Strategy and Technique of Endonasal Endoscopic Bony Decompression and Selective Tumor Removal in Symptomatic Skull Base Meningiomas of the Cavernous Sinus and Meckel's Cave

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BACKGROUND: **Parasellar meningiomas involving the cavernous sinus and Meckel's cave pose a management challenge because of invasion around neurovascular structures and the pituitary gland. The management options range from aggressive resection to focused radiotherapy alone. We present a strategy for these tumors that includes endonasal bony decompression, partial tumor removal, and stereotactic radiotherapy (SRT) in select cases.**

METHODS: **The tumor location, previous treatments, cranial neuropathies, pituitary dysfunction, tumor control rates, use of stereotactic radiosurgery, SRT, and complications were retrospectively evaluated.**

RESULTS: **Twenty patients (age range, 43–81 years; 65% women; 90% with World Health Organization grade I; median follow-up, 57 months; 14 without previous debulking and RT; 6 with previous debulking and RT) underwent endonasal bony decompression and partial tumor removal. The most common tumor locations were cavernous sinus (95%), Meckel's cave (95%), sella (75%), petroclival (60%), and optic canal/orbit (30%). Three patients with large meningiomas underwent staged transcranial and endonasal debulking. Of the 14 patients without previous debulking and RT, 11 had undergone postoperative SRT, with tumor shrinkage in 3 (27%). At the last follow-up examination, for these 14 patients and the 6 patients who had undergone previous surgery and RT, tumor control was 100% and 33% (P < 0.001) and the cranial neuropathies had improved in 57% and 33%, respectively. Major complications occurred in 2 patients: a permanent sixth cranial nerve palsy and cerebrospinal fluid leakage requiring reoperation.**

CONCLUSIONS: **Endonasal bony decompression and selective tumor removal, followed by SRT, appears to be a reasonable treatment option for most previously untreated parasellar meningiomas. For patients who have undergone previous debulking and RT, new targeted treatment strategies are needed.**

INTRODUCTION

Parasellar and cavernous sinus (CS) meningiomas pose significant management challenges because they will frequently invade around the cranial nerves (CNs), pituitary gland, and circle of Willis vessels. Attempts at aggressive gross total resection or near total resection have been associated with high rates of new cranial neuropathies and little improvement in pre-existing CN deficits.[1-3] Because of the known risks of transcranial surgery and relatively high rates of tumor control with radiotherapy (RT)[4-7] and radiosurgery,[5,7-11] some have advocated

Key words
- Cranial neuropathy
- Double vision
- Endocrinopathy
- Endonasal approach
- Endoscopic
- Meningioma
- Neurosurgery
- Tumor

Abbreviations and Acronyms
CN: Cranial nerve
CS: Cavernous sinus
CSF: Cerebrospinal fluid
MRI: Magnetic resonance imaging
RT: Radiation therapy
SRS: Stereotactic radiosurgery
SRT: Stereotactic radiotherapy
WHO: World Health Organization

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the use of RT as first-line treatment in the management of many skull base meningiomas.[9,11] This strategy, however, has potential drawbacks: the lack of a tissue diagnosis and the increasing ineffectiveness and potential complications of stereotactic radiosurgery (SRS) or stereotactic RT (SRT) with increasing tumor size.[12,13] An alternative approach that has been applied to invasive parasellar meningiomas is limited debulking via transcranial or microscopic transsphenoidal approaches, followed by SRS or SRT.[14,15] During the past 10 years, we have used a similar endoscopic approach, which offers effective CN and pituitary gland decompression, potentially enhances the efficacy and safety of SRT, and provides definitive tissue specimens for diagnosis and genomic analysis.[16] In the present report, we have described this approach, the technical nuances, and outcomes for a consecutive series of patients.

Video

Video available at www.sciencedirect.com

METHODS

Data Evaluation

After obtaining institutional review board approval with a waiver of the informed consent requirement, we identified patients who had undergone endonasal surgery for meningiomas by the senior author (D.F.K.) from 2009 through 2015 through a retrospective review of the patients' medical records. Tumors not involving the CS or Meckel's cave were excluded. Data were collected regarding patient demographics, tumor characteristics, previous treatments, pre- and postoperative neurological and endocrinological status, and surgical and nonsurgical complications. The pre- and postoperative magnetic resonance imaging (MRI) scans were reviewed for tumor progression. The tumor location was determined from the MRI findings and classified as involving the CS, Meckel's cave, sella, orbit/optic canal and/or petroclival region. All the patients had undergone at least a 3-month follow-up clinic visit and MRI.

The patients were stratified into 2 groups according to their treatment history: 14 patients without previous RT or surgical debulking (2 had undergone a biopsy via an endonasal or transcranial approach) and 6 patients with previous surgical debulking and RT. The categorical variables were compared with the outcomes using χ^2 analysis. A probability value of $P < 0.05$ was considered to indicate statistical significance.

Surgical Technique and Perioperative Care

Early in our series, an endonasal microscopic approach with endoscopic assistance was used. However, since 2010, we have used a fully endoscopic approach. This approach has been previously described in detail.[16-18] In brief, it entails a 2-surgeon (otolaryngologist and neurosurgeon) team using a binostril, bimanual technique to complete a posterior septectomy with a large bilateral sphenoidotomy. Harvesting of a nasoseptal flap was performed in specific cases when a large (grade 3) cerebrospinal fluid (CSF) leak was anticipated.[19] A key part of the procedure is bony decompression of the involved skull base region, including the sella, CS, Meckel's cave, optic canals, and/or clivus For tumors involving Meckel's cave, we would also perform medial pterygoidectomy.[20] Although all these tumors, by definition, will be intimately involved with the parasellar and, often, the paraclival segments of the carotid artery, the bony decompression and dural opening is guided by the frequent use of Doppler ultrasound localization of the carotids. Excessive tumor vascularity was not an issue in any of our patients, despite leaving residual tumor in all cases. Hemostasis was obtained in standard fashion with warm irrigation, Surgifoam (Johnson & Johnson, Somerville, New Jersey, USA), and the occasional use of muslin gauze.[17]

The tumor is removed selectively with the goal of decompressing the pituitary gland, optic apparatus, CS nerves, Meckel's cave, and brainstem (**Figures 1** and **2** and **Supplementary Video 1** of patient 10, which demonstrates our technique). In patients who have undergone previous surgery and RT (**Figure 3**), tumor removal will generally be less aggressive. In many cases, in particular, CS, Meckel's cave, and sellar tumors, the firm and fibrous tumor texture will often preclude substantial tumor removal. For fibrous tumors, the side-cutting aspirator (NICO Myriad, Indianapolis, Indiana, USA) will occasionally be used. An additional goal was to create a 2-mm separation between the residual tumor and optic apparatus to allow for a safe margin for radiosurgery. However, tumor firmness and microvasculature adhesions to the optic apparatus typically precluded such aggressive removal. Ultimately, all the patients in the present series who had undergone RT underwent SRT and not SRS.

After tumor removal and hemostasis, closure and skull base reconstruction were performed as recently described.[19] We have routinely used an abdominal fat graft to fill dead space created by the extensive tumor removal, followed by a collagen sponge (Helistat [Collagen Hemostatic Sponge, Integra LifeSciences Corp., Plainsboro, New Jersey]). If a high-flow (grade 3) CSF leak occurred, a nasoseptal flap was used. Merocel packs (foam polymer of polyvinyl alcohol, Merocel, Medtronic Inc., Minneapolis, Minnesota, USA) were often used to buttress the layered reconstruction. These were removed on the fifth day after surgery. The patients were given antibiotic therapy (amoxicillin/clavulanate or clindamycin) while the Merocel packing was in place.

Postoperative Care

All patients were seen as outpatients by the neurosurgery and otolaryngology department within 10 days for immediate postoperative evaluation and at 3 months to assess the early postoperative outcome. Semiannual or annual imaging with office visits or telephone follow-up were used for subsequent follow-up. Pituitary hormonal function was assessed within 3 months for all patients and, subsequently, on an ongoing basis in conjunction with the endocrinologist.

Stereotactic RT

The decision to give SRT (instead of SRS) was reached by consensus among the neurosurgeon and RT oncologists according to the proximity of the optic apparatus to the residual tumor mass. Postoperative SRT was given to all patients who had not received previous RT when radiographic evidence of tumor growth was noted. The typical dosing regimen was delivered using a Varian linear accelerator for a total of 5400 cGy given in 30 fractions (180 cGy/fraction) within 6 weeks with a 3-mm volume expansion.

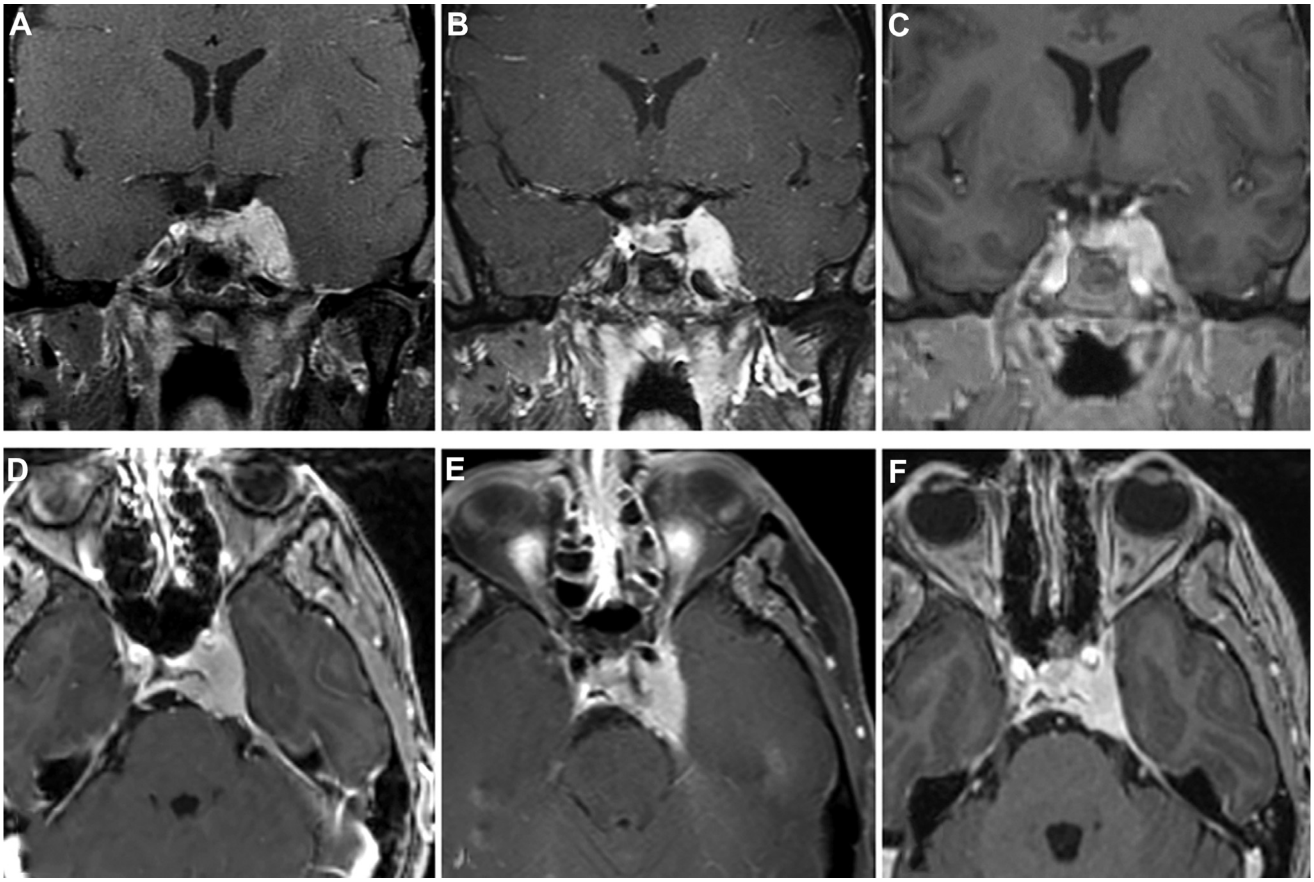


Figure 1. Patient 9. A 53-year-old woman had presented with intermittent double vision. Examination revealed mild left-sided ptosis. Coronal (**A**) and axial (**D**) T1-weighted magnetic resonance imaging (MRI) studies with gadolinium enhancement showed a parasellar tumor with extension into the left cavernous sinus (CS) and Meckel's cave. The findings from the endocrinologic evaluation were normal. Endonasal endoscopic bony decompression of the sellar and left CS was performed with tumor debulking with left sella and medial CS. Coronal (**B**) and axial (**E**) T1-weighted MRI studies with gadolinium enhancement on postoperative day 1 demonstrating decompression of the left medial CS. Pathological evaluation confirmed World Health Organization grade I meningothelial-type meningioma with low Ki-67 expression. Postoperatively, the patient's ptosis and diplopia improved. She underwent stereotactic radiotherapy 5 months after surgery for mild tumor progression. Coronal (**C**) and axial (**F**) MRI scans at 72 months after surgery showing stable tumor within the left CS. The patient remained clinically stable, without endocrinological evidence of pituitary dysfunction.

RESULTS

Demographic Data and Previous Treatments

During the study period, the senior author (D.F.K.) performed selective endonasal bony decompression and tumor removal in 21 patients with meningiomas involving the CS and/or parasellar regions (Table 1). One patient, who had been lost to follow-up after the immediate postoperative visit, was excluded from the present series. All 20 patients in the present his series had $\geq$1 year of follow-up data available. Of the 20 patients analyzed (age range, 43–81 years; 65% women), the tumor location was the CS (95%), Meckel's cave (95%), sella (75%), petroclival region (60%), and optic canal/orbit (30%). Of the 20 patients, 17 (85%) had had tumor in multiple locations. Eight patients (40%) had undergone previous treatment at other institutions, including endonasal biopsy in 1 patient, tumor debulking surgery in 7, and RT in 6. Of the patients who had undergone RT before treatment at our institution, 2 had undergone multiple rounds of SRS, 3 had undergone multiple rounds of SRS plus SRT, and 1 had undergone only SRT (Figure 4). Of our 20 patients, 14 (70%) had not undergone preoperative RT.

Indications for Surgery

All the patients were symptomatic before surgery and/or had documented tumor progression on serial MRI studies. The symptoms included cranial neuropathy (80%), headache (10%), and endocrinopathy (35%; Table 1). Preoperative tumor progression had been documented in 100% of the previously operated tumors and 8% of the untreated tumors.

Surgical Approach Details and Pathological Data

The first 2 patients in the present series had undergone a predominantly microscopic approach with endoscopic assistance. The remaining 18 patients had undergone a fully endoscopic

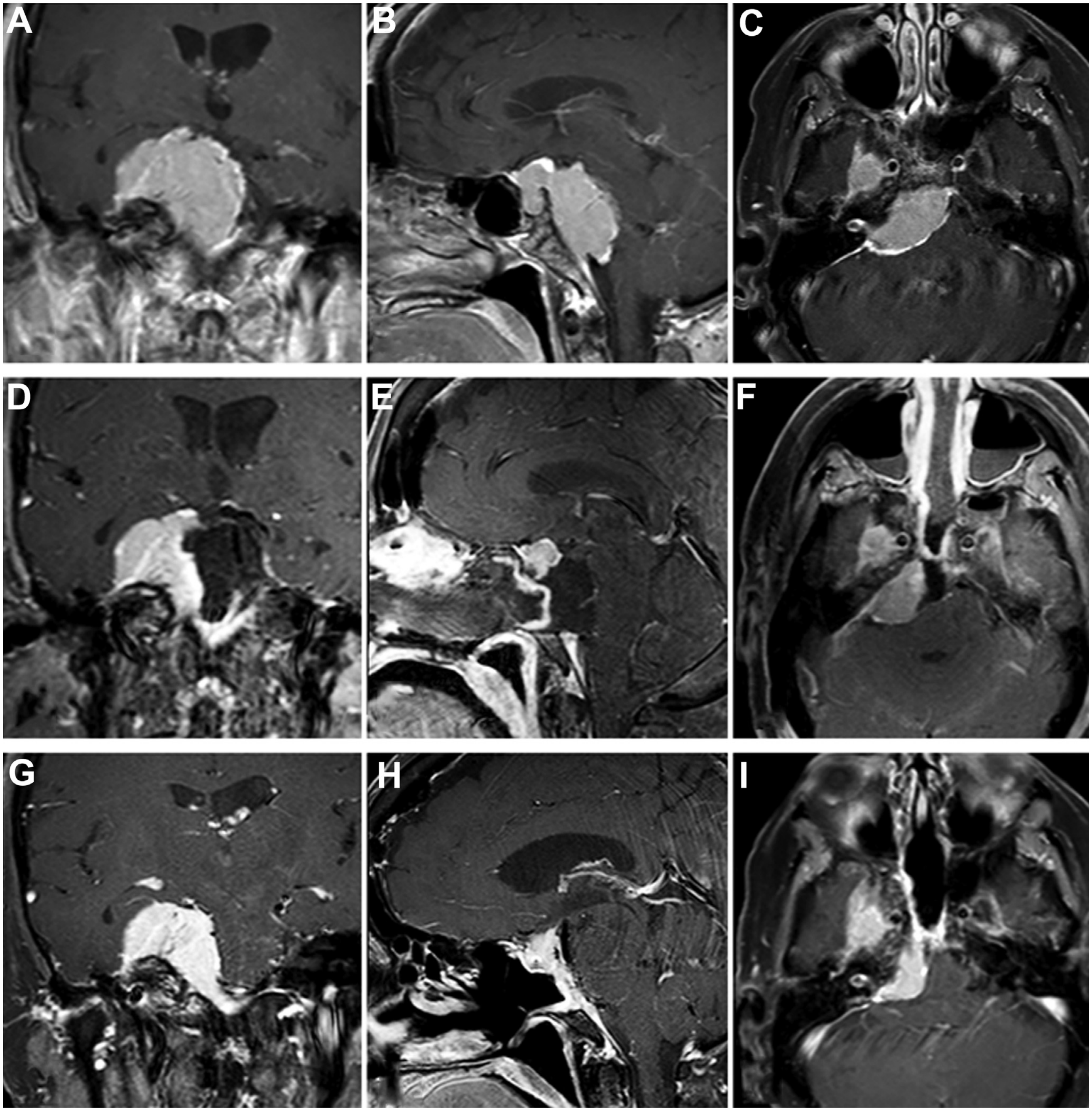
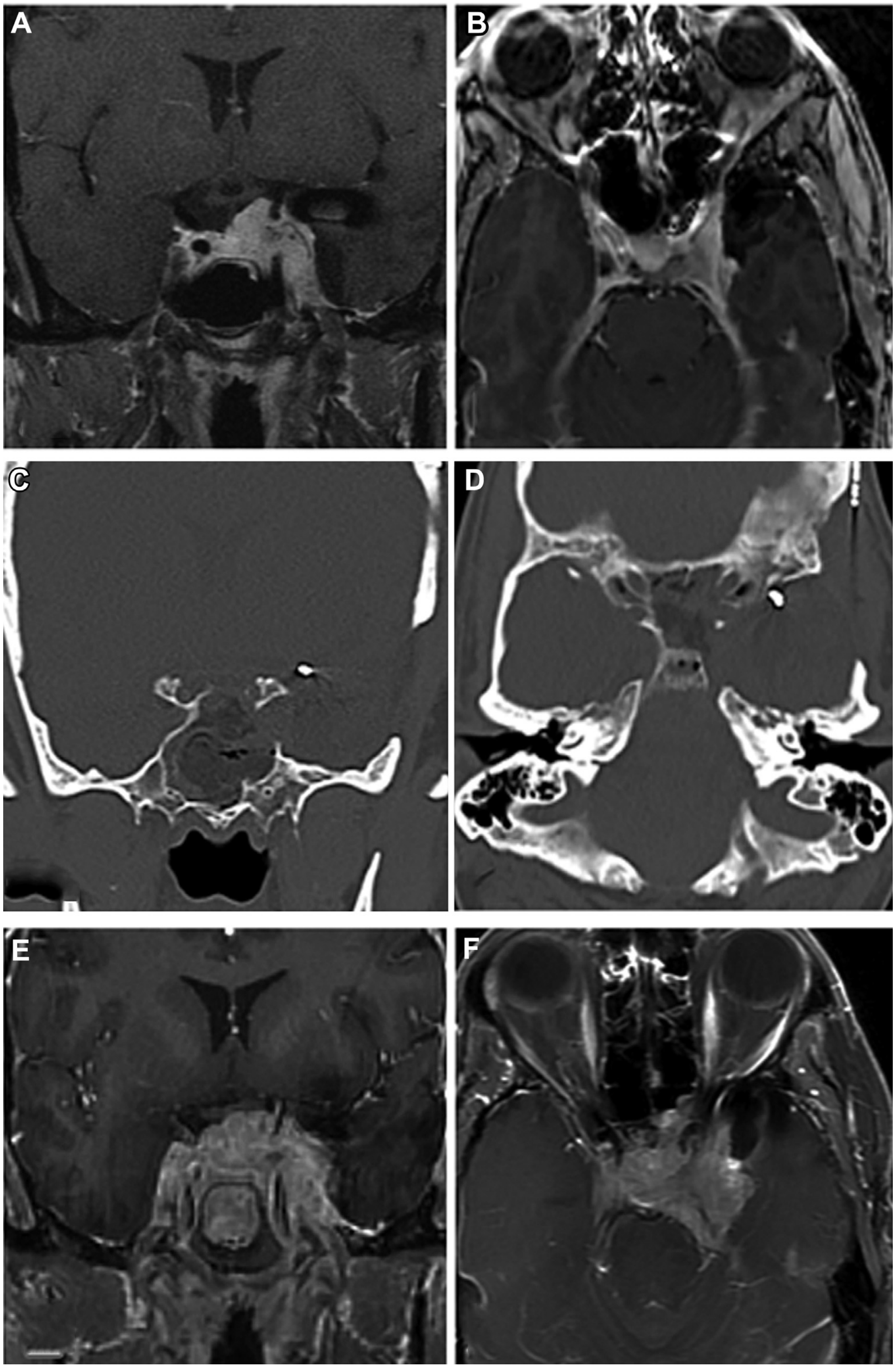


Figure 2. Patient 10. A 59-year-old woman had presented with increasing dizziness, balance problems, right orbital pain, and right cheek numbness. (**A**) Coronal, (**B**) sagittal, and (**C**) axial T1-weighted magnetic resonance imaging (MRI) studies with gadolinium enhancement revealing a large parasellar tumor with extension into the right cavernous sinus (CS), Meckel's cave, and the petroclival region, resulting in significant brainstem compression. An endonasal endoscopic transsellar, transplanum, transclival approach was used to debulk the tumor in the suprasellar cistern, medial CS, and posterior fossa. A grade 3 cerebrospinal fluid leak was repaired with abdominal fat, a collagen sponge, a nasoseptal flap, and tissue glue. The right CS, Meckel's cave, sella, and brainstem were decompressed, and the right sixth cranial nerve was exposed and preserved, aided by intraoperative nerve stimulation. Significant decompression of the brainstem was achieved. (**D**) Coronal, (**E**) sagittal, and (**F**) axial T1-weighted MRI scans with gadolinium enhancement on postoperative day 1 showing effective brainstem decompression and the nasoseptal flap. Pathological analysis confirmed a World Health Organization grade I meningothelial-type meningioma with low Ki-67 expression. Postoperatively, the patient recovered well, with preservation of normal extraocular movements. Her dizziness, balance, right orbital pain, and facial numbness had also all improved after surgery. She underwent stereotactic radiotherapy 9 months after surgery for mild tumor progression. (**G**) Coronal, (**H**) sagittal, and (**I**) axial MRI studies 53 months after surgery showing stable tumor burden and significantly improved pontine compression. The patient remained clinically stable, with normal pituitary gland function.



approach. Three previously untreated patients with large meningiomas (patients 12, 13, and 14) had undergone a planned staged approach several days apart. In 2 patients (patients 12 and 13), the craniotomy had preceded the endonasal debulking, and in 1 (patient 14), the endonasal debulking had preceded the craniotomy. All 3 patients had had large tumors with an estimated volume of ≥80 cm^3 and a maximal tumor diameter >6 cm. One additional patient who had undergone multiple previous treatments also had undergone supraorbital tumor debulking 5 months after the endonasal debulking.

All 20 patients had undergone planned partial tumor removal of <50% of the overall tumor volume. Intraoperative CSF leaks occurred in 13 patients (65%): 2 grade 1 (15%), 2 grade 2 (15%), and 9 grade 3 (69%) leaks. A nasoseptal flap was used in 10 patients (50%); 9 with grade 3 intraoperative CSF leakage and 1 with a grade 2 CSF leakage. The median hospital stay was 2.5 days (range, 1–18). Pathological analysis confirmed World Health Organization (WHO) grade I meningioma in 18 patients (90%) and WHO grade II tumors in 2 patients, 1 of whom had received preoperative SRS and SRT.

Tumor Control. At a median clinical follow-up duration of 57 months (range, 4–95), tumor control (Figure 5) had been achieved in all 14 patients (100%) without previous RT. In contrast, tumor control had been achieved in only 2 of the 6 patients with previous surgery and RT ($P < 0.001$). Postoperative SRT had been used in 11 of the 14 patients (79%) without previous treatment. Of these 11 patients, 3 (27%) experienced a decrease in the tumor size and 8 had stable tumor size. In the 6 patients with previous surgery and SRS or SRT, 2 tumors (33%) had remained stable in size and 4 (67%) had increased in size. Two of these patients died (patients 17 and 18). Patient 17 died of progressive brainstem compression almost 3 years after our original endonasal debulking, 18 months after a follow-up debulking, and 26 years after his original surgery and multiple rounds of SRS. Patient 18 died of progressive disease 24 months after our surgery after undergoing additional surgery and RT at another institution 18 months after our surgery.

Cranial Neuropathy. Of the 14 patients without previous treatment, 57% experienced improvement in preoperative cranial neuropathies. In contrast, of the 6 patients with previous surgery and RT, only 2 (33%) experienced improvement in cranial neuropathies ($P = 0.33$).

Visual and Ocular Motility Outcomes. Of the 8 patients who had presented with declining visual acuity, 6 had undergone optic canal bony decompression because of MRI evidence of tumor extending into the optic canal on the affected side. Vision improved in the postoperative period in 4 patients (66%) and had remained stable in 2 (33%), 1 of whom had undergone preoperative radiosurgery.

Eight patients, who had presented with complete or partial ophthalmoplegia secondary to meningioma invasion of the CS, had undergone bony decompression of the affected CS with selective medial CS tumor debulking. At the latest follow-up examination, the ophthalmoplegia had improved in 2 patients (25%) and had remained stable in 3 (38%). However, ocular motility had worsened in 3 patients (38%), 2 of whom had received preoperative SRS and 1 who had developed a new and permanent CN VI palsy immediately after surgery. Of these 8 patients, 4 were ineligible for SRT because of previous SRS. Three of these patients had received postoperative SRT, with none experiencing worsening ophthalmoplegia after treatment. The fourth patient experienced resolution of diplopia after surgery and underwent monitoring by serial imaging without postoperative SRT.

Trigeminal Function Outcomes. Four patients had undergone bony decompression of an affected Meckel's cave for trigeminal nerve symptoms. The symptoms improved in 2 patients (50%), remained stable in 1 (25%), and worsened in 1 (25%) in delayed fashion. Two of the patients in this subcohort had received postoperative SRT, and neither had experienced worsening symptoms after treatment. The patient with worsening trigeminal nerve symptoms after surgery had received preoperative SRS.

Endocrinopathy. No patient developed new gland dysfunction after surgery. Of the 7 patients with pre-existing pituitary gland dysfunction, 2 of 3 patients with hyperprolactinemia from a stalk effect had improvement after surgery. One patient had stable mild hyperprolactinemia without clinical symptoms at the 18-month follow-up visit. Of the remaining 4 patients with pre-existing gland dysfunction, 3 required continued hormonal replacement therapy and 1 was monitored without medical therapy for a low insulin-like growth factor-1 level. No significant difference was found in the improvement of endocrinopathy between the 6

Figure 3. Patient 16. A 55-year-old man had initially been treated 9 years earlier at an outside hospital with left frontotemporal craniotomy and debulking of a large parasellar meningioma with extension into the cavernous sinus (CS) and Meckel's cave invasion. Surgery had been followed by 2 rounds of radiosurgery 8 years and 1 year before his presentation to our hospital. On presentation, he had mildly decreased visual acuity in the left eye and mild diplopia. The findings from the endocrine workup were normal. Preoperative (**A**) coronal and (**B**) axial T1-weighted magnetic resonance images with gadolinium enhancement showing tumor progression into the suprasellar cistern and left CS with encroachment into the left optic canal. Endonasal endoscopic bony decompression of the left optic canal, CS, and Meckel's cave was performed, with tumor debulking from the suprasellar cistern, left medial CS, and left Meckel's cave. The patient's vision and diplopia improved in the immediate postoperative period. (**C**) Coronal and (**D**) axial computed tomography scans after surgery illustrating bony decompression of the CS and Meckel's cave region. Pathological evaluation confirmed a World Health Organization grade I meningothelial-type meningioma with low Ki-67 expression. The patient had begun to have progressive double vision and numbness in his left face ∼24 months after surgery. Imaging studies revealed increased fullness of the meningioma in the left CS and Meckel's cave region. He has been monitored by the neuro-oncology department. At his latest follow-up examination, he was receiving bevacizumab (Avastin) and octreotide (Sandostatin) therapy, with stable neurological examination findings and no pituitary dysfunction. (**E**) Coronal and (**F**) axial T1-weighted magnetic resonance images with gadolinium enhancement 64 months after surgery showing stable tumor burden within the suprasellar cistern, left CS, and Meckel's cave.

Table 1. Patient Characteristics and Clinical Outcomes

Pt. No.	Age, Sex	Previous Treatment	Tumor Location	Tumor Volume (cm^3)	WHO Grade	Preoperative CN Palsy	Pituitary Dysfunction	Staged Craniotomy	Postoperative SRT	CN Palsy (at Last Follow-Up)	Recurrence or Regrowth	Clinical Follow-Up (months)	Clinical Outcome
1	70, F	No	CS, sella	1.8	I	No	No	No	No	No	S	95	S
2	81, F	Craniotomy	CS, MC, sella, O	15.8	I	II	No	No	Yes	II	S	55	I
3	49, F	No	CS, MC, sella	2.9	I	No	Yes	No	Yes	No	S	95	I
4	44, F	No	CS, MC, PC, sella, O	19.2	I	III, IV, VI	Yes	No	Yes	III, IV, VI	S	42	S
5	56, F	No	CS, MC, PC, sella	0.9	I	VI	No	No	Yes	VI	S	83	I
6	71, F	No	CS, MC, PC, sella	13.8	I	II, VIII	No	No	No	II	S	87	I
7	56, F	No	MC	4.6	I	V1-V2	No	No	Yes	V1-V2	S	77	S
8	69, M	No	CS	4.4	I	III	No	No	Yes	III, V1, VI	S	80	D*
9	53, F	No	CS, MC, PC, sella	6.6	I	III, VI	No	No	No	III	S	72	I
10	59, F	No	CS, MC, PC, sella	41.4	I	V2	No	No	Yes	No	S	53	I
11	75, F	No	CS, MC, sella, O	35.3	I	II, III	No	No	Yes	II	S	42	I
12	53, M	No	CS, MC, PC, sella	80	I	V1-V3, VIII	Yes	Retrosigmoid	Yes	III, V1-V3, VIII	S	60	I
13	69, M	No	CS, MC, PC, sella	113	I	No	Yes	Pterional	Yes	No	S	36	I
14	43, F	Endonasal biopsy	CS, PC, O	86	II	No	No	Minipterional	Yes	No	S	54	I
15	58, M	SRT, surgery	CS, MC, PC, sella	23.1	I	II, III	Yes	No	No	II, III, IV	S	59	S
16	55, M	SRS ×2, surgery	CS, MC, sella	11.6	I	III	No	No	No	III, V3	R	74	D*
17	58, M	SRS, SRT, surgery ×3	CS, PC, sella, O	18.4	I	II	Yes	No	No	II	R	34	D†
18	71, F	SRS ×3, surgery	CS, MC, PC	32.1	I	II, V1-V3, VI, VII, VIII	No	No	No	II, III, V1-V3, VI, VII, VIII	R	24	D‡
19	64, F	SRS, SRT surgery ×4	CS, O	1.4	I	II	No	No	No	II	S	32	I
20	52, M	SRS ×2, SRT, surgery ×2	CS, MC, PC, sella	26.0	II	II, III, V2-V3	Yes	Supraorbital	No	II, III, V1-V3	R	13	D

Pt. No., patient number; WHO, World Health Organization; CN, cranial nerve; SRT, stereotactic radiosurgery; F, female; CS, cavernous sinus; S, stable disease; MC, Meckel's cave; O, orbit; I, improved; PC, petroclival; M, male; D, died; R, recurrence or regrowth; SRS, stereotactic radiosurgery.

*Patient 16 had undergone 2 repeat craniotomies (pterional and retrosigmoid) at an outside institution in the previous year; at 74 months of follow-up after our endonasal surgery, the patient had new deficits and persistent, but stable, tumor.

†Patient 17 had died of progressive disease almost 3 years (34 months) after our last procedure.

‡Patient 18 had died of progressive disease 2 years after our surgery; in those 2 years, the patient had undergone another craniotomy (elsewhere) 18 months after our surgery and then additional radiotherapy and died 24 months after our surgery.

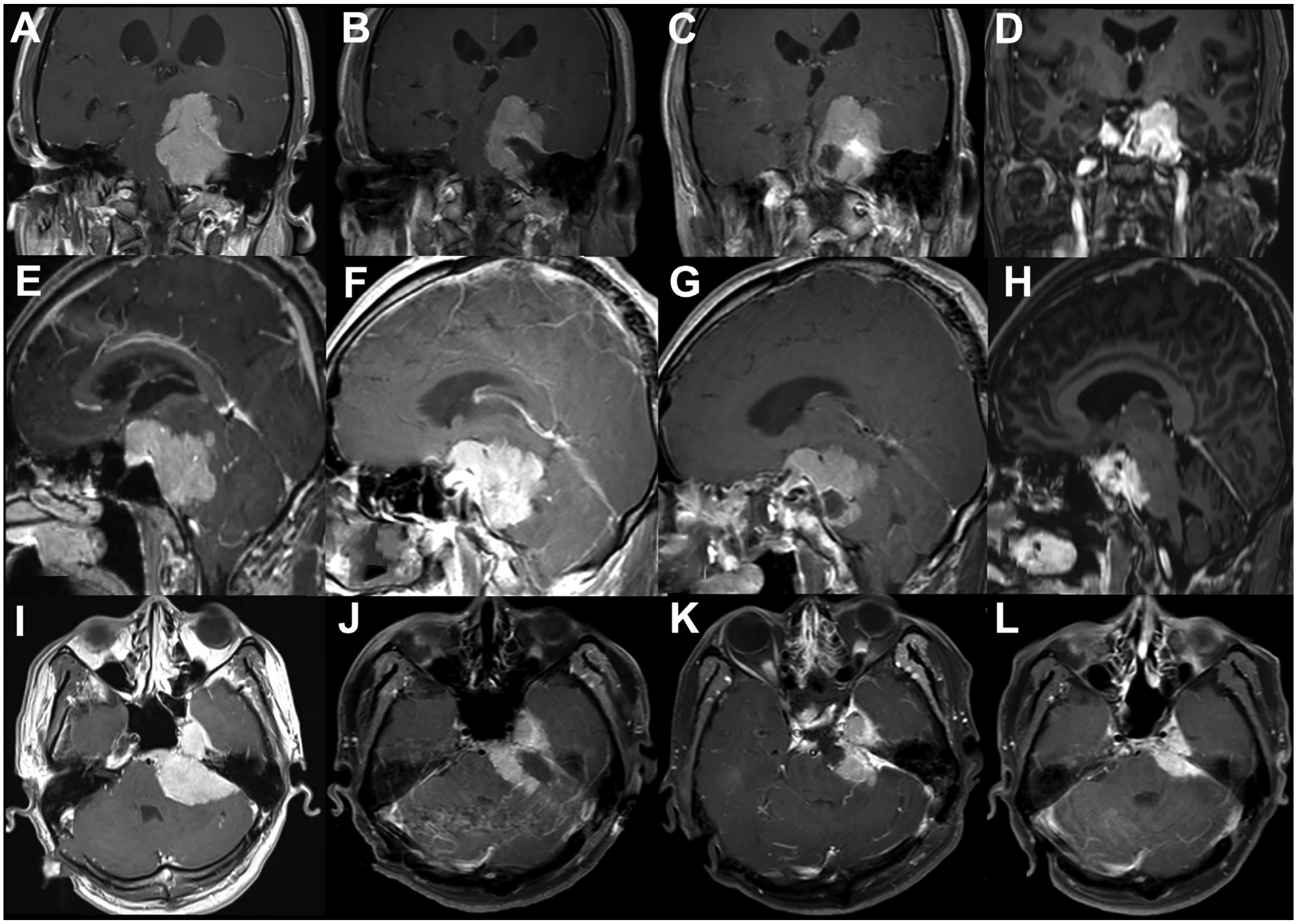


Figure 4. Patient 12. A 53-year-old man had presented with facial numbness and hearing loss. Preoperative coronal (**A**), sagittal (**E**), and axial (**I**) T1-weighted magnetic resonance imaging (MRI) scans with gadolinium enhancement showing extensive tumor involving the suprasellar cistern, left cavernous sinus, Meckel's cave, and petroclival region causing brainstem compression (estimated volume, 80 cm^3). He underwent planned retrosigmoid craniotomy for brainstem decompression, followed by endoscopic bony decompression and selective tumor debulking of the cavernous sinus, suprasellar cistern, and petroclival tumor. Coronal (**B**), sagittal (**F**), and axial (**J**) MRI scans after retrosigmoid craniotomy showing mild decompression of the brainstem. Pathological evaluation confirmed a World Health Organization grade I meningioma. Endonasal endoscopic bony decompression of the left cavernous sinus, Meckel's cave, and the petroclival region was performed, with tumor debulking from the suprasellar cistern, left medial cavernous sinus, left Meckel's cave, and petroclival region. Coronal (**C**), sagittal (**G**), and axial (**K**) MRI scans after endonasal decompression with brainstem decompression. Surgery was followed by stereotactic radiotherapy. Imaging studies during the past 5 years revealed progressive shrinkage of the residual tumor at 60 months after surgery and 57 months after stereotactic radiotherapy (**D,H,L**), without significant brainstem compression. The patient has remained neurologically intact, without endocrinopathy.

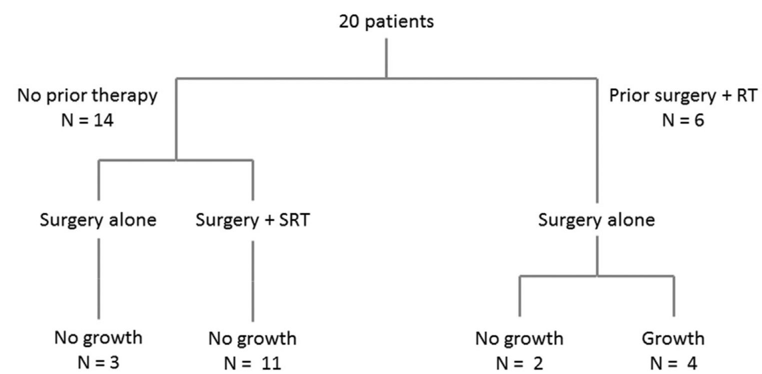
patients who had received previous surgery and RT and the 14 patients without previous RT ($P = 0.28$).

Surgical Complications. A total of 2 major and 6 minor complications occurred. Of the 14 patients without previous treatment, 1 had developed permanent CN VI palsy (as previously described) and 1 had developed a delayed postoperative CSF leak with meningitis despite the initial use of a nasoseptal flap and fat graft at the initial surgery. Six minor complications occurred in the 6 previously treated patients: aspiration pneumonia, delayed epistaxis, transient hyponatremia, and transient diabetes insipidus in 1 each and chronic sinusitis in 2 patients.

DISCUSSION

In our relatively small retrospective study of patients with invasive parasellar meningioma involving the CS, Meckel's cave, and sellar region, we have demonstrated that a strategy of bony skull base decompression and limited tumor removal can be effective in most patients for alleviating symptoms and achieving tumor control when combined with SRT, especially for patients without previous treatment. At a median follow-up period of almost 5 years, the 14 patients without previous treatment had significantly greater tumor control and cranial neuropathy improvement rates compared with those for the 6 patients with previous surgery and RT.

The extent of tumor removal in these challenging skull base tumors will typically depend on several key factors, including



	Improved	Stable	Worsened	New
Cranial neuropathy N = 16	9/16 (56.2%)	7/16 (43.8%)	NA	3
Endocrinopathy N = 7	5/7 (71.4%)	2/7 (28.6%)	NA	NA

	Improved	Stable	Worsened	New
Cranial neuropathy N = 13	1/13 (7.7%)	9/13 (69.2%)	3/13 (23.1%)	3
Endocrinopathy N = 13	6/13 (46.2%)	7/13 (53.8%)	NA	NA

Tumor control	No prior therapy (%)	Prior therapy (%)	P-value
Tumor control	16 (100)	2 (33.3)	< 0.001

Cranial neuropathy	No prior therapy (%)	Prior therapy (%)	P-value
Improved/Stable	16 (100)	10(76.9)	0.042

Endocrinopathy	No prior therapy (%)	Prior therapy (%)	P-value
Improved	5 (71.4)	6(46.3)	0.28

Figure 5. Flow chart illustrating previous treatment and patient outcomes. RT, radiotherapy; SRT, stereotactic radiotherapy.

tumor invasiveness, tumor firmness, tumor adherence to critical neurovascular structures, and the carotid corridor width. Historically, aggressive removal of tumor in the CS was the goal, with mixed results. DeMonte et al.[2] reported their results of aggressive surgery for 41 patients with benign CS meningioma. Gross total removal was achieved in 76%; however, only 14% of the patients had improvement in CN deficits.[2] In addition, 6% of existing neuropathies had worsened, 10 new CN deficits had developed in 7 patients, 2 patients developed hemiplegia, and 1 had died of vasospasm.[2] Despite gross total resection, 5% of the patients had developed recurrence at 5 years. Similarly, O'Sullivan et al.[1] reported a total tumor removal rate of 21% in 39 patients treated with aggressive surgery for CS meningioma. However, 7 of 10 patients with previously normal extraocular motion developed new permanent oculomotor dysfunction, and only 12% of the patients with preoperative oculomotor dysfunction showed improvement.[1]

More recently, less aggressive treatment strategies with limited debulking and/or radiosurgery for CS and parasellar meningiomas have led to improved functional outcomes.[14,21] In a series of 11 patients, Couldwell et al.[14] reported the results from their use of craniotomy for selective safe tumor removal and postoperative SRS or SRT. Of 5 patients with ocular palsies and 4 with visual loss, 3 and 2, respectively, showed improvement, and no patient developed new CN deficits.[14] Tumor control was achieved in all 9 patients, with a median follow-up period of 22 months. Kano et al.[22] reported that patients who had undergone previous surgery of CS meningioma were less likely than those treated with radiosurgery alone to experience cranial neuropathy improvement (14% vs. 39%). One explanation for this difference might be that the patients who had been previously treated with microsurgery had permanently damaged CNs as a result of the surgery with little chance of CN recovery.[23]

The transsphenoidal approach for CS and parasellar meningiomas has the advantages of avoiding direct brain manipulation and the ability to decompress multiple CNs and the pituitary gland. Akutsu et al.[15] described using a microscopic endonasal approach for CS meningiomas in 21 patients (none with previous therapy), with the goal of decompressing the sellar floor and pituitary gland and opening the inferomedial triangle of the CS for selective tumor removal. With this approach, 32 of 34 pre-existing cranial neuropathies improved, hyperprolactinemia had resolved in 13 of 17 patients, and recovery from growth hormone deficiency and hypogonadism occurred in 37.5% and 33.3% of the patients, respectively.[15] In addition, tumor control had been achieved in all 21 patients (100%) at a median follow-up period of 65 months.[15]

The addition of the endoscope in the treatment of invasive parasellar meningiomas has afforded increased lateral exposure and more panoramic visualization of the parasellar skull base compared with the microscopic approach. This advantage will arguably enable the surgeon to perform more aggressive and precise bony decompression and tumor removal around the sella, medial CS, clivus, optic canal, orbital apex, and Meckel's cave with conservative tumor debulking that minimizes direct CN manipulation. Although we were unable to reproduce the high rates of CN and pituitary function improvement reported by Akutsu et al.,[15] who had not included patients who had undergone previous therapy, we did achieve a similar rate of CN improvement to that described by Kano et al.[22] for a cohort of patients treated with radiosurgery alone (38% vs. 37%). Furthermore, none of our patients experienced new endocrinopathy during our relatively short follow-up period, which has been reported in previous studies after SRS and fractionated SRT.[22,24,25] Although postoperative RT was used in 79% of our patients who had not received previous RT, we used only SRT. The use of this fractionated regimen, with a median follow-up period of >3 years, appeared to have been effective in halting tumor growth in our cohort. The efficacy of SRT has been equivalent to that of radiosurgery for skull base meningiomas in several retrospective series.[4,11,21] In most cases, radiosurgery was not an option because of the close proximity of the residual tumor to the optic apparatus.[5-7]

In our series, all 4 tumors that grew had been previously treated with ≥2 rounds of SRS and/or SRT. Data on the efficacy of repeat SRS/SRT for meningiomas are limited. In a multicenter retrospective review of 4565 patients treated with radiosurgery for intracranial meningiomas, 13 patients had undergone repeat radiosurgery or conventional RT for recurrent tumors. Of these, only 1 patient had required additional surgery because of tumor enlargement.[13] Skeie et al.[26] reported that 12 of 100 patients with CS meningiomas treated with radiosurgery required further treatment because of tumor regrowth, including 5 who underwent repeat radiosurgery. The effective tumor control rate in this population who had received repeat radiosurgery was only 40%. RT-induced gliomas and meningiomas have been reported in patients who had received previous irradiation for acute lymphoblastic leukemia and tinea capitis. However, few data are available to support the idea that the growth in this subset of patients had been induced by RT.[27,28] Whether the 4 tumors in our series that had progressed were inherently more aggressive because of repeated RT remains unclear; however, our results should raise concern about the repeated use of SRS or SRT in patients with skull base meningioma.

In our series, tumor growth in 1 patient with a progesterone receptor-positive typical meningioma had continued despite mifepristone therapy, and the patient died 26 years after his original diagnosis and the first operation. Another patient with a history of childhood RT and multiple failed rounds of previous radiosurgery also experienced tumor progression after surgery. After starting bevacizumab, the patient had stable tumor for ∼6 months. However, significant tumor progression was found on the most recent imaging studies, with additional surgery planned for the near future. Although mifepristone[29-31] and bevacizumab[32-34] have been described as promising agents for recurrent meningiomas, little evidence is available from large case series or randomized trials to validate the findings from isolated reports.[35] Nonetheless, these drugs, which target tumor receptors, highlight the importance of obtaining tumor tissue for genomic and epigenomic profiling to identify potentially more effective targeted therapies.

CONCLUSIONS

The outcomes of our small series suggest the early efficacy of a surgical strategy of endoscopic endonasal bony skull base decompression and limited selective tumor removal for invasive parasellar and petroclival meningiomas, followed by adjuvant SRT in specific cases. This focused approach allows for preservation of pituitary gland function and maintains or improves CN function in most patients. With an admittedly short follow-up period, averaging just <5 years, the selective addition of SRT yielded excellent tumor control rates in previously untreated patients.

REFERENCES

1. O'Sullivan MG, van Loveren HR, Tew JM Jr. The surgical resectability of meningiomas of the cavernous sinus. *Neurosurgery*. 1997;40:238-244 [discussion: 245-247].
2. DeMonte F, Smith HK, al-Mefty O. Outcome of aggressive removal of cavernous sinus meningiomas. *J Neurosurg*. 1994;81:245-251.
3. Sindou M, Wydh E, Jouanneau E, Nebbal M, Lieutaud T. Long-term follow-up of meningiomas of the cavernous sinus after surgical treatment alone. *J Neurosurg*. 2007;107:937-944.
4. Pamir MN, Kilic T, Bayrakli F, Peker S. Changing treatment strategy of cavernous sinus meningiomas: experience of a single institution. *Surg Neurol*. 2005;64(suppl 2):S58-S66.
5. Metellus P, Regis J, Muracciole X, et al. Evaluation of fractionated radiotherapy and gamma knife radiosurgery in cavernous sinus meningiomas: treatment strategy. *Neurosurgery*. 2005;57:873-886 [discussion: 873-886].
6. Correa SF, Marta GN, Teixeira MJ. Neurosymptomatic cavernous sinus meningioma: a 15-years' experience with fractionated stereotactic radiotherapy and radiosurgery. *Radiat Oncol*. 2014; 9:27.
7. Han J, Girvigian MR, Chen JC, et al. A comparative study of stereotactic radiosurgery, hypofractionated, and fractionated stereotactic radiotherapy in the treatment of skull base meningioma. *Am J Clin Oncol*. 2014;37:255-260.
8. Roche PH, Regis J, Dufour H, et al. Gamma knife radiosurgery in the management of cavernous sinus meningiomas. *J Neurosurg*. 2000;93(suppl 3): 68-73.
9. Lee JY, Niranjan A, McInerney J, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery providing long-term tumor control of cavernous sinus meningiomas. *J Neurosurg*. 2002; 97:65-72.
10. Iwai Y, Yamanaka K, Ishiguro T. Gamma knife radiosurgery for the treatment of cavernous sinus meningiomas. *Neurosurgery*. 2003;52:517-524 [discussion: 523-524].
11. Nicolato A, Foroni R, Alessandrini F, Maluta S, Bricolo A, Gerosa M. The role of Gamma Knife radiosurgery in the management of cavernous sinus meningiomas. *Int J Radiat Oncol Biol Phys*. 2002; 53:992-1000.
12. DiBiase SJ, Kwok Y, Yovino S, et al. Factors predicting local tumor control after gamma knife stereotactic radiosurgery for benign intracranial meningiomas. *Int J Radiat Oncol Biol Phys*. 2004;60: 1515-1519.
13. Santacroce A, Walier M, Regis J, et al. Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients. *Neurosurgery*. 2012;70:32-39 [discussion: 39].

14. Couldwell WT, Kan P, Liu JK, Apfelbaum RI. Decompression of cavernous sinus meningioma for preservation and improvement of cranial nerve function. Technical note. *J Neurosurg*. 2006;105: 148-152.

15. Akutsu H, Kreutzer J, Fahlbusch R, Buchfelder M. Transsphenoidal decompression of the sellar floor for cavernous sinus meningiomas: experience with 21 patients. *Neurosurgery*. 2009;65:54-62 [discussion: 62].

16. Lobo B, Zhang X, Barkhoudarian G, Griffiths CF, Kelly DF. Endonasal endoscopic management of parasellar and cavernous sinus meningiomas. *Neurosurg Clin N Am*. 2015;26:389-401.

17. Dusick JR, Esposito F, Malkasian D, Kelly DF. Avoidance of carotid artery injuries in transsphenoidal surgery with the Doppler probe and micro-hook blades. *Neurosurgery*. 2007;60(suppl 2): 322-328 [discussion: 328-329].

18. Griffiths CF, Cutler AR, Duong HT, et al. Avoidance of postoperative epistaxis and anosmia in endonasal endoscopic skull base surgery: a technical note. *Acta Neurochir (Wien)*. 2014;156: 1393-1401.

19. Conger A, Zhao F, Wang X, et al. Evolution of the graded repair of CSF leaks and skull base defects in endonasal endoscopic tumor surgery: trends in repair failure and meningitis rates in 509 patients. *J Neurosurg*. 2018;130:861-875.

20. Kassam AB, Prevedello DM, Carrau RL, et al. The front door to Meckel's cave: an anteromedial corridor via expanded endoscopic endonasal approach- technical considerations and clinical series. *Neurosurgery*. 2009;64(suppl):71-83.

21. Abdel-Aziz KM, Froelich SC, Dagnew E, et al. Large sphenoid wing meningiomas involving the cavernous sinus: conservative surgical strategies for better functional outcomes. *Neurosurgery*. 2004; 54:1375-1383 [discussion: 1383-1384].

22. Kano H, Park KJ, Kondziolka D, et al. Does prior microsurgery improve or worsen the outcomes of stereotactic radiosurgery for cavernous sinus meningiomas? *Neurosurgery*. 2013;73:401-410.

23. Conti M, Prevedello DM, Madhok R, et al. The antero-medial triangle: the risk for cranial nerves ischemia at the cavernous sinus lateral wall. Anatomic cadaveric study. *Clin Neurol Neurosurg*. 2008;110:682-686.

24. Sheehan JP, Starke RM, Kano H, et al. Gamma Knife radiosurgery for sellar and parasellar meningiomas: a multicenter study. *J Neurosurg*. 2014; 120:1268-1277.

25. Fernandez A, Brada M, Zabuliene L, Karavitaki N, Wass JA. Radiation-induced hypopituitarism. *Endocr Relat Cancer*. 2009;16:733-772.

26. Skeie BS, Enger PO, Skeie GO, Thorsen F, Pedersen PH. Gamma knife surgery of meningiomas involving the cavernous sinus: long-term follow-up of 100 patients. *Neurosurgery*. 2010;66: 661-668 [discussion: 668-669].

27. Banerjee J, Paakko E, Harila M, et al. Radiation-induced meningiomas: a shadow in the success story of childhood leukemia. *Neuro Oncol*. 2009;11: 543-549.

28. Elsamadicy AA, Babu R, Kirkpatrick JP, Adamson DC. Radiation-induced malignant gliomas: a current review. *World Neurosurg*. 2015;83: 530-542.

29. de Keizer RJ, Smit JW. Mifepristone treatment in patients with surgically incurable sphenoid-ridge meningioma: a long-term follow-up. *Eye (Lond)*. 2004;18:954-958.

30. Haak HR, de Keizer RJ, Hagenouw-Taal JC, van Seters AP, Vielvoye GJ, van Dulken H. Successful mifepristone treatment of recurrent, inoperable meningioma. *Lancet*. 1990;336:124-125.

31. Touat M, Lombardi G, Farina P, Kalamarides M, Sanson M. Successful treatment of multiple intracranial meningiomas with the antiprogesterone receptor agent mifepristone (RU486). *Acta Neurochir (Wien)*. 2014;156:1831-1835.

32. Ly KI, Hamilton SR, Rostomily RC, Rockhill JK, Mrugala MM. Improvement in visual fields after treatment of intracranial meningioma with bevacizumab. *J Neuroophthalmol*. 2015;35:382-386.

33. Lou E, Sumrall AL, Turner S, et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. *J Neurooncol*. 2012; 109:63-70.

34. Puchner MJ, Hans VH, Harati A, Lohmann F, Glas M, Herrlinger U. Bevacizumab-induced regression of anaplastic meningioma. *Ann Oncol*. 2010;21:2445-2446.

35. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro Oncol*. 2014;16:829-840.

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