Pituitary macroadenomas with oculomotor cistern extension and tracking: implications for surgical management

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OBJECTIVE Oculomotor cistern extension of pituitary adenomas is an overlooked feature within the literature. In this study, 7 cases of pituitary macroadenoma with oculomotor cistern extension and tracking are highlighted, and the implications of surgical and medical management are discussed.

METHODS The records of patients diagnosed with pituitary macroadenomas who underwent resection and in whom preoperative pituitary protocol MRI scans were available for review were retrospectively reviewed. The patient and tumor characteristics were reviewed along with the operative outcomes and complications.

RESULTS Seven patients (4.1%) with oculomotor cistern extension and tracking were identified in a cohort of 170 patients with pituitary macroadenoma. The most common presenting symptoms were visual deficit (6 patients; 86%), apoplexy (3 patients; 43%), and oculomotor nerve palsy (3 patients; 43%). Lone oculomotor nerve palsy was seen in 2 patients without apoplexy and 1 patient with an apoplectic event. Gross-total resection was achieved via a microscopic endonasal transsphenoidal approach with or without endoscopic aid to the sella in 14%, near-total resection in 29%, and subtotal resection in 57% of patients in the data set.

CONCLUSIONS Pituitary adenoma extension along the oculomotor cistern is uncommon; however, preoperatively recognizing such extension should play an important role in the surgeon’s operative considerations and postoperative clinical management because this extension can limit gross-total resection using the transsphenoidal approach alone.

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KEY WORDS pituitary macroadenoma; oculomotor palsy; oculomotor cistern; endonasal transsphenoidal pituitary surgery

TREATMENT management strategies for pituitary macroadenomas depend on numerous factors that guide the determination of medical management, surgical approach, and/or adjuvant therapeutic options. Maximal resection and adequate decompression of the neurological structures is the paradigm of care for symptomatic pituitary macroadenomas, with the exception of medically responsive prolactinomas.

Since its inception by Schloffer in 1907 and then refinement and popularization by Hirsch, Guiot, and Hardy, the transsphenoidal approach has become the preferred route to the sella because of its relative safety profile.9,14,16,17 The transcranial route still plays an important role in providing access to the sella in 1% to 4% of pituitary macroadenomas where direct visualization and accessibility via the transsphenoidal approach are limited.38

A transcranial approach should be considered in the surgical management of pituitary adenomas that display constriction at the diaphragma sellae, parasellar extension or inaccessible suprasellar extension off the midline, tumors of fibrous consistency with large suprasellar extension, and in patients with an active sinus infection or a coexisting adjacent aneurysm. Other cases that should be approached transcranially include those patients with ectatic intrasellar carotid arteries,40 retrosellar extension, brain invasion with edema, involvement or vasospasm of the arteries of the circle of Willis, or encasement of the optic apparatus or invasion of the optic foramina.41,42 In a series of 494
patients with pituitary adenomas, Pratheesh et al.\textsuperscript{30} operatively approached the sella transcranially in 23 instances. They found several common characteristics among their cases: extension lateral to the supraclinoid internal carotid artery (ICA), asymmetrical subfrontal tumor extension, a small sella in relation to the entire tumor volume, and diaphragmatic constriction of the tumor at its waist. A volumetric threshold greater than 10 cm\textsuperscript{3} was found for lesions that demonstrated high perioperative morbidity and a high rate of subtotal resection following endonasal endoscopic surgery.\textsuperscript{18} The tumor characteristics that are independent predictors of subtotal resection include significant vertical intracranial extension,\textsuperscript{15,19,42} irregular and multilobular configuration, fibrous and firm consistency,\textsuperscript{29,30} and cavernous sinus invasion.

In this report, we highlight the oculomotor cisternal extension pattern and tracking of pituitary adenoma growth, which has not been addressed in the literature. This particular subset of pituitary macroadenomas carries implications regarding surgical resectability via a transsphenoidal approach. In some cases, adjuvant therapy or a secondary surgical approach to management is appropriate.

**Methods**

After obtaining institutional review board approval, we retrospectively reviewed the medical records of patients with pituitary macroadenoma who underwent surgical resection by a single neurosurgeon (W.T.C.) at the University of Utah Hospital between 2001 and 2013. Within our data pool, we identified patients who were diagnosed with pituitary macroadenoma (defined radiologically as ≥ 10 mm in maximum diameter) who met our inclusion criteria of having pre- and postoperative-specific pituitary protocol imaging available for review. Among this set of patients, we identified those with pituitary adenomas with complex extension and tracking along the oculomotor nerve cistern.

Presurgical patient data, including patient demographics, symptomatic presentation, and neurological and ophthalmological examination results, were obtained from the medical records and reviewed. Postsurgical reports, including the findings of histopathological, surgical, neurological, and ophthalmological examinations, were also obtained on follow-up.

Preoperative MRI of the pituitary was verified by a board-certified neuroradiologist. The tumor dimensions and characteristics were analyzed on T1-weighted imaging with gadolinium contrast enhancement in the axial and coronal planes. Tumor measurements were analyzed in 3 dimensions (transverse, craniocaudal, and anteroposterior), and volume was approximated by a modified ellipsoid volume (anteroposterior × transverse × craniocaudal/2). Knosp criteria were used to evaluate the potential for cavernous invasion.\textsuperscript{23}

The criterion for oculomotor cisternal tracking was based on evaluation of the T2-weighted coronal and axial images in conjunction with T1-weighted images with contrast enhancement.\textsuperscript{11,12,26,27} Oculomotor cisternal tracking was noted if the anatomical tumor extension pattern encompassed the supracervenous roof of the cavernous sinus, lateral to the clinoid and supraclinoid segments of the ICA, with direct extension posteriorly into the prepontine cisterns on axial imaging.\textsuperscript{27} The lesions also demonstrated characteristic obliteration of the normal hyperintense “ring” of the CSF in the oculomotor cistern, which was replaced by regional enhancement surrounding an isointense “dot” of the oculomotor nerve (Figs. 1–3).\textsuperscript{12}

The pathological findings were evaluated and confirmed by the authors. The length of the follow-up was determined from the clinical records and defined as the time from resection to the last documented MRI scan.

**Results**

**Patient Characteristics**

One hundred seventy patients were diagnosed with pituitary macroadenoma and had pre- and postoperative-specific pituitary protocol imaging available for review. Of these, 7 patients (6 males and 1 female; ages 47–72 years; median 59 years) had pituitary macroadenoma with oculomotor cisternal extension into the interpeduncular and prepontine cisterns (Table 1). The most common presenting symptom was visual deficit (86%; 6 patients); other symptoms were apoplexy (43%; 3 patients), headache (29%; 2 patients), and symptomatic hypogonadism (14%; 1 patient). The visual deficits included visual field cuts (71%; 5 patients), diminished visual acuity (57%; 4 patients), and oculomotor nerve palsy (43%; 3 patients), which occurred more often without associated apoplexy. Two patients presented with isolated oculomotor nerve palsy with complete or partial ophthalmoplegia, mydriasis, and ptosis without apoplexy or demonstrated acute pituitary hemmorrhage on MRI, and 1 patient presented with oculomotor nerve palsy with apoplexy.
Pituitary macroadenomas with oculomotor cistern extension

Among all pituitary macroadenomas in our cohort, oculomotor tracking was an infrequent occurrence (Table 2). Oculomotor extension demonstrated a total prevalence of 4.1% in comparison with 21.8%, 94.1%, and 24.1% for parasellar, suprasellar, and infrasellar tracking, respectively. The median cranio-caudal, transverse, and anteroposterior tumor dimensions of the tumors with oculomotor extension were 4.3 cm (range 1.9–6.7 cm), 3.4 cm (range 2.6–4.4 cm), and 3.7 cm (range 1.8–5.5 cm), respectively. The median approximated tumor volume was 27.9 cm³ (range 8.9–81 cm³). All pituitary macroadenomas were multilobular in shape because of this atypical extension pattern. There were 3 null cell adenomas, 2 lactotroph adenomas, 1 corticotroph adenoma, and 1 mixed adenoma with positive staining for prolactin, luteinizing hormone, and follicle-stimulating hormone secretory cells. The secretory status of the adenomas was confirmed histologically. Cavernous sinus invasion, which was preoperatively analyzed on MRI, was based on the Knosp criteria and reaffirmed intraoperatively when mentioned within the operative reports. Five patients had pituitary adenomas with total encasement of the intercavernous ICA, with 4 of these extending into the middle cranial fossa. Interestingly, 2 tumors extended lateral to the lateral tangent of the intra- and supracavernous ICA, and 1 tumor only extended to the intercarotid line. These tumors based on Knosp criteria demonstrated a low probability of cavernous sinus invasion. While the oculomotor cistern is within the lateral-most dura of the cavernous sinus, frank cavernous sinus invasion was not seen in 3 cases of oculomotor cistern tracking. This is most likely because the Knosp criteria are based on a single slice within the mid-sella, and invasion anterior or posterior within the cavernous sinus may not be apparent. Among this set of pituitary macroadenomas, 4 tumors extended to the optic chiasm.
and 4 tumors extended above the optic chiasm into the third ventricle.

**Operative Outcomes and Complications**

The operative outcomes and complications are presented in Table 3. All patients underwent an endonasal transsphenoidal approach (endoscopic or microscopic with endoscopic assistance). Gross-total resection was achieved in 1 patient (14%), near-total resection in 2 patients (29%), and subtotal resection in 4 patients (57%). Among the 6 patients with preoperative visual symptoms, initial resolution of visual symptoms was seen in 4 patients (67%), while 2 patients (33%) had stable visual symptoms postoperatively. Tumor recurrence or progression was seen in 3 patients (43%) with an average time to progression of 18.0 months. Four patients received adjuvant or salvage radiation therapy. One patient received adjuvant fractionated radiation therapy, 2 patients received fractionated radiation therapy after progression, and 1 patient underwent a second operation and subsequent stereotactic radiation therapy after progression. Visual field deficits were stable at follow-up in 4 patients (80%) who presented initially with a field defect (n = 5). One patient had improvement and near-resolution of the visual field deficits, and no patients had worsening visual changes. Of the 3 patients who had third cranial nerve palsies at presentation, 2 patients had complete resolution and 1 had near-resolution.

The median follow-up time was 49.2 months; 1 patient was lost to follow-up. There was 1 patient (14%) with new postoperative panhypopituitarism that required hormonal supplementation. One patient who presented initially with panhypopituitarism after apoplexy had stable pituitary dysfunction and was continued on hormonal supplementation. One patient was started prophylactically on stress-dose steroids for pituitary apoplexy, and at 1-month follow-up demonstrated normal pituitary function and was tapered off steroids.

### Illustrative Cases

**Case 1**

This 47-year-old man presented with bitemporal hemianopia, loss of visual acuity bilaterally, and generalized fatigue. MRI demonstrated a pituitary macroadenoma measuring $3.2 \times 2.7 \times 1.5$ cm with suprasellar extension that displaced the prechiasmatic optic nerves superiorly with compression against the hypothalamus and infiltration of the cavernous sinuses bilaterally (Fig. 1A and B). On T2-weighted imaging, the tumor extended along the left oculomotor cistern with opacification of the CSF signal in comparison with the right oculomotor cistern (Fig. 1A and C).

The patient underwent endoscopic endonasal transsphenoidal surgery with resection of the pituitary macroadenoma and harvesting of the abdominal fat graft. The pathology of the tumor was mixed adenoma secreting prolactin, luteinizing hormone, and follicle-stimulating hormone. Postoperative imaging demonstrated near-total resection of the suprasellar elements with the exception of the posterosilateral element that extended into the oculomotor cistern and basal cistern (Fig. 1C and D).

The patient’s vision was initially stable postoperatively, but he subsequently developed panhypopituitarism and worsening peripheral vision in his right eye. Postoperative MRI at 22.7 months showed interval growth of the tumor with compression against the hypothalamus and infiltra
tion of the cavernous sinuses bilaterally (Fig. 1A and B). On T2-weighted imaging, the tumor extended along the left oculomotor cistern with opacification of the CSF signal in comparison with the right oculomotor cistern (Fig. 1A and C).

**Case 2**

This 72-year-old woman presented with right-sided
pituitary macroadenomas with oculomotor cistern extension

The pathology of the tumor was an adrenocorticotropic hormone–secreting pituitary macroadenoma.

Postoperatively, her third nerve palsy initially improved. She returned on follow-up at 13.3 months with worsening

table 2. Characteristics of 7 pituitary macroadenomas with oculomotor cistern extension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Tumor dimensions, cm (range)</td>
<td></td>
</tr>
<tr>
<td>Craniocaudal</td>
<td></td>
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<tr>
<td>Median</td>
<td>4.3</td>
</tr>
<tr>
<td>Range</td>
<td>1.9–6.7</td>
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<tr>
<td>Transverse</td>
<td></td>
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<tr>
<td>Median</td>
<td>3.4</td>
</tr>
<tr>
<td>Range</td>
<td>2.6–4.4</td>
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<tr>
<td>Anteroposterior</td>
<td></td>
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<tr>
<td>Median</td>
<td>3.7</td>
</tr>
<tr>
<td>Range</td>
<td>1.8–5.5</td>
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<tr>
<td>Median vol (cm³)</td>
<td>20.7</td>
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<td>Multilobular shape</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
</tr>
<tr>
<td>Null cell adenoma</td>
<td>3 (42.8)</td>
</tr>
<tr>
<td>Corticotrophic adenoma</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Lactotrophic adenoma</td>
<td>2 (28.5)</td>
</tr>
<tr>
<td>Mixed adenoma (prolactin, luteinizing hormone, follicle-stimulating hormone)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Extension pattern</td>
<td></td>
</tr>
<tr>
<td>Oculomotor cistern tracking prevalence</td>
<td>4.1%</td>
</tr>
<tr>
<td>Parasellar invasion</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>21.8%</td>
</tr>
<tr>
<td>Knosp Grade 2</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Knosp Grade 3</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Knosp Grade 4</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Middle fossa</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Suprasellar</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>94.1%</td>
</tr>
<tr>
<td>To optic chiasm</td>
<td>3 (42.8)</td>
</tr>
<tr>
<td>Above optic chiasm</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Infrasellar</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>24.1%</td>
</tr>
<tr>
<td>Sphenoid</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Clival</td>
<td>3 (42.8)</td>
</tr>
<tr>
<td>Retroclival</td>
<td>1 (14.3)</td>
</tr>
</tbody>
</table>

* Values are presented as the number of patients (%) unless specified otherwise.

third nerve palsy. MRI demonstrated a pituitary macroadenoma measuring 1.8 × 2.8 cm with suprasellar extension to the optic chiasm and lateral invasion of the right cavernous sinus; there were no signs of acute hemorrhage (Fig. 2A and B). She underwent subtotal resection of the suprasellar midline lesion via a microscopic transsphenoidal approach, but the posterolateral extension along the oculomotor nerve could not be fully debulked (Fig. 2C). The pathology of the tumor was an adrenocorticotropic hormone–secreting pituitary macroadenoma.

Postoperatively, her third nerve palsy initially improved. She returned on follow-up at 13.3 months with worsening...
third nerve palsy; on MRI surveillance, she demonstrated progression of the pituitary adenoma within the oculomotor cistern with extension into the basal cisterns (Fig. 2D). She underwent a second microscopic transsphenoidal debulking resection followed by adjunct 20-Gy radiosurgery. Her third nerve palsy resolved on follow-up.

Discussion

Cavernous Sinus Invasion and Oculomotor Tracking

In their analysis of the meningeal architecture of the cavernous sinus, Kawase et al.\(^3\) showed that there are structurally weak points that have clinical and surgical implications. In contrast to the lateral wall, the medial wall of the cavernous sinus is thin and loose, especially the meninges juxtaposing the pituitary body. This inherent weakness provides a route for invasion and indirect compression in sellar lesions. The dural layer of the oculomotor nerve cistern was also found to be extremely thin or missing in some cadaver specimens, providing a weak point where pituitary adenomas can easily extend. Hence, there is cavernous sinus invasion in a significant percentage of pituitary macroadenomas; however, in addition to cavernous extension, the tumor may course through the posterolateral roof of the cavernous sinus via the oculomotor cistern. We identified this growth pattern in a small subset of pituitary macroadenomas, which has implications for therapy.

Oculomotor cisternal extension of pituitary adenomas has been underreported within the literature. Distinguishing the involvement of the oculomotor cistern may be critical to performing resection of pituitary macroadenomas, as well as adequately decompressing the oculomotor nerve and preserving oculomotor nerve function. Oculomotor cisternal extension of pituitary adenomas has a characteristic clinical presentation and radiographic findings. The typical presentation may include oculomotor nerve palsy without signs of pituitary apoplexy, often without concomitant chiasmal visual deficits that may help the clinician distinguish these rare tumors. Radiographically, extension into the oculomotor cistern is seen by the obliteration of the CSF signal on T2-weighted imaging and a “dark dot sign” on the coronal section (Fig. 2). Extension is clearly seen as a separate lobule with superior extension from the posterior lateral roof of the cavernous sinus that exits the oculomotor trigone, which can be differentiated from the more midline suprasellar extensions of the tumor.

Oculomotor nerve palsy is seen in 2.4% to 17% of pituitary adenomas,\(^2\)\(^3\)\(^3\)\(^5\)\(^6\) and most of these cases are related to a pituitary apoplectic event.\(^7\) The mechanism includes direct compression, indirect edematous expansion onto the cavernous sinus wall, direct infiltration of the tumor, and vascular compromise of the nerve.\(^3\)\(^4\) Suprasellar tumor extension through the diaphragma provides the path of least resistance for the growth of most macroadenomas. Oculomotor cistern tumor extension may be overlooked in many cases with coexisting predominant suprasellar extension. While the extension of pituitary adenoma into the oculomotor cistern is less common, it is important to be aware that third nerve palsies in pituitary adenomas can occur regardless of chiasmal visual deficits with suprasellar compression/extension. Within our cohort of patients with macroadenomas, the prevalence of oculomotor cistern extension was 4.1% in comparison with 94.1%, 21.8%, and 24.1% of patients suprasellar, parasellar, and infrasellar extension, respectively.

Surgical Implications

The preoperative finding of oculomotor cistern extension of pituitary macroadenomas on fine-cut, coronal, pituitary MRI raises surgical and clinical management questions. Extension into the oculomotor cistern can limit the descent of the pituitary tumor into the operative field, and this component of the tumor will not communicate with the central suprasellar extension and will not descend with sellar decompression. In such cases, we have made no attempts to traverse the cavernous sinus, but instead attempt surgical decompression of the oculomotor cistern and nerve using the transsphenoidal route. Furthermore, supracavernous extension of the tumor will be difficult to manage from below, as it usually will have extension lateral to the proximal ICA and optic nerve.

Limits of Endoscopic Visualization of the Cavernous Sinus

Endoscopic endonasal approaches to the sella improve suprasellar visualization and widen the skull base approach along different anatomical corridors, allowing for an array of skull base targets.\(^2\)\(^4\)\(^5\)\(^7\)\(^8\)\(^1\)\(^9\)\(^2\)\(^0\)\(^2\)\(^4\)\(^3\)\(^4\) Tracking along the oculomotor cistern leads to tumor extension that is not midline but laterally exits the oculomotor trigone into the lateral interpeduncular and ambient cisterns. Resection would require access to these deep regions, which have traditionally been approached transcranially for resection. Hidden posterolateral to the posterior clinoid process and within the lateral wall of the cavernous sinus, the oculomotor triangle must be approached in a fashion that requires a direct endoscopic endonasal transcavernous approach or indirect endonasal posterior clinoectomy in order to access the basal cisterns.\(^1\)\(^2\)\(^3\)\(^4\) In their endoscopic study of the oculomotor nerve, Abuzayed et al.\(^1\) were able to visualize the courses of the interpeduncular and intercavernous segments via extended endonasal suprasellar and endonasal ethmoidopterygosphephoid approaches, respectively, but found exposing the cisternal segment to be extremely difficult because of its hidden location in the superior part of the cavernous sinus, forming a posteroinferior border with the anterior clinoid process that is anterolateral to the posterior clinoid process. They noted that endoscopic exposure of the cistern would lead to reduced maneuverability because of the positioning of the endoscope within the constricted chiasmatic cistern required for the endonasal suprasellar approach. To access the lateral endoscopic endonasal corridor during a transethmoidopterygoidosphenoidal approach, the endoscope must be positioned in the cavernous sinus with retraction of the parasellar ICA medially in order to properly expose the oculomotor cistern. This positioning does not permit adequate maneuverability for full exposure of the cistern. Abuzayed et al. thus deemed the cisternal portion of cranial nerve III to be an endoscopic endonasal “blind spot.”
Recently Fernandez-Miranda et al. introduced a variant of endoscopic endonasal transcavernous posterior clinoidectomy with interdural pituitary transposition that works through a lateral corridor within the cavernous sinus. This required meticulous dissection of the interdural plane separating the cavernous sinus and lateral mobilization of the ICA in order to expose the posterior clinoid and dorum sellae. Wakuta et al. described an endoscopic endonasal transcavernous dissection and approach to the oculomotor trigone. They accessed the oculomotor trigone after medial mobilization of the intracavernous ICA and identified a triangular area defined by the abducens nerve, oculomotor nerve, and posterior vertical segment of the ICA, which lead to the oculomotor trigone. They presented a case of a pituitary macroadenoma that had completely filled the sphenoid and cavernous sinuses with postero-lateral extension, which they removed via the endoscopic endonasal transcavernous approach followed by transcranial surgery. Such a transcavernous approach, as described above, is not without risk as it necessitates the mobilization of the ICA with the potential risk for injury.

Transcranial Exposure
A transcranial approach for pituitary adenomas with oculomotor cistern extension into the lateral interpeduncular cistern can be accomplished using the previously described historic approaches to this region, including subtemporal, perional-transsylvian, combined orbitozygomatic/subtemporal, and Kawase approaches. Using a perional approach, Tanriover et al. accessed the oculomotor cistern through an incision along the roof of the cavernous sinus in order to reach an oculomotor nerve schwannoma. Given the limitations of access to the region of the oculomotor cistern using a transnasal approach, the senior author preoperatively identifies the tumor growth pattern, counsels the patient about the plan for subtotal resection, and plans observation or adjuvant treatment postoperatively. If a second surgical approach is used, a transcranial frontotemporal approach has provided excellent access to this region for direct decompression of the oculomotor cistern and dissection of the tumor within the subarachnoid space.

Conclusions
Pituitary adenoma extension along the oculomotor cistern is uncommon; however, the preoperative recognition of such extension should play an important role in a surgeon’s operative considerations and clinical management because this extension can limit gross-total resection from the transsphenoidal approach alone. Oculomotor extension can be best recognized on preoperative radiological assessment with specific findings of postero-lateral extension and obliteration of the normal CSF signal in the oculomotor cistern on T2-weighted MRI imaging and a clinical presentation of lone third nerve palsy in the absence or presence of apoplexy.

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J Neurosurg Volume 125 • August 2016 321
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**Disclosures**

Dr. Osborn is a consultant for Elsevier.

**Author Contributions**

Conception and design: WT Couldwell, Hoang, Osborn. Acquisition of data: Hoang, Tran, Herde, GC Couldwell. Analysis and interpretation of data: Hoang. Drafting the article: Hoang. Critically revising the article: WT Couldwell, Hoang, Tran, Herde. Reviewed submitted version of manuscript: WT Couldwell, Hoang, Tran, Herde. Reviewed submitted version of manuscript: WT Couldwell, Hoang, Tran, Herde, Osborn. Approved the final version of the manuscript on behalf of all authors: WT Couldwell. Statistical analysis: Hoang. Study supervision: WT Couldwell, Osborn.

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