Targeted sequencing of *SMO* and *AKT1* in anterior skull base meningiomas

*Matthew R. Strickland, MD,¹ Corey M. Gill, BS, BA,^{1,2} Naema Nayyar, BS,¹ Megan R. D'Andrea,¹ Christian Thiede, MD,⁵ Tareq A. Juratli, MD,⁶ Gabriele Schackert, MD,⁶ Darrell R. Borger, PhD,⁴ Sandro Santagata, MD, PhD,⁷ Matthew P. Frosch, MD, PhD,⁴ Daniel P. Cahill, MD, PhD,⁸ Priscilla K. Brastianos, MD,^{1–3} and Fred G. Barker II, MD⁸

¹Cancer Center and Departments of ²Neurology, ³Medicine, and ⁴Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; Departments of ⁵Medicine I and ⁶Neurosurgery, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany; ⁷Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston; and ⁸Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

OBJECTIVE Meningiomas located in the skull base are surgically challenging. Recent genomic research has identified oncogenic *SMO* and *AKT1* mutations in a small subset of meningiomas.

METHODS The authors performed targeted sequencing in a large cohort of patients with anterior skull base meningiomas (n = 62) to better define the frequency of *SMO* and *AKT1* mutations in these tumors.

RESULTS The authors found *SMO* mutations in 7 of 62 (11%) and *AKT1* mutations in 12 of 62 (19%) of their cohort. Of the 7 meningiomas with *SMO* mutations, 6 (86%) occurred in the olfactory groove. Meningiomas with an *SMO* mutation presented with significantly larger tumor volume (70.6 ± 36.3 cm³) compared with *AKT1*-mutated (18.2 ± 26.8 cm³) and wild-type (22.7 ± 23.9 cm³) meningiomas, respectively.

CONCLUSIONS Combined, these data demonstrate clinically actionable mutations in 30% of anterior skull base meningiomas and suggest an association between *SMO* mutation status and tumor volume. Genotyping of *SMO* and *AKT1* is likely to be high yield in anterior skull base meningiomas with available surgical tissue.

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KEY WORDS meningioma; skull base; targeted sequencing; clinically actionable; oncology

MENINGIOMAS are thought to arise from arachnoidal cap cells found in the meninges of the brain and spinal cord and constitute the most frequently reported intracranial tumor (30%–35%).¹⁵ Incidence rates are 7.61 per 100,000, and the median age of diagnosis is 65 years.¹⁸ There is an approximately 3.5:1 female-to-male predilection for developing meningiomas.¹¹ According to the 2007 WHO grading system, meningiomas are classified into 3 distinct tumor grades. Grade I meningiomas

occur most frequently (80%–90%) and recur 7%–20% of the time. Grade II meningiomas occur less frequently (5%–15%) and recur 30%–40% of the time. While relatively rare (1%–3%), Grade III meningiomas represent the most aggressive phenotype with recurrence rates reported as high as 50%–80%.¹⁴

Location of tumor origin is an important predictor of resectability and prognosis in meningiomas.²² Meningiomas located on the convexity are typically more acces-

ABBREVIATIONS AUC = area under the curve; CSA = cross-sectional area; FFPE = formalin-fixed paraffin-embedded; GTR = gross-total resection; ROC = receiver operating characteristic; SHH = sonic hedgehog; WT = wild-type.

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* Dr. Strickland and Mr. Gill contributed equally to this work. Drs. Cahill, Brastianos, and Barker share senior authorship.

sible, circumscribed, and well demarcated from neural and vascular structures as well as brain parenchyma. In contrast, skull base meningiomas are extensive, invasive, and intimately associated with cranial nerves, vessels, and the brainstem.^{10,17} Following incomplete resection, adjuvant radiation may be used for local tumor control. However, radiation to the skull base portends an increased risk to vital structures, including the optic and cranial nerves.^{4,7,12,13,16}

Given the higher degree of surgical inaccessibility and inability to achieve gross-total resection (GTR) in meningiomas of the skull base, coupled with the inherent risks of radiation treatment, recent genomic investigations have sought to identify clinically actionable mutations in these tumors. Emerging data suggest underlying genomic differences between meningiomas of the skull base compared with other locations. We have previously reported recurrent *SMO* and *AKT1* mutations in subsets of non-*NF2* mutated meningiomas.³ Clark and colleagues also demonstrated mutations in these genes in clinically distinctive subsets: in tumors that were nearly always benign and chromosomally stable and that often originated from the medial skull base.⁵ In both studies, the most common *AKT1* mutation was E17K, which has been similarly described to correlate with skull base location.²¹

Here, we focus on anterior skull base meningiomas due to their increased difficulty and morbidity of treatment, as new options for treatment are especially needed in this group. *SMO* and *AKT1* mutations already represent promising therapeutic targets in systemic diseases as exhibited by promising response rates in patients with *SMO*-altered basal cell carcinomas²⁷ and multiple other cancer types with underlying PI3K/AKT/mTOR pathway activation.⁹ Therefore, we sought to further characterize the frequency of *SMO* and *AKT1* mutations using targeted sequencing in anterior skull base meningiomas, tumors whose anatomical locations present a therapeutic challenge.

Methods

Subject Cohort

This study was reviewed and approved by the human subjects institutional review boards of the Dana-Farber Cancer Institute and Massachusetts General Hospital and complied with HIPAA (Health Insurance Portability and Accountability Act of 1996) guidelines. Representative formalin-fixed paraffin-embedded blocks were selected from 62 patients from institutional databases for which there was available archival tissue of adequate quality for sequencing. All samples were from patients who had undergone surgery for an anterior skull base meningioma. A board-certified neuropathologist (M.P.F.) reviewed the histopathological diagnosis, grade, and purity of each case.

Sequencing

DNA was extracted from 20- to 40- μ m sections or one or two 1-mm biopsy cores taken from archived formalin-fixed paraffin-embedded (FFPE) tissue using standard technique (GeneRead DNA FFPE kit, QIAGEN). DNA concentration was measured using PicoGreen dye (Invitrogen). Hotspot cancer gene mutations in *AKT1* (NM_005163

c.49G>A [p.Glu17Lys]) and *SMO* (NM_005631 c.1234C>T [p.Leu412Phe]; NM_005631 c.1604G>T [p.Trp535Leu]) were evaluated using a focused panel based on the Applied Biosystems (ABI) Prism SNaPshot Multiplex system previously described,⁸ with selected cases reconfirmed using established primers²⁶ and Sanger BigDye Terminator v3.1 chemistry (Life Technologies), per the manufacturer. Briefly, exon 1 of *AKT1* and exons 6 and 9 of *SMO* were co-amplified using flanking polymerase chain reaction primers listed in Supplemental Table 1 with up to 20 ng of DNA (94°C $\times$ 2 minutes; 40 cycles of 94°C $\times$ 30 seconds, 57°C $\times$ 30 seconds, 72°C $\times$ 45 seconds; 72°C $\times$ 10 minutes). Following Exo 1 and shrimp alkaline phosphatase treatment (37°C $\times$ 60 minutes, 72°C $\times$ 15 minutes), specific mutation hotspots were subsequently evaluated using a pool of allele-specific extension primers (Supplemental Table 1) that annealed directly adjacent to the nucleotide position of interest. A single-base extension step was performed using the ABI SNaPshot Multiplex Ready Reaction Mix, incorporating one of 4 possible dideoxynucleotide bases labeled with a distinct reporter fluorophore (96°C $\times$ 30 seconds; 25 cycles of 96°C $\times$ 10 seconds, 54°C $\times$ 5 seconds, and 60°C $\times$ 30 seconds). Following treatment with shrimp alkaline phosphatase, labeled extension products were separated by size on an ABI 3500 Genetic Analyzer, and data analysis was performed using GeneMapper Analysis Software (Life Technologies/Applied Biosystems). Sanger sequencing reactions were analyzed on an ABI 3130xl instrument (Life Technologies), and resulting sequence data were analyzed using the Geneious software version R6 (Biomatters Ltd.).

Imaging

Axial T1-weighted postcontrast gadolinium-enhanced MR images of the brain were reviewed and analyzed using OsiriX (v.6.5, Pixmeo SARL). Perpendicular lines on the axial slice demonstrating the maximal tumor area were drawn with line-length multiplied to create a value for tumor cross-sectional area (CSA) (cm²). Additionally, a region of interest was manually drawn around each slice that demonstrated tumor, and a tumor volume (cm³) was annotated. Axial T2-weighted FLAIR images were analyzed to evaluate edematous involvement of the tumor. In cases in which a preoperative MR image was not available, a contrast-enhanced CT image was used to measure tumor size. Tumor edema was not evaluated in these cases.

Statistical Analysis

Statistical database software (JMP version Pro 12) and MedCalc (version 12.7) were used for statistical analysis. Variables were assessed for normality using the Shapiro-Wilk test. Variables not normally distributed were log transformed. The Pearson's chi-square test was used to detect statistical differences in categorical variables. Multiple comparisons of continuous variables were performed using the Tukey-Kramer method. Receiver operating characteristic (ROC) curve analyses of tumor CSA and tumor volume were performed for sensitivity and specificity and area under the curve (AUC), with threshold values to detect *SMO* mutations in skull base meningiomas; $p \leq 0.05$

was used to denote significance. Data are presented as the mean $\pm$ SD, unless otherwise specified.

Results

Overall Cohort

Our patient cohort consisted of 62 patients, 19 male and 43 female, who underwent resection for a skull base meningioma with available archival FFPE tissue at our institution between 1993 and 2015 (Table 1). Tumor location included clinoid ($n = 5$), olfactory groove ($n = 18$), optic nerve sheath ($n = 1$), orbital roof ($n = 4$), sphenoid wing ($n = 12$), and tuberculum sellae ($n = 22$). The median age at surgery for the cohort was 55.4 years (range 30.6–81.8 years). WHO Grade I histology was seen in 79% ($n = 49$) of samples and WHO Grade II in 21% ($n = 13$).

Mutation Frequency

We identified recurrent *SMO* c.1234C>T (L412F) mutations in 7 (11%) patients, and the *AKT1* c.49G>A (E17K) mutation in 12 (19%) patients. Of the 7 meningiomas with *SMO* mutations, 5 were WHO Grade I and 2 were WHO Grade II. Of the 12 tumors with *AKT1* mutations, 8 were WHO Grade I and 4 were WHO Grade II. Thus, actionable mutations were observed in both WHO Grade I and II tumors.

Clinical Correlates of *SMO* and *AKT1* Mutations

We first examined the relationship between age and mutational status. We noted that patients with *AKT1*-mutated meningiomas presented at a younger age (45.0 ± 8.5 years) than those with wild-type (WT) tumors (57.9 ± 12.0 years, $p = 0.002$) and tumors with *SMO* mutations (61.7 ± 15.1 years, $p = 0.01$). Data on progression ($n = 8$ recurrences) and survival ($n = 11$ deaths) were limited and therefore were not powered to correlate with mutation status.

We then examined the relationship between tumor size and mutational status. There was no significant difference in tumor CSA or volume between *AKT1*-mutated and WT meningiomas ($p > 0.6$). Notably however, *SMO*-mutated skull base meningiomas measured 29.6 ± 10.1 cm² by CSA, larger than tumors with *AKT1* mutations, which measured 9.0 ± 10.3 cm² ($p = 0.001$, Fig. 1 left). A similar difference was noted when measuring by volume (tumors with *SMO* mutations: 70.6 ± 36.3 cm³ vs those with *AKT1* mutations: 18.2 ± 26.8 cm³, $p = 0.003$, Fig. 1 right). Tumors with *SMO* mutations were also larger than WT meningiomas measured by CSA (12.6 ± 9.9 cm², $p = 0.02$) and by volume (22.7 ± 23.9 cm³, $p = 0.02$).

Of the 7 meningiomas with *SMO* mutations, 6 (86%) were seen in the olfactory groove and 1 was at the tuberculum. When comparing mutation status within the olfactory groove samples, localization of tumors with *SMO* mutations to the olfactory groove was significant ($p = 0.001$) when compared with the olfactory groove location of WT tumors (18.6%, 8 of 43) and *AKT1*-mutated tumors (33.3%, 4 of 12). However, of all meningiomas presenting in the olfactory groove ($n = 18$), meningiomas with *SMO* mutations were found more frequently in older patients than *SMO* WT tumors: median age 64.7 years versus 48.0 years ($p = 0.02$, Fig. 2).

Recognizing the possibility that meningiomas present-

TABLE 1. Clinical characteristics by mutation status

Variable	WT (n = 43)	<i>AKT1</i> (n = 12)	<i>SMO</i> (n = 7)
Mean age (yrs)	57.9 $\pm$ 12.0	45.0 $\pm$ 8.5*	61.7 $\pm$ 15.1†
F/M	30:13	8:4	5:2
WHO Grade			
Grade I	36 (73.5)	8 (16.3)	5 (10.2)
Grade II	7 (53.9)	4 (30.8)	2 (15.4)
Histological subtype			
Atypical	4 (50.0)	2 (25.0)	2 (25.0)
Meningothelial	25 (67.6)	9 (24.3)	3 (8.1)
Microcystic	1 (100.0)	0 (0)	0 (0)
Mixed	1 (100.0)	0 (0)	0 (0)
Psammomatous	4 (66.7)	1 (16.7)	1 (16.7)
Secretory	3 (100.0)	0 (0)	0 (0)
Transitional	5 (83.3)	0 (0)	1 (16.7)
Tumor location			
Clinoid	3 (60.0)	2 (40.0)	0 (0)
Olfactory groove	8 (44.4)	4 (22.2)	6 (33.3)‡
Optic nerve sheath	1 (100.0)	0 (0)	0 (0)
Orbital roof	3 (75.0)	1 (25.0)	0 (0)
Sphenoid wing	11 (91.7)	1 (8.3)	0 (0)
Tuberculum sellae	17 (77.3)	4 (18.2)	1 (4.6)
Mean MIB-1	2.6 $\pm$ 2.1	3.3 $\pm$ 1.4	2.0 $\pm$ 0.3
Mean tumor CSA (cm ²)	12.6 $\pm$ 9.9	9.0 $\pm$ 10.3	29.6 $\pm$ 10.1*†
Mean tumor vol (cm ³)	22.7 $\pm$ 23.9	18.2 $\pm$ 26.8	70.6 $\pm$ 36.3*†
T2 FLAIR signal present	16 (64.0)	3 (12.0)	6 (24.0)
GTR achieved	26 (61.9)	10 (23.8)	6 (14.3)
Bony involvement	9 (60.0)	6 (40.0)	0 (0)‡
Presenting symptoms			
Headache	15 (62.5)	6 (25.0)	3 (12.5)
Altered mental status	5 (50.0)	1 (10.0)	4 (40.0)‡
Cranial nerve neuropathy	30 (68.2)	11 (25.0)	3 (6.8)
Cerebellar dysfunction	2 (66.7)	0 (0)	1 (33.3)
Seizure	2 (66.7)	0 (0)	1 (33.3)
Asymptomatic	2 (100.0)	0 (0)	0 (0)

Values are presented as the number of patients (%) unless indicated otherwise. Percentages represent the percentage within a row.

* $p < 0.05$ compared to WT, adjusted for multiple comparisons using the Tukey-Kramer test.

† $p < 0.05$ compared to *AKT1*, adjusted for multiple comparisons using the Tukey-Kramer test.

‡ $p < 0.05$. Pearson's chi-square test used to determine significance in categorical variables.

ing in the olfactory groove may grow to a larger size prior to clinical presentation, when compared with other skull base lesions, we attempted to control for tumor location when evaluating the relationship between *SMO* mutation and tumor size. When analyzing only the samples from the olfactory groove, tumors with *SMO* mutations remained significantly larger. Thus, larger volume of tumors with *SMO* mutations in our cohort appears to be a result of both olfactory groove location and mutation sta-

FIG. 1. Box plots showing CSA (left) and tumor volume (right) by mutation status for all samples. Meningiomas with *SMO* mutations were larger in tumor CSA and volume, compared with WT and *AKT1*-mutated meningiomas.

tus, as independent additive factors. Indeed, ROC curve analysis indicated that tumor CSA and volume can predict *SMO* mutation status with high sensitivity and specificity (Fig. 3).

In addition, tumors with *SMO* mutations tended to have increased prevalence of T2 FLAIR signal on MRI ($p = 0.08$) seen in 100% of the available MR images ($n = 6$ of 6; 1 patient had only CT for review). Bony involvement did not occur in the tumors with *SMO* mutations ($p = 0.046$); however, it did occur with 9 WT and 6 *AKT1*-mutated tumors. Additionally, 57.1% (4 of 7) of patients harboring meningiomas with *SMO* mutations presented primarily with altered mental status, compared with 12.2% of WT (5 of 41) and 8.3% (1 of 12) of *AKT1*-mutated meningiomas ($p = 0.009$). When evaluating only the olfactory groove samples, this association between altered mental status and mutation status lost significance. Thus, some components of the mutation-specific presentation of tumors with *SMO* mutations may be solely accounted for by their olfactory groove location.

Discussion

The gold standard for therapeutic management of meningiomas has classically been surgery. Surgical outcome predicts recurrence rate.²⁵ However, anatomical location represents a major variable that limits surgical access and, therefore, resectability.

Skull base meningiomas highlight this therapeutic dilemma. Currently, meningiomas for which GTR cannot be achieved are typically managed with adjuvant radiotherapy. There are no known reported chemotherapeutic agents shown to successfully treat meningiomas, with only early trials underway targeting recently described clinically actionable mutations. Should these chemotherapeutic agents prove efficacious, a targeted neoadjuvant therapeutic strategy may represent a promising approach to decrease overall tumor burden prior to resection or radiation therapy in the treatment of meningiomas.

Whole exome sequencing studies of meningiomas have suggested that recurrent *SMO* and *AKT1* mutations occur in skull base tumors at low frequency.^{3,5} In our study, we performed targeted sequencing for *SMO* and *AKT1* mutations, across a large focused cohort of 62 anterior skull base meningiomas, to identify mutation rates in these surgically challenging tumors. Our data found recurrent mutation rates of 11% for *SMO* and 19% for *AKT1* in both WHO Grade I and Grade II skull base meningiomas. Our finding of recurrent mutations in Grade II tumors contrasts with that of Sahm et al., who noted only rare mutation of *AKT1*E17K in Grade II lesions.²¹

We found a strong preponderance of *SMO* mutations occurring in the olfactory groove (6 of 7, 86%). We re-

FIG. 2. Box plot showing age by mutation status for olfactory groove meningiomas. Patients with *SMO*-WT olfactory groove meningiomas ($n = 12$) presented at a younger age than patients with *SMO*-mutated olfactory groove meningiomas ($n = 6$).

FIG. 3. Tumor CSA (left) and tumor volume (right) results of ROC curve analyses to detect *SMO* mutation. ROC curve analysis demonstrates that tumor CSA predicts *SMO* mutation status with a threshold greater than 25.8 cm², with 83% sensitivity and 93% specificity (AUC 0.905, $p < 0.0001$). Similarly, tumor volume predicts *SMO* mutation with a threshold greater than 48.6 cm³, with 83% sensitivity and 88% specificity (AUC 0.893, $p < 0.0001$).

port for the first time skull base meningiomas with *SMO* mutations presented with a substantially larger tumor size than *AKT1*-mutated and WT meningiomas. Larger tumor volume was due, in part, to the predilection of tumors with *SMO* mutations to initiate within the olfactory groove but remained significant in our cohort even after controlling for olfactory groove location. Thus, tumor size may have the potential to serve as an imaging biomarker to predict *SMO* mutation status in skull base meningiomas.

A recent study by Abedalthagafi et al. reported copy number changes and mutational profiling of 150 meningiomas (73 lesions across the anterior and posterior skull base), finding 6 of 73 *AKT1* and 4 of 73 *SMO* mutations.¹ The authors' lower observed mutation frequency may be due to differences in technique; however, overall their observations are not significantly different from our findings. The age association observed in our study was not apparent in the fewer skull base meningiomas with *AKT1* and *SMO* mutations in the study by Abedalthagafi et al. In addition, this prior study did not assess tumor size. Further studies are needed in larger validation cohorts to confirm our findings.

Not only were meningiomas with *SMO* mutations larger in tumor CSA and volume in our cohort, but they also presented in older patients in the olfactory groove. This clinical association between age and genotype will require prospective validation in larger cohorts, as this clinical phenotype (older age and larger tumor size) portends an increased likelihood for perioperative morbidity.² One can envision a role for neoadjuvant targeted therapies against the sonic hedgehog (SHH) signaling pathway in patients harboring meningiomas with *SMO* mutations to potentially minimize subsequent surgical morbidity, thereby optimizing frontal lobe functional out-

come in these patients who characteristically present with altered mental status.

Mutations in the SHH pathway, in which *SMO* is a part, are seen in systemic and central nervous system tumors, and are responsible for transforming adult stem cells into cancer stem cells, leading to malignant growth.²⁴ Recent studies have shown efficacy for *SMO* inhibitors in basal cell carcinoma.²⁸ One such inhibitor, vismodegib, received FDA approval in 2012²⁰ for the treatment of locally advanced or metastatic basal cell carcinoma.^{23,27} Moreover, patients with recurrent medulloblastomas with mutations in the SHH pathway exhibited an increase in progression-free survival after treatment with vismodegib compared with SHH-WT medulloblastomas.¹⁹

In addition to the SHH pathway, the PI3K/AKT/mTOR signaling pathway is one of the most frequently mutated oncogenic pathways in human cancer.⁶ A number of AKT inhibitors are being investigated preclinically and clinically. Davies and colleagues demonstrated that inhibition of AKT using these inhibitors reverses pathway activation driven by *AKT1*E17K mutations.⁶ In particular, AZD5363 monotherapy induced partial responses in 2 patients with tumors containing *AKT1*E17K mutations in a Phase I clinical trial (NCT01353781). Their work adds to the mounting evidence that the *AKT1*E17K mutation is a rational target. As we currently do not know whether the utilization of these pharmacological agents in meningiomas will induce measurable tumor response or stability, we await the results of a multicenter, National Cancer Institute-sponsored Phase II clinical trial now underway (NCT02523014).

One limitation of our study is its retrospective, single-institution design; thus, these findings should be assessed in a larger validation cohort. Indeed, mutational annota-

tion of clinical material from ongoing trials offers the opportunity for validation of demographic and radiographic findings in patients harboring tumors with *SMO* and *AKT1* mutations on initial presentation. An additional limitation of our study is the paucity of recurrence and survival data in our cohort given the limited follow-up time. Further study of the influence of mutation status on these outcomes is warranted.

Conclusions

We find mutation rates at high frequency for *SMO* (11%) and *AKT1* (19%) in both WHO Grade I and Grade II anterior skull base meningiomas. As has been suggested previously, we have definitively demonstrated that *SMO* mutations were most frequently seen in the olfactory groove, and we report here for the first time tumors with *SMO* mutations presented with a clinical phenotype of older age and larger tumor volume, even after controlling for olfactory groove location. As potential imaging biomarkers, tumor volume and CSA have strong sensitivity and specificity to predict *SMO* mutations. Routine testing of skull base meningiomas for these potentially actionable mutations is supported by our findings. While surgical management has traditionally driven treatment in meningiomas, targeted therapy for tumors in surgically challenging locations may represent a future shift in the treatment paradigm for a substantial proportion of these tumors.

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Disclosures

Dr. Thiede reports that he has ownership in AgenDix GmbH. Dr. Brastianos reports that she is a consultant for Genentech and has received speaker's honoraria from Merck. Dr. Cahill reports that he has received speaker's honoraria from Merck.

Author Contributions

Conception and design: Barker, Strickland, Gill, Cahill, Brastianos. Acquisition of data: Barker, Strickland, Gill, Nayyar, D'Andrea, Thiede, Juratli, Schackert, Borger, Frosch, Cahill, Brastianos. Analysis and interpretation of data: Barker, Strickland, Gill, Nayyar, Thiede, Juratli, Schackert, Borger, Cahill, Brastianos. Drafting the article: Barker, Strickland, Gill, Nayyar, Cahill,

Brastianos. Critically revising the article: Barker, Strickland, Gill, Santagata, Frosch, Cahill, Brastianos. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Barker. Statistical analysis: Barker, Strickland, Gill, Cahill. Administrative/technical/material support: Barker, Strickland, Gill, Nayyar, D'Andrea, Borger, Frosch. Study supervision: Barker, Cahill, Brastianos.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Table 1. <https://thejns.org/doi/suppl/10.3171/2016.8.JNS161076>.

Correspondence

Fred G. Barker II, Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., Yawkey 9E, Boston, MA 02114. email: barker@helix.mgh.harvard.edu.