial surgery.[3,6,9,10,14,22,24] In a series of 51 patients with parasellar meningiomas, de Divitiis et al.[5] reported that morbidities attributed to transcranial resection, such as hematomas, seizures, and injuries to surrounding neurological structures, were lower in patients treated with a transnasal approach. However, CSF leak was increased with the transnasal approach. A comparison between transcranial and TNE resection is not feasible based on the available data. The major limit of TNE surgery for meningiomas is the lateral extent of the tumor and therefore, surgical series of TNE surgery are skewed toward smaller, midline lesions, while transcranial surgery series encompass the entire variety of these tumors, which often are asymmetrical with significant lateral extension and, especially in cases of the olfactory groove variant, can reach a large size.

Cerebrospinal fluid leaks are common after TNE removal of anterior fossa meningiomas (Table 2). The overall CSF leakage rate for this meta-analysis was 32% (with leaks occurring in 22 of 69 reported cases).[3,5,6,10,14,24] Cerebrospinal fluid leaks were reported to occur between 0% and 40% of the time in individual experiences.[3,24] In the only interinstitutional series reported, the rate of CSF leakage after TNE was 14%, whereas for transcranial surgery it was 0%.[9,10] Despite advances in reconstruction techniques, postoperative CSF leakage remains a significant complication associated with TNE. However, the rate of morbidities such as meningitis is very low despite the need at times for multiple repeated treatments for a recalcitrant CSF leak.[9,10] Furthermore, although most papers discuss the drastic reduction in postoperative CSF leaks in these patients using vascularized nasoseptal flaps, such as the Janus flap, there is no case series or report formally supporting this notion.[21] In the series of 13 patients reported herein, we did not encounter any case of CSF leakage. Important factors to consider to explain the very low incidence in our series are the careful selection of patients (many more patients were treated via the transcranial route during the period of this study by one of the senior authors [G.F.]) and the fact that the senior authors (G.F. and E.P.) embraced the TNE approach for anterior cranial base meningioma "late" in their evolution after many years of experience with a variety of other primary sellar lesions.

Visual improvement is the norm after optic nerve decompressive therapy, which appears to be enhanced by the TNE approach.[24] Authors laud the TNE approach for early decompression of the optic canal and 270° release compared with transcranial approaches.[4–6] Typically, visual improvement is reported in 70%–80% of patients who had deterioration of vision preoperatively, and 7%–12% of patients experience worsening of vision postoperatively.[8–10] Regarding transcranial approaches for parasellar meningiomas, deterioration of vision has been reported as occurring in 19% of cases.[1] Further, Nakamura et al.[20] evaluated vision outcomes based on the size of parasellar meningiomas and the transcranial approach. They reported that for patients with meningiomas less than 30 mm in diameter, the rate of visual decline after surgery was 9.7% versus 16% in those with meningiomas greater than 30 mm. Overall, there appears to be no difference in reported visual outcomes for transcranial versus TNE procedures.[22] However, we think that the TNE approach may offer some advantages for resection of small midline (usually pure parasellar tumors) causing early visual deficits. In these cases, management of the portion of the tumor under the ipsilateral optic nerve can be challenging, especially in the setting of marginal preoperative visual function. Management of the optic apparatus may not be as challenging or traumatic from

TABLE 2: Summary of reported series of anterior skull base meningiomas series treated via TNE approaches*

Authors & Year	Total No. of Cases	OG	PS	Years	No. of Cases w/ CSF Leak (%)	Mean FU (mos)
Fatemi et al., 2009	14	0	14	2000–2008	4 (29)	27
Wang et al., 2009	7	0	7	2002–2007	1 (14)	23
Gardner et al., 2008†	28	15	13	2002–2005	12 (43)	—
de Divitis et al., 2008	11	4	7	2004–2007	3 (27)	19
Dehdashti et al., 2009	1	0	1	—	1 (100)	—
Cook et al., 2004	3	0	3	—	0 (0)	—
Laufer et al., 2007	5	0	5	—	1 (20)	9
present series	13	0	13	2003–2010	0 (0)	14

* OG= olfactory groove; PS = parasellar.

† Seven cases were excluded due to probable petroclival origin of tumor.

an "inferior" view/approach like the one provided by the TNE exposure.

As expected, patient selection and the surgeon's degree of comfort with one approach over the other are crucial when determining the best surgical strategy for the resection of anterior fossa meningiomas. Patient age, comorbidities, tumor size, relationship to surrounding neurovascular structures, and lateral extension are also important issues to consider. An additional important factor is the consistency of the meningioma. There is an expanding number of series in the literature in which MR imaging has been used to try and predict whether a meningioma is soft/suckable or firm/fibrous.[17,19] Determining this consistency might assist the surgeon in preoperative planning, patient counseling, and intraoperative decision-making.

Conclusions

A review of early series and our own experience suggests that TNE resection of anterior cranial fossa meningiomas can be safely achieved in selected cases (usually involving small and midline lesions). Cerebrospinal fluid leakage is a significant complication of this approach although its incidence may be decreasing with more experienced and better closure techniques. Visual outcomes are comparable to those achieved with a transcranial approach. However, there is not adequate information regarding the long-term efficacy of TNE surgery for anterior cranial base meningiomas, given that the mean follow-up of published series is only 21 months. Of course, patient selection and surgeon degree of comfort with one approach over the other are important factors in determining the surgical strategy to follow. However, for small, purely midline meningiomas arising from the posterior portion of the planum and/or the tuberculum, the TNE approach may provide some advantages over classic transcranial techniques especially in regard to management of the tumor/optic apparatus interface.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Van Gompel, Frank, Pasquini, Lanzino. Acquisition of data: all authors. Analysis and interpretation of data: Van Gompel, Frank, Pasquini, Zoli, Lanzino. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Van Gompel. Administrative/technical/material support: Zoli. Study supervision: Frank, Pasquini, Lanzino.

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Editorial

Endonasal versus transcranial resection

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Anterior skull base meningiomas are among the easiest to remove completely with a very low morbidity rate and excellent long-term outcome.[11] This goal can be reached in nearly all frontobasal midline meningiomas by using a small minimally invasive frontolateral craniotomy. The approach allows one to achieve optimal functional results (both ophthalmological and endocrinological) and to avoid new deficits and complications in general, which is the second goal of their treatment.

From a historical point of view larger craniotomies have been favored because they offer a better overview of the whole tumor and of the surrounding structures, as well as more space for manipulations, giving a feeling of safety to the surgeon. The anatomical location and relations of some meningiomas to the surrounding vital structures restrict the operative radicality, whatever approach is used. Examples of such tumors are the cavernous sinus and the petroclival meningiomas.

The introduction of the surgical microscope improved intraoperative illumination and visualization. Tumor removal became feasible through smaller craniotomies. However, the use of the microscope did not necessarily mean that a less invasive technique was applied. Such less-invasive miscrosurgical techniques were developed later by neurosurgical masters, such as Yaşargil and Samii. The keyhole concept, which benefits from the application of both microscope and endoscope, was elaborated by Perneczky. In the case of frontobasal meningiomas, the gentle dissection of the tumor capsule from the optic nerve/tract and from the hypothalamopituitary system with their sophisticated vascular supply became possible. Samii described recently his interindividual improvement in terms of achieving more radical resection and better functional results. In a series of 72 cases with tuberculum sellae meningiomas, in which the bifrontal, then the pterional and then—the frontolateral approach were used, total resection was achieved in 92%.[10] Notably, the rate of visual improvement increased from 46% to 64%, and then to 78% with each of the approaches. Fahlbusch published a series of 47 patients operated on in the period 1982–2002: 46 of 47 of the meningiomas were removed totally and the rate of visual improvement was 80%.[6] Until 2006, additional 22 cases were operated and further improvement of the results was possible: all tumors were resected completely and the visual improvement rate was 85%. Mathiesen,[9] who favors the routine opening of both optic foramina, achieved even better rate of visual improvement—90%. Currently at the International Neuroscience Institute, we approach all frontobasal midline, including the large and giant olfactory meningiomas, via the minimally invasive frontolateral craniotomy.[5]

We cannot avoid the impression that some neurosurgeons—those that are not satisfied with their own surgical results, those who have never had the chance to be trained in microsurgery by experts, and those who started their neurosurgical training with endoscopy and want to expand its indications—are inclined to favor the endonasal transsphenoidal, respectively transethmoidal approach to the anterior skull base.

Harvey Cushing himself, who had pioneered the transsphenoidal approach for pituitary adenomas, changed from the transsphenoidal to the transcranial technique, which offered better visualisation and allowed more radical tumor resection. The first renaissance of transsphenoidal surgery occurred with the introduction of operating microscope; the second one, with the introduction of the endoscope. The latter technique, pioneered first by Jho, and then by Diviitis and Cappabianca, allows for even better illumination and visualisation of all structures, a panoramic overview of the operative field, and a possibility to "look around the corner." The excellent operative results of microsurgery for pituitary adenomas in experienced hands are meanwhile going to be achieved also with the pure endoscopic technique. Adequate publications on the outcome of endoscopic surgery should be expected.

The extended transsphenoidal approach to suprasellar lesions via the tuberculum sellae is best suited for surgery of small lesions.[2] Larger tumors, such as craniopharyngiomas extending to the foramen of Monro or tumors with lateral parasellar extension, are less suitable. For us, the main domain of the extended endonasal transsphenoidal approach is not the anterior but the posterior parasellar and clival area, for example, in cases of chordomas.

In this article, the authors from Rochester and Bologna present a series of 13 patients with frontobasal meningiomas, surgically treated by Frank and Pasquini in Bologna.[12] Meta-analysis of the literature is also per-

formed and includes 69 cases: 19 olfactory meningiomas and 50 suprasellar meningiomas. In this selective series, 7 (54%) of 13 tumors were removed completely, visual improvement occurred in 8 (62%) of 13, and 1 patient had a stroke. Unfortunately, no data regarding the pituitary function are provided. Commendably, CSF leaks could be avoided. In contrast, the literature review showed that the average CSF leakage rate was 32%: 26% in olfactory groove and 34% in suprasellar meningiomas. Although not discussed in this review, relatively high rates of pituitary insufficiency were reported in other series: 14%–20% rates of permanent diabetes insipidus[3,4,8] and up to a 7.7% rate of panhypopituitarism.[7] In a recently published selective series of 9 cases there were no CSF leaks but only 6 of 9 tumors were removed totally; visual improvement occurred in 6 patients, and 1 patient had permanent diabetes insipidus.[1]

The comparison of these selective series that exclude tumors with asymmetric extension to the major (lateral) vascular structures with the craniotomy series shows that in the latter total resection is feasible in nearly all cases, the rate of visual improvement is higher and hormonal disturbances develop only exceptionally.[6]

The authors of the present paper[12] conclude that "Transnasal endoscopic resection of anterior cranial base meningiomas is feasible in selected cases" and that "long-term results are necessary before considering transnasal endoscopic resection removal as a valid alternative in selected cases, to the more established transcranial techniques." For an ultimate comparison of the 2 techniques the following additional criteria should be met: standardized ophthalmological protocol (as the one used by Fahlbusch and Schott[6]), long-term follow up, pre- and postoperative endocrine dynamic test results, postoperative MR imaging follow-up, and larger patient series. In our point of view, the frontolateral approach is the most appropriate and favorable approach in all meningiomas of the anterior midline. Total removal can be achieved in nearly all cases and long-term follow-up studies are available.

Still, we would not neglect the possibility that the endonasal approaches to skull base tumors will benefit from future developments and optimization of the visualization tools. At present, however, the question on the optimal management of frontobasal meningiomas is already answered. *(DOI: 10.3171/2011.2.FOCUS1161)*

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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