Neurological Institute Journal

- Treating Intracranial Atherosclerotic Disease with Stenting
- Treating Vision, Eye Movement, and Balance Disorders
- Ohio Brain Tumor Study
- Petroclival Meningiomas
- Transforming the Culture of Health Care

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Neurological Institute Journal

FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Summer 2009 issue of the University Hospitals Neurological Institute Journal.

Through continuing collaboration with scientists at Case Western Reserve University School of Medicine, physicians at the UH Neurological Institute test and refine the latest advances in treatment for patients with disabling neurological disorders. The UH Neurological Institute Journal highlights these advances and demonstrates our interdisciplinary strengths. As an added benefit for our readers, CME credit is readily available in each issue for the busy practitioner interested in receiving *AMA PRA Category 1 Credits*™.

Our third issue speaks strongly of this collaboration, featuring articles written by members of the UH Neurological Institute, the Case Comprehensive Cancer Center, and the University Hospitals Ireland Cancer Center.

In this issue, Jason Wilson, MD, and colleagues discuss how stenting and angioplasty have become excellent options for treating Intracranial Atherosclerotic Disease. The article highlights current clinical trials that may prove these techniques more effective than medical management.

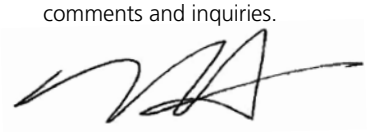
Robert Leigh, MD, and colleagues take us inside the Neuro-Ophthalmology Center and the Daroff-Dell'Osso Ocular Motility Laboratory. State-of-the-art technology and the collective expertise of neuro-ophthalmologists, neurotologists, and basic scientists offer hope to those who suffer from disorders of vision, eye movement and balance.

Jill Barnholtz-Sloan, PhD, and colleagues introduce us to the Ohio Brain Tumor Study, a new multicentered Ohio-based research endeavor at the Case Comprehensive Cancer Center and Brain Tumor and Neuro-Oncology Center. By gathering vital information to guide targeted patient therapies, the Study has the potential to improve the survival of brain tumor patients.

Sunil Manjila, MD, and colleagues explore management of complex skull base tumors, specifically petroclival meningiomas. The article reviews past techniques and describes how stereotactic radiosurgery is changing how these challenging lesions are met at the UH Neurological Institute.

Finally, Wendy Miano and Linda Mangosh highlight patient- and family-centered care at the UH Ireland Cancer Center, an approach to health care that extends the collaboration noted among our staff, physicians and scientists to include a collaboration with patients and families for better patient outcomes, safety and quality.

We are pleased to share our clinical findings with others in the neuroscientific community and hope our readers can benefit from them. We welcome your comments and inquiries.



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Dr. Furlan is a consultant with NMT Medical Inc. and a member of the speakers bureaus for Bristol-Myers Squibb Co. and Sanofi-aventis, but receives no direct payments from any commercial entity related to articles in this publication. Dr. Riley has received research support from Cleveland Medical Devices, the Parkinson Study Group, the Dystonia Study Group, the Evans Foundation, the estate of Nina Kramer, the Gift of Nina and Sandy McAfee, Allergan, Schwarz Pharma and Medtronic, and honoraria for presentations and consulting from Teva, Boehringer-Ingelheim, GlaxoSmithKline, Novartis and Valeant. Other editorial board members report no financial relationships related to articles appearing in this issue of the Neurological Institute Journal.

On the cover: Extra-axial tumor arising from the petroclival region compressing the brainstem and cranial nerves. Read more about this case in the article by Manjila and colleagues on page 16. (Illustration by Ravin Art & Design.)

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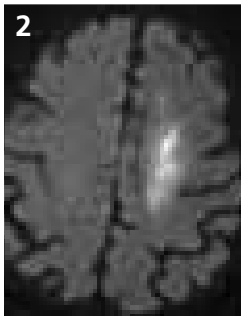

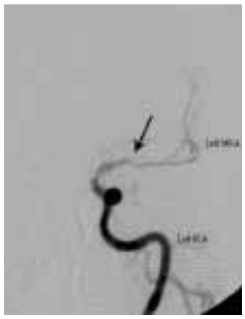

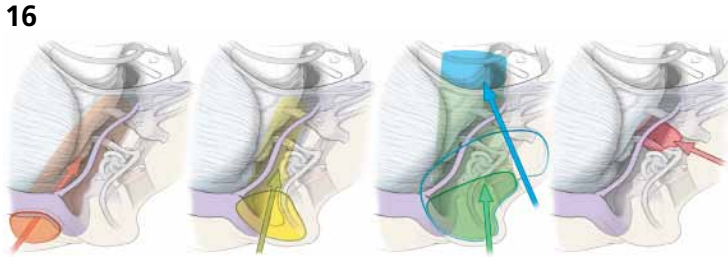

Treating Intracranial Atherosclerotic Disease with Stenting and Angioplasty

By
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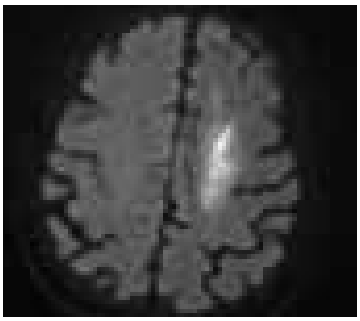

Figure 1. Diffusion-weighted image demonstrating acute to subacute ischemia in the left centrum semiovale.

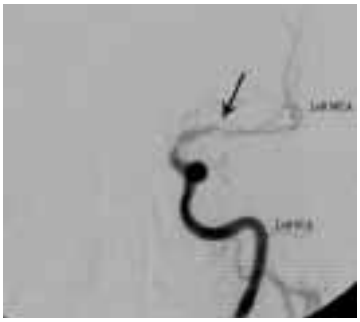

Figure 2. Left internal carotid artery (ICA) angiogram demonstrating severe stenosis of the M1 segment of the left middle cerebral artery (MCA) (arrow).

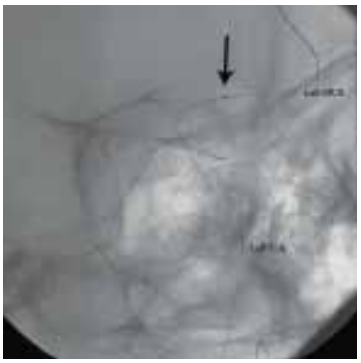

Figure 3. Native view of the skull at angiography with micro guidewire in the left internal carotid artery (ICA) and middle cerebral artery (MCA) traversing the stenosis. The pre-stent angioplasty balloon is inflated.

Case Study

A 65-year-old Caucasian female presented with worsening right-sided weakness and aphasia, two weeks following a left middle cerebral artery (MCA) stroke. The National Institutes of Health Stroke Scale (NIHSS) score was 7 (Figure 1). The symptoms were worsening despite a medication regimen of daily aspirin and clopidogrel bisulfite (Plavix). On MRA and confirmed by catheter angiography, a severe left MCA stenosis was found (Figure 2). The patient had multiple areas of atherosclerotic stenosis throughout the brain. The lesion was predilated with an angioplasty balloon to allow for stent passage (Figure 3). The post-stent angiogram is illustrated in Figure 4 with less than 30% residual stenosis. There were no complications, and the patient was discharged with an NIHSS score of 5. At the six-month follow-up, the symptoms were stable and there was no further neurologic decline.

The Evolution of Stenting and Angioplasty

In 1964, Charles Dotter, a peripheral vascular radiologist, introduced the concept of peripheral vascular transluminal balloon angioplasty to the United States but was met with resistance in the United States for many years.[1] The idea was embraced and refined by European investigators, and in 1977, Dr. Andreas Gruentzig performed the first successful human coronary angioplasty in Zurich, Switzerland.[2] The concept of the stent developed from a decade of experience with angioplasty and re-stenosis in the 1980s. The term "stent" is thought to be derived from an English dentist, Charles Stent (1845–1901), who had a breakthrough refinement making a compound used to form dental impressions.[3] The compound, later known as "Stent's mold," was used by surgeons during World War I to stretch and fixate skin grafts. "Stent" is now widely known throughout medical literature as a metal mesh cylinder designed to counteract a disease-induced flow constriction in a vessel or other tubular conduit in the body. Historically, treatment of intracranial stenosis has lagged behind coronary and carotid disease. The advent of new flexible balloons, stents, and delivery systems has made intracranial angioplasty and stenting a feasible option for the treatment of intracranial occlusive pathology.

Stenting for Intracranial Atherosclerotic Disease

Intracranial atherosclerotic disease (ICAD) is attributed with causing 7–40% of ischemic strokes each year.[4,5] The Northern Manhattan study confirms that ICAD is most common in Hispanic and African-American populations due to a greater prevalence of diabetes and hypercholesterolemia.[6]

The risk of stroke and death with medical management of ICAD has been addressed by the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial and the Groupe d'Etude des Sténoses Intra-Crâniennes Athéromateuses symptomatiques (GESICA) study.[7,8] The initial retrospective WASID study showed that warfarin was more effective than aspirin at preventing recurrent stroke in ICAD. The prospective WASID trial was a randomized, double-blind, clinical trial comparing warfarin with INR of 2–3 and 1300mg daily aspirin in patients with symptomatic intracranial stenosis of 50–99%. After 569 patients had undergone randomization, enrollment was stopped because of concern for the safety of the patients who had been assigned to receive warfarin (major hemorrhage 8% versus 3% in the aspirin group). From the limited 1.8-year mean follow-up data, there was a 12% and 15% recurrence rate of stroke in the territory of the stenotic artery

for patients treated with aspirin and warfarin, respectively.[7] The calculated annual rate of same territory strokes was 8.5%. A subgroup analysis identified two groups of patients at greatest risk of subsequent stroke in the territory of the stenotic artery: women and those with stenosis greater than or equal to 70%; after recent symptoms, 18% of those patients with stenosis greater than or equal to 70% had ipsilateral stroke at 1 year.[9]

From 1999 to 2003, the GESICA study evaluated the natural history of 102 patients with symptomatic intracranial stenosis of 50–99% while undergoing medical treatment.[8] Despite medical treatment, 38% of the patients experienced a recurrent cerebrovascular event in the territory of the stenotic artery at the two-year follow-up. A subgroup of patients found to be at higher risk of recurrent stroke were those with a "hemodynamically significant stenosis" as defined by symptoms related to the stenosis occurring during a change of position (supine to prone), an effort, or the introduction or increase of an antihypertensive medication. These characteristics were observed in 27% of patients, and of these patients, 61% had a recurrent stroke or TIA in the territory of the stenotic artery.

Endovascular Treatment

The lack of successful medical therapy for intracranial stenosis combined with early reports of successful balloon angioplasty for basilar stenosis[10] prompted the study of endovascular intervention as an option for prevention of stroke. Surgical treatment of symptomatic intracranial stenosis failed to demonstrate beneficial reduction in stroke and death from the External Carotid/Internal Carotid Artery Bypass Trials of 1985.[11] The goal of endovascular therapy is to prevent stroke from hypoperfusion or occlusion of the stenosed vessel. For several decades, numerous investigators have reported technical feasibility in treating intracranial stenosis with angioplasty with and without stenting. Until recently, the only available stents were designed for cardiac use.[10,12-15] Histologically, compared to the peripheral vasculature, intracranial vessels have a thinner layer of adventitia and lack a consistent muscular layer. The introduction of thinner, flexible, dedicated intracranial stents and more flexible catheters and balloons have increased technical success and interest in endovascular intervention for the treatment of intracranial stenosis.

Angioplasty Alone

Difficulties with angioplasty for intracranial stenosis in early experiences focused on intimal dissection, rebound stenosis, and vessel rupture. Subsequently, Mori and colleagues described a clinically relevant angiographic classification to determine the risk and success of angioplasty of intracranial stenosis.[17] In 1999, Conners and Wojak published their experience and learning curve in treating 70 patients by intracranial angioplasty for atherosclerotic diseases over a nine-year period.[12] Their technique evolved from approximating the size of the balloon to the vessel caliber with rapid inflation to undersizing the balloon compared to the treated vessel and using extremely slow inflation. The rate of vessel occlusion and dissection decreased from 75% to 14%. They also noted that a significant number of patients had residual stenosis of greater than 50%. Other authors also reported higher rates of residual stenosis associated with angioplasty alone.[15,18,19] Whether or not this residual stenosis is clinically significant has been difficult to determine, with few studies reporting long-term patient outcome data.[16,20,21] These studies, which followed small groups of patients for 22 to 42 months, report a 0-3.6% annual stroke risk in the treated territory, which is a favorable outcome when compared to medical treatment. Routine angiographic follow-ups are usually not performed unless the patient is symptomatic; therefore, the true rate and significance of re-stenosis is unclear. Symptomatic re-stenosis would likely require a repeat endovascular intervention, thereby incurring additional periprocedural risks. In addition, evidence from the cardiac literature has shown better long-term outcome with angioplasty and stenting over angioplasty alone.

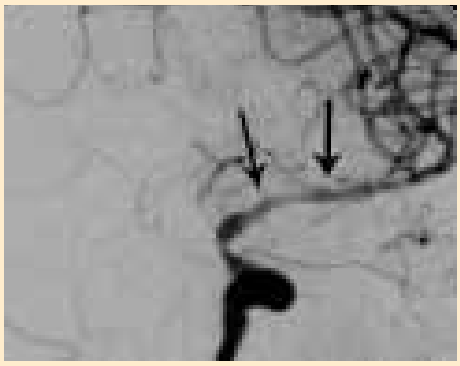

Figure 4. The post-stent angiogram demonstrates less than 30% residual stenosis. The arrows mark the proximal and distal ends of the stent.

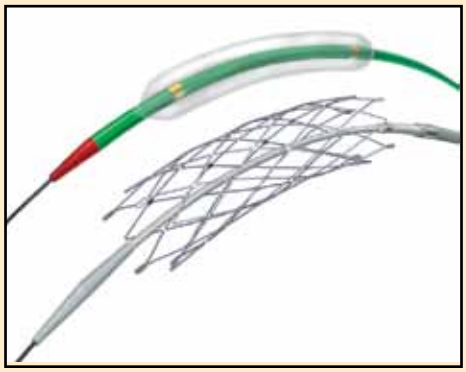

Figure 5. Wingspan Stent System with Gateway Percutaneous Angioplasty Balloon Catheter. Image courtesy of Boston Scientific Corporation.

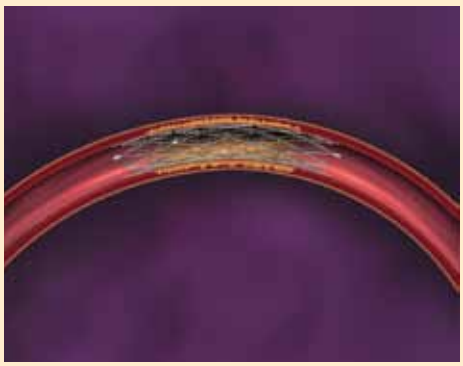

Figure 6. Graphical illustration of the Wingspan stent within an atherosclerotic stenosis. Image courtesy of Boston Scientific Corporation.

PROCEDURE AND COMPLICATIONS

Patient and clinical characteristics that favor intracranial stenting include a greater than 70% stenosis of a major intracranial vessel that is refractory to medical management, a minimum vessel diameter of 2.0mm, and a previous stroke or TIA with symptoms as a result of the target lesion. Characteristics unfavorable for stenting include a severe deficit from stroke, a chronic total occlusion of the artery, a hemorrhagic stroke or stroke with mass effect within six weeks of the procedure, and a contraindication or resistance to antiplatelet medications.[29]

After selection for endovascular treatment, a baseline neurological exam is performed. Formal catheter angiography is used to assess the degree of stenosis before stent placement. Patients receive Plavix at 75mg per day, five to seven days before the procedure. As a Plavix alternative, aspirin or aspirin/extended-release dipyridamole (Aggrenox) can be administered. Following the procedure, patients are maintained on Plavix for a minimum of six weeks.

After induction of general anesthesia, a 6 French sheath is placed in the common femoral artery. After gaining vascular access, a heparin bolus and drip are started, and the activated clotting time is maintained at two times the baseline. After access to the intracranial circulation is achieved, stenting is performed with the assistance of balloon angioplasty as needed. There are several potential serious procedural complications, including dissection, stroke, and vessel rupture. The procedure should only be performed by experienced operators in a center with neurosurgical and endovascular expertise. A neurological exam is performed before discharge, at 30 days following the procedure, and again at six months. Follow-up angiogram can be performed between six and eight months.

(Treating Intracranial Atherosclerotic Disease with Stenting and Angioplasty continued)

Angioplasty and Stenting

The decision to perform angioplasty versus angioplasty plus stenting for intracranial stenosis needs to take into consideration the potential increased periprocedural risk associated with the technical challenges of stent delivery, which in the past was not insignificant in neurointerventional procedures that utilized coronary equipment.[22] Theoretically, the sustained radial force of the stent improves the patency and minimizes embolic events by trapping the plaque between the stent and the vessel wall. Stenting is hypothesized to lower the risk of vessel dissection, acute vessel occlusion, and rebound stenosis associated with angioplasty alone.

In 193 symptomatic intracranial lesions, Siddiq and colleagues found a residual stenosis rate of 4% versus 15% in their patients after treatment with angioplasty and stenting compared to angioplasty alone, respectively.[18] Other authors have also shown improved durability with stenting, though it remains unclear as to whether stenting reduces the rate of recurrent ischemia over angioplasty alone.[22,23] Most series reported periprocedural risks of 8–30% using balloon-mounted coronary stents, which until recently were the only stents available for intracranial stenting. Clearly, reducing periprocedural risks with dedicated intracranial equipment is desirable. In 2004, a multicenter, prospective feasibility study was published that utilized a dedicated intracranial stent for symptomatic ICAD: the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study.[24] The study used the Guidant Corporation's NEUROLINK system, which provided successful stent placement in 95% of patients with a 6% complication rate. The study found that stroke occurred in 6% of patients within 30 days and 7% of patients between 30 days and one year. Re-stenosis occurred in 33% of intracranial lesions; 61% of all patients with greater than 50% stenosis at six months remained asymptomatic.

Prospective randomized trials comparing maximal medical therapies versus angioplasty and stenting have been lacking. In August 2005, the Food and Drug Administration approved the use of Boston Scientific's Wingspan stent (Figures 5 and 6), a self-expanding nitinol intracranial stent, as a humanitarian device exemption for symptomatic patients with intracranial stenosis greater than or equal to 50% while on antithrombotic therapy. Initial data from a prospective, single-arm Wingspan safety and efficacy trial showed a similar safety profile and patient outcome when compared to the SSYLVIA study.[25,26] An evaluation of the National Institutes of Health registry on use of the Wingspan stent for symptomatic 70–99% intracranial stenosis compared to the WASID subgroup analysis of the same patient population found that the post-procedure event rates for the stented population do not rule out that stenting could be associated with a substantial relative risk-reduction or that stenting lacks an advantage over medical therapy, thus indicating a need for a randomized clinical trial comparing stenting with medical therapy.[27]

Current Clinical Trials

Currently, the Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial is open for enrollment to determine whether intracranial angioplasty and stenting with intensive medical therapy is superior to intensive medical therapy alone in preventing a second stroke in symptomatic patients with 70–99% stenosis in a major intracranial artery.[28] The primary endpoint is to determine whether there is a reduction of a second stroke within two years from the initiation of the treatment regimen. Intensive medical therapy includes management of blood pressure, lipids, diabetes, and other risk factors for vascular events. Outcome data from the SAMMPRIS trial will determine if stenting of symptomatic intracranial stenosis will provide any reduction in stroke risks.

Conclusion

Advances in technology and technique have made intracranial stenting a technically feasible and effective option for the treatment of ICAD. As the pathophysiology of intracranial occlusive disease becomes better understood, endovascular therapies may become a more prevalent treatment option. Current clinical trials, such as SAMMPRIS, are a first step toward elucidating whether stenting is superior to medical management.

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Treating Vision, Eye Movement, and Balance Disorders: Recent Advances from the Neuro-Ophthalmology Service and the Daroff-Dell'Osso Ocular Motility Laboratory

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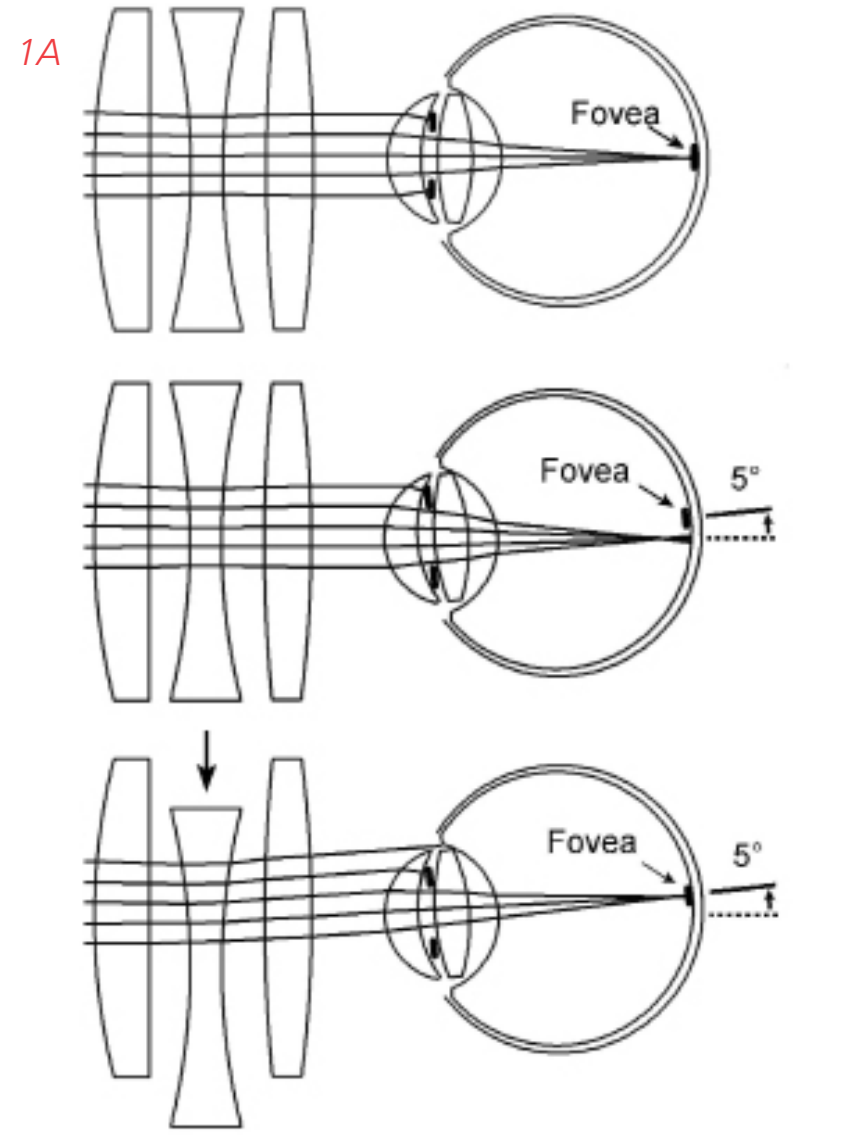
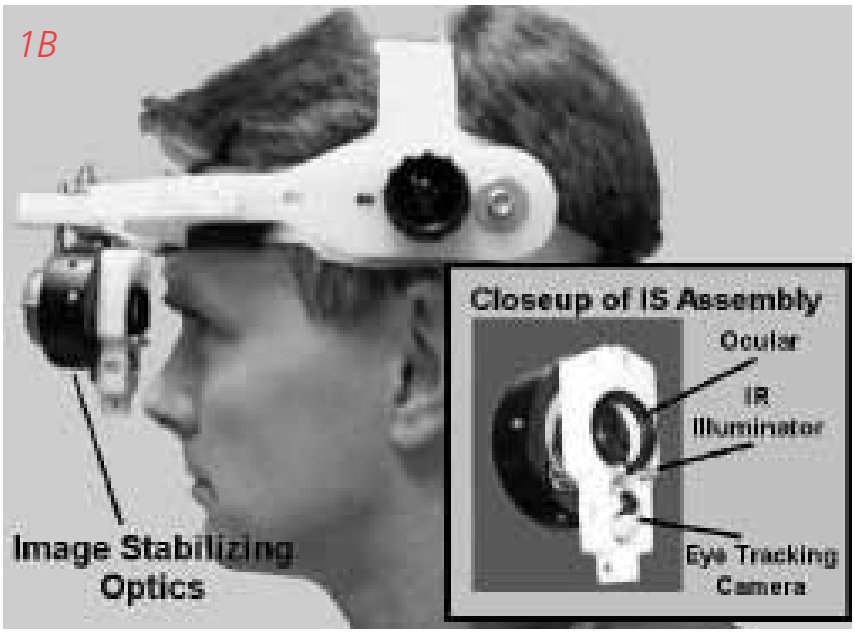
Disorders of vision, eye movement, and balance remain important public health issues. Sudden visual loss and falls are two of the most common causes for individuals older than 65 years coming to the emergency department. Basic research has provided insight into the pathogenesis of visual and balance disturbances, and eye movement measurements, once purely a research tool, are now being used to probe a broad range of neurological disorders.[1] The Neurological Institute has a team of neuro-ophthalmologists, neurotologists, and basic scientists who have pursued disorders of vision, eye movements, and balance for more than a quarter-century. This research group was founded in 1980, when Dr. Robert Daroff became Chair of Neurology and set up the laboratory with Drs. Louis Dell'Osso, Todd Troost, and Larry Abel. In 2006, a new facility with six experimental rooms and state-of-the-art technology, the Case Daroff-Dell'Osso Ocular Motility Laboratory, opened at the Louis Stokes Veterans Affairs Medical Center. Their collective expertise is displayed in more than 500 publications, three international conferences hosted in Cleveland, and research training for more than 50 young scientists and is supported by sustained federal research grants.[2,3]

New Insights into Disorders of Vision

Nonarteritic Anterior Ischemic Optic Neuropathy:

An ongoing controversy exists regarding the use of Viagra and related drugs, the phosphodiesterase type-5 inhibitors (PDE5i), for the treatment of erectile dysfunction and the possibility of developing visual loss from nonarteritic anterior ischemic optic neuropathy (NAION). NAION is the most common cause of acquired optic neuropathy, other than glaucoma, in persons over the age of 50 years. Based on personal observations and a review of published cases, Drs. Thurtell and Tomsak, with University Hospitals Case Medical Center urologist Dr. Allen Seftel, concluded that permanent visual loss caused by these drugs is very unusual, except in selected individuals with specific risk factors for NAION.[4] Risk factors include having structurally congested optic discs, hypertension, diabetes, nocturnal hypotension, and myocardial infarction, and suffering an attack of NAION prior to the use of PDE5i. The visual risk of PDE5i in those with pre-existing optic nerve disease, such as glaucoma, is unknown.





Multiple Sclerosis:

A common feature of multiple sclerosis (MS) is optic neuritis, characterized by monocular visual loss, usually with good recovery within a few months. By testing with low-contrast optotypes, it has been possible to demonstrate residual visual defects in patients with a history of optic neuritis. Whereas the exacerbations in MS are associated with acute demyelination, deficits that are more chronic have been attributed to axonal loss. Acute and chronic phases of optic neuritis provide a new window on these separate processes in MS. Thus, on one hand, demyelination of the optic nerve is associated with a delayed "P100" wave of the visual evoked potential (VEP). On the other hand, the novel technique of optical coherence tomography (OCT) provides a sensitive way to measure the thickness of the nerve fiber layer of the retina. Drs. Thurtell, Bala, and Yaniglos have recently investigated the relationship between low-contrast visual acuity, VEP, and OCT in 20 eyes of MS patients and found that the VEP to low-contrast stimuli is more likely to show evidence of optic nerve demyelination, and that OCT measurements correlate well with low-contrast visual acuity.

Ocular Oscillations that Degrade Vision

Infantile Nystagmus:

Infantile nystagmus occurs in association with disorders affecting the visual system, such as albinism, but also in individuals with normal visual and nervous systems (infantile nystagmus syndrome or INS). Based on a seminal observation that surgical treatments, of whatever approach, partially quelled INS, Dr. Dell'Osso proposed that muscle sensation (proprioception) plays an important role in the control of slow eye movements.[5] By disturbing proprioceptors, which lie close to the insertion of the eye muscles on the globe (the site of eye muscle surgery), the underlying oscillatory mechanism was reduced, damping the nystagmus

Figure 1: A 3-lens image-shifting device that nulls the visual effects of ocular oscillations. The line diagrams summarize the optical principals used in the device (A). Starting with the eyes and optics in a neutral position (top), light from a distant target is brought to the fovea of the retina. If the eye is rotated downward (middle), the image is displaced from the fovea. However, if the central lens is moved downward by the appropriate amount (bottom), the image is brought back onto the fovea.[14] The photo shows a prototype of the electro-optical device, which incorporates an eye movement monitor to measure the patient's ocular oscillations and drive the optical system (B).

and improving vision.[6] Indeed, an operation that simply detaches and then reattaches extraocular muscles has been shown to broaden the range of gaze angles for which the eye remains on target and even improve acquisition of new visual targets.[7] The net result of this tenotomy procedure has been that INS patients can see better and inspect their visual world more efficiently. These therapeutic effects of tenotomy have contributed to a re-evaluation of the role of proprioception from the extraocular muscles. Basic studies have demonstrated the location of extraocular proprioceptors,[8] their apparent innervation by a separate population of ocular motor neurons, and the presence of proprioceptive signals in the cerebral cortex.[9]

One disorder in humans that causes blindness from birth is Leber's congenital amaurosis (LCA). Individuals with LCA have continuous instability of gaze, including nystagmus. A canine model for LCA exists, and gene therapy has recently been shown to reverse the retinal abnormalities and damp the associated nystagmus in affected dogs.[10] The sensory and motor success of gene therapy in the canine LCA model has resulted in preliminary trials in human patients. The therapeutic improvements in the first few patients have been promising.[11]

Acquired Nystagmus:

Several disorders, including MS and stroke, may lead to the development of nystagmus in adults, with visual blurring and the illusion of oscillations of the seen world (oscillopsia). Several drugs have been suggested as treatments for acquired forms of nystagmus, including gabapentin, which was shown to be effective for some patients in a masked trial.[12] Most recently, gabapentin is being compared with memantine, a non-competitive glutamate antagonist, as a treatment for acquired nystagmus. Memantine has also been reported to suppress excessive rapid eye movements (saccades), which degrade vision in patients with a form of hereditary cerebellar ataxia.[13]

When drug therapies for acquired nystagmus fail to reduce nystagmus and improve vision, the tenotomy operation developed for infantile nystagmus sometimes provides improvement. A high-tech approach to the problem is to use an electro-optical device to cancel the visual effects of the ocular oscillations. Dr. Stahl has used image-stabilization optics, which are a feature of modern digital cameras, to cancel image motion induced by ocular oscillations (Figure 1).[14] One goal of this work is to develop a stabilization device that can be used by physicians to test how much an individual can expect his or her vision to improve if the oscillations are controlled. The patients who derive strong benefits would be appropriate for surgical or pharmacological therapies.

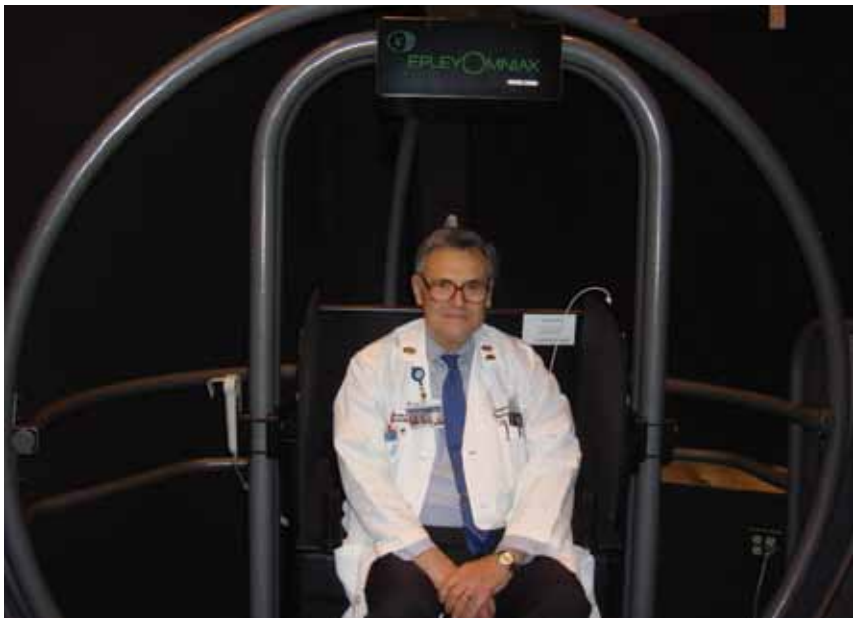


Figure 2: The Epley Omniax System allows patients to be rotated about any axis. Originally designed to treat benign paroxysmal positional vertigo by repositioning otolithic debris out of the posterior semicircular canal, the rotator provides opportunities for studying a broad range of vestibular and neurological disorders. The patient is secured with belts and restraints prior to being rotated. Eye movements are monitored using a video-based system.

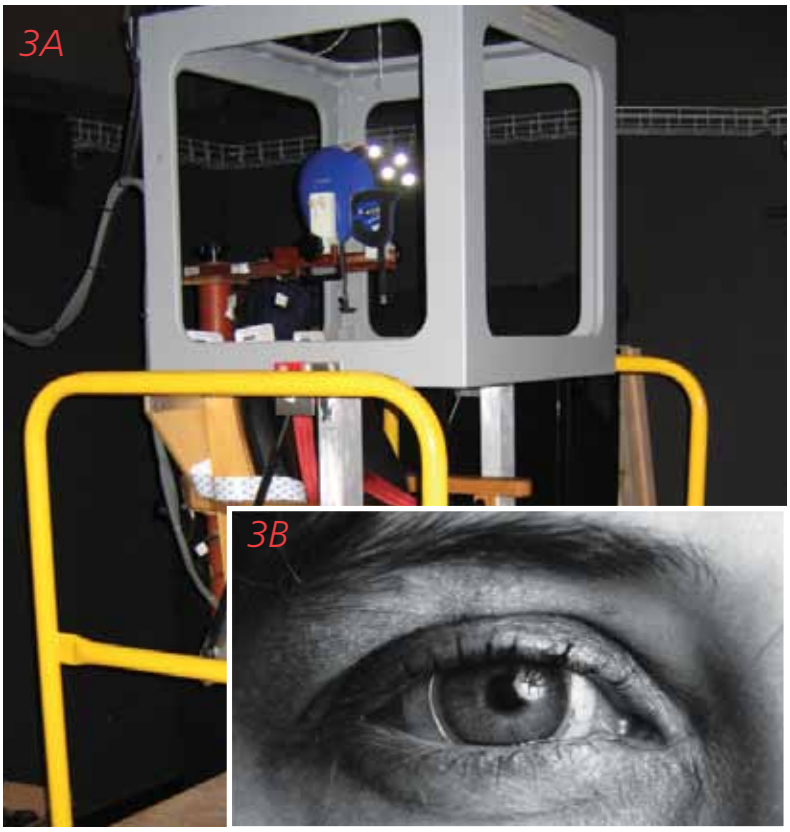
Using Eye Movements as Experimental Tools

The study of eye movements offers several distinct advantages for neuroscientists interested in learning how the brain controls balance and movement and how diseases disrupt normal behaviors.[1] First, eye movements are rotations in three directions that can be reliably measured and analyzed. Second, the apparent lack of a stretch reflex and other factors mean that the relationship between the neural signals of ocular motor neurons for eye movements and eye rotations is quite linear. Third, distinct functional classes of eye movements can be distinguished, each class possessing properties that suit it to specific purposes. Fourth, a good deal is known about the anatomy, physiology, and pharmacology of central pathways for the control of each functional class of eye movements. Taken together, this means that eye movements can be used as experimental probes of a broad range of diseases affecting the nervous system. Here we provide examples from our lab of how studies of eye movements illuminated the pathogenesis of a number of disorders, starting from the eyeball, and moving centrally to the brainstem, cerebellum, basal ganglia, and cerebral cortex (a bottom-up approach).

The extraocular muscles (EOM) possess unique properties, including high-energy requirements, and most fiber types are rich in mitochondria. Thus, EOM are particularly sensitive to mitochondrial disorders that cause ptosis and chronic progressive external ophthalmoparesis.[15] It has been shown that pale, fast fibers (with few mitochondria) may be relatively spared so that high eye accelerations remain possible. Myasthenia gravis has a predilection for eye muscles; 50% of patients present with ocular symptoms, and 80% eventually develop them. One factor contributing to the susceptibility of EOM to myasthenia is that the neuromuscular junction of most fiber types shows little post-junctional folding, thereby reducing the area available for acetylcholine receptors. Only the fast, pale fibers exhibit well developed post-junctional folding, accounting for preservation of fast (quiver) movements despite a limited range of movement in ocular myasthenia.[16]

Fatigue is a distressing symptom in MS, with no good measure or reductionist model at present, though one may be within reach with further eye movement research. Internuclear ophthalmoplegia (INO), a common eye movement disorder in MS, is characterized by slowing of the adducting eye during horizontal saccades. The pathogenesis of INO is well known, being caused by demyelination in a single brainstem pathway, the medial longitudinal fasciculus. Working in collaboration with Dr. Manuela Matta in Sassari, Italy, Drs. Serra and Leigh have shown that, when patients with INO due to MS make repetitive saccades for 10 minutes, the properties of their INO change, indicating fatigue and the brain's attempt to "repair" the slowed eye adduction. Thus, INO may provide a reductionist model, whereby potential treatments for fatigue in MS can be tested.

The genetic basis for hereditary ataxias has made great strides over the past decade. Because the contributions of the cerebellum are so well worked out, it is possible to offer hypotheses to account for the phenotypic features of each genetically defined disorder. Furthermore, researchers at the Daroff-Dell'Osso Laboratory have identified a new form of autosomal recessive ataxia with prominent saccadic intrusions.[17] Affected individuals have linkage to a gene on chromosome 1 corresponding to the protein kinesin that normally promotes transport of nutrients along axonal microtubules. These patients have a pronounced axonal neuropathy, saccadic hypermetria, and disruption of steady fixation by uncalled-for saccades. Delayed transmission in peripheral nerves accounts for delayed sensation, and we postulate that delayed transmission of saccadic signals in cerebellar cortical parallel fibers accounts for late arrival of a "stop" signal, so that the saccadic eye movement overshoots the target. Dr. Serra has also shown that the drug memantine suppresses saccadic intrusions, perhaps by restoring normal inhibitory governance by the cerebellar cortex of when to make a saccade.[13] Another group of hereditary ataxias is composed of ataxias arising from mutations of neuronal calcium channels. Dr. Stahl studies eye movements and cerebellar neuronal activity in mouse models of these human diseases, with a goal of identifying signaling abnormalities that might be corrected by drug therapy.[18]



Using Eye Movements as a Probe of Disorders of Balance

Studies of the vestibulo-ocular reflex have traditionally been used as a means to understand disorders that cause an imbalance from ear to brain.[1] The vestibular labyrinth senses both head rotations and linear movements (translations) but until recently, only responses to rotations about an earth-vertical axis have been possible. With the development of affordable devices, it is now possible to rotate subjects about any axis (Figure 2) and impose translations along three axes (Figure 3).[19] Because the head movements that occur during natural locomotion comprise multidirectional rotations and translations, such devices become pertinent to understanding disorders of imbalance in patients with a range of neurological and otological disorders. Thus, Drs. Walker and Leigh, in collaboration with Dr. David Riley, have studied vertical head translational movements (bob) in patients with two disorders that often lead to falls: progressive supranuclear palsy and cerebellar ataxia.[20,21] In both cases, abnormalities of the translational vestibulo-ocular reflex were demonstrated, providing insights into the underlying abnormality. The ability to rotate patients with nystagmus about any axis provides the opportunity to understand how misinterpretation of gravity signals by the otoliths of the inner ear contribute to the disorder. These studies are currently in progress.

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Figure 3: The Moog platform allows patients to be moved linearly (translated) or rotated in any direction (A). The patient is secured with belts and a helmet, and eye movements are measured using the magnetic search coil technique. The small cube mounted on the chair consists of three field coils. In a method used for precise measurement of horizontal, vertical, and torsional eye rotations, the patient wears a silastic annulus embedded with two coils of wire, one wound in the frontal plane (to sense horizontal and vertical movements) and the other wound in the sagittal plane (to sense torsional eye movements) (B). A silastic annulus is placed on the sclera of the eye after application of topical anesthesia. With the patient sitting in a magnetic field, voltages are induced in the search coils, which are used to measure eye position.

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(Treating Vision, Eye Movement, and Balance Disorders continued)

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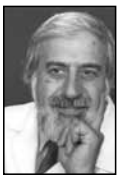

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The Ohio Brain Tumor Study:
Characterizing Tumors for Better Patient Prognosis

By
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Karl Kortepeter, MBA, MS, RD, LD
Andrew E. Sloan, MD, FACS

The Case Comprehensive Cancer Center of Case Western Reserve University has partnered with the Brain Tumor and Neuro-Oncology Center within the University Hospitals Neurological Institute, to embark on a new multicenter, Ohio-based research endeavor called the Ohio Brain Tumor Study. Through this study, we hope to convey vital predictive and prognostic information about brain tumors that could help guide novel targeted patient therapies, thereby improving overall survival and/or recurrence time for these patients. Dr. Barnholtz-Sloan of the Case Comprehensive Cancer Center is the study's principal investigator.

Brain tumors account for only 1-2% of all cancers in adults and, therefore, are considered rare. The overall incidence of brain tumors for benign and malignant tumors combined is 14.1 per 100,000 person years (6.8 for benign tumors and 7.3 for malignant tumors).[1] Though rare, brain tumors result in a disproportionate share of the cancer morbidity and mortality rates. The five-year survival rates for brain tumors are the sixth lowest among all types of cancer, following pancreas, liver, esophagus, lung, and stomach, respectively.[2]

Determining Risk Factors and Tumor Types

Aside from rare genetic syndromes, which account for <5% of all brain tumors, no risk factor accounting for the majority of brain tumors has been identified. The only widely accepted environmental risk factor for development of a brain tumor is ionizing radiation,[3-5] particularly for meningiomas and other benign brain tumors, though a multitude of other possible risk factors has been studied with inconsistent results.[6-8] The majority of primary brain tumors are sporadic and could be caused by a combination of genetic factors and environmental exposures.

The World Health Organization lists more than 125 histological types of brain tumors that correlate with grade of tumor.[9] Incidence, response to treatment, and survival after diagnosis vary greatly by histological type.[10] The most common benign tumor in adults is meningioma or pituitary tumor, and the most common malignant tumor is glioblastoma multiforme (GBM) or an astrocytoma grade IV. Most malignant tumors are gliomas and are most common in men. Meningiomas arise in the meninges and are more common in women.[6] Pituitary tumors become more common with age and, hence, are more common in adults than children and adolescents. One of the most significant factors for prognosis is histological type of tumor. For example, the five-year relative survival rate for benign tumors – specifically meningiomas – can be as high as 70%, while the rate for GBMs is about 3%.[10-12] Survival also varies by one's age at diagnosis, the degree of neurological compromise, and the extent of surgical resection.[13]

Brain tumors have a wide morphological spectrum, and no antibodies have been identified that could be used to unequivocally determine tumor types; therefore, inaccuracies in the assignment of histological type of tumor can easily occur. A patient's diagnosis is based on the most malignant part of the tumor; thus, an adequate volumetric sample of the tumor is needed.[14] However, brain tumors are highly heterogeneous. Because of tumor heterogeneity and the large number of histological types of brain tumors, an accurate histopathological diagnosis can be highly subjective and varies greatly from pathologist to pathologist.[15] The use of genetic and molecular markers may refine the current pathological diagnosis of brain tumors with sophisticated subclassifications that correlate better with tumor staging and patient prognosis in a less subjective manner.

Figure 1: Study sites of the OBTS. Locations are starred.

Despite cytogenetic and genetic findings in primary gliomas and benign brain tumors, classification of these tumors continues to be based almost entirely on conventional histological criteria. Further studies in molecular classification of these tumors with larger sample sizes would help to resolve a multitude of threshold issues of many brain tumor samples involving heterogeneity and tissue type. Because of the lack of identification of risk factors for brain tumors, the lack of accuracy of histopathological diagnosis, and the lack of understanding of differences between individuals and groups of people diagnosed with brain tumors, prevention and treatment decisions are difficult. Large prospective studies that incorporate investigation of all of these issues are needed.

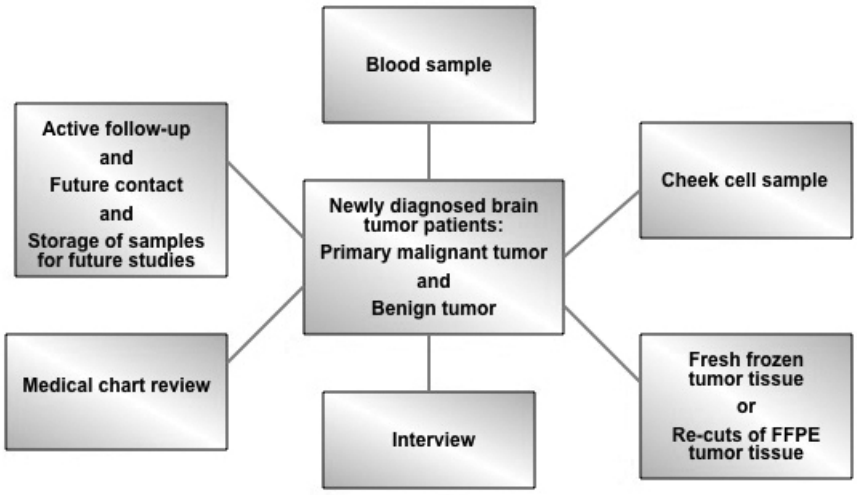

Figure 2: Approved components of IRB protocol for the OBTS.

Study Objectives

The purpose of the Ohio Brain Tumor Study (OBTS) is to objectively characterize subtypes of primary benign and malignant brain tumors using genomic and environmental exposure information and associate these with clinical outcome. To achieve this objective, we are:

- Prospectively enrolling newly diagnosed adult (18 years and older) primary benign and malignant brain tumor patients from multiple centers throughout the state of Ohio (Figure 1).
- Obtaining biological samples, environmental exposure data via an interview, and clinical data via a medical chart review for each patient consenting to the study.
- Investigating genomic patterns by the histological type of brain tumor.
- Correlating these genomic patterns with the clinical outcome stratified by the histological type of brain tumor.

The OBTS is directly aligned with the strategic plan of the Case Comprehensive Cancer Center and the Brain Tumor and Neuro-Oncology Center within the University Hospitals Neurological Institute to strengthen translational research of brain tumors.

Study Protocol

The current study protocol involves multiple steps to ensure that the appropriate patients are identified and approached for study, that biospecimens are obtained and handled in a systematic fashion, and that correlative demographic, treatment, clinical, pathological, and active follow-up information is systematically collected while maintaining the integrity of the study and respect for those participating in the study (Figure 2). Eligible patients are newly diagnosed with a primary malignant or benign brain tumor and have not had chemotherapy and/or radiotherapy prior to surgery. The steps in the protocol are as follows:

1. The principal investigator or institution-specific research nurse identifies eligible patients, approaches them about participation in the study, and obtains informed consent. The research nurse securely accesses the study database to enter all pertinent information on the consented patient, and the patient is assigned a unique study ID for future study purposes.

2. Each patient is asked to provide a blood sample and a saliva sample at the time of consent. Excess tumor tissue that is not required for diagnostic studies is placed into tubes and snap frozen within 15 minutes of surgical resection for future DNA/RNA extraction. All nucleic acid extraction from all biospecimens is centrally processed through Core facilities at the Case Comprehensive Cancer Center according to standardized protocols and is labeled with the unique study ID.

3. Each patient is asked to participate in a short interview regarding demographics, medical history, family history, medication history, tobacco use, and other environmental exposure history. To acquire accurate clinical treatment patterns and pathology information, each patient's medical chart is abstracted. Patients are asked for permission to contact them in the future (i.e., active follow-up) and for storage of their information and biological samples for future brain tumor research.

Sites of Active Brain Tumor Patient Recruitment

In September 2007, Dr. Barnholtz-Sloan received initial Institutional Review Board (IRB) approval to begin accruing OBTS patients at University Hospitals Case Medical Center. Much work has been accomplished to actively recruit patients for the OBTS at the Cleveland Clinic Foundation (CCF), Ohio State University (OSU), and Mayfield Clinic/University of Cincinnati Medical Center (Mayfield/UC). In the near future, we hope to expand recruitment to other key metropolitan areas in Ohio. Currently, 259 patients have been approached for the study and 230 have consented (89% participation rate). Of these 230 patients, 22 were deemed ineligible and 23 have their histopathology pending; therefore, the current working total for the OBTS is 185 patients (Figure 3).

Multidisciplinary Research Team

The assembled multidisciplinary team includes basic scientists, clinicians, and nurses caring for patients with brain tumors on a daily basis. The team at each site is essential to the success of the project. The clinicians and nurses not only help with patient recruitment but are instrumental in defining the relevant set of clinical and pathological variables for analyses and defining the treatment pattern categories based on medical chart review information. The clinicians and the scientists have invaluable input during the analytical portion of the study and can identify potential translational opportunities affecting brain tumor patients in general. All of the clinicians involved in the project have research interests in genomics and/or the prognosis of patients with brain tumors. The basic scientists bring the necessary statistical, epidemiological, and human genomics knowledge to the proposed project and provide invaluable input on study design, analysis, and interpretation of results.

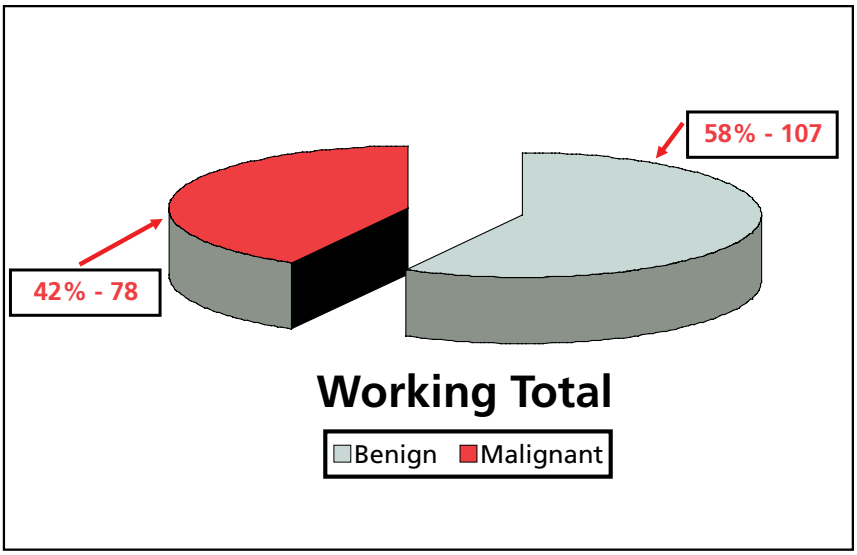

Figure 3: Distribution of recruited patients for the OBTS by histological type of tumor.

Significance of the OBTS

The OBTS is a novel study and significant for several reasons. Firstly, the identification of brain tumor patients with common "genomic" signatures associated with important clinical outcomes will inform unique molecular and prognostic groups supporting a personalized cancer treatment model. Secondly, genetic modifications are appealing therapeutic targets. Indeed, this study may lead us to identify preliminary candidate genes for further study as potential new brain tumor therapeutic targets. Thirdly, this study marks the first time that a group of investigators from several centers in Ohio has come together for a common research goal, creating a multidisciplinary brain tumor research collaborative and allowing for the necessary patient accrual with biological specimens and other important correlative information for meaningful research studies. Fourthly, the formation of a statewide brain tumor research collaborative is a necessary step enabling Ohio institutions to use novel agents or other genomics studies in initial therapeutic clinical trials. In addition, this study will establish a multicenter biorepository with correlative information from brain tumor patients that will be a tremendous resource for testing other scientific hypotheses in the future and would be available for use by other researchers in the field. Lastly, the type of multidisciplinary, cross-institutional, translational research involved in the OBTS is critical for the care of brain tumor patients and for the future of neuro-oncology.

In sum, the knowledge gained from the Ohio Brain Tumor Study has the potential to convey vital predictive and prognostic information and could guide novel targeted patient therapies, thereby improving overall survival and/or recurrence time for these patients.

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BRAIN TUMOR AND NEURO-ONCOLOGY CENTER

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Director

The Brain Tumor and Neuro-Oncology Center offers a world-class level of care, combining the experience, expertise, technical abilities and resources of recognized authorities in the field. The center offers highly individualized treatment plans for each patient. The Brain Tumor and Neuro-Oncology Center staff takes an aggressive, proactive approach to caring for patients. An expert panel of neurologists, neurosurgeons, medical oncologists, radiation oncologists, radiologists and brain tumor neuropathologists reviews each case and then collaborates to recommend a treatment plan. Daily interactions of this multidisciplinary team, combined with the most current treatment protocols, facilitate rapid response to individual therapeutic needs and allow appropriate medications to be made without delay.

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Petroclival Meningiomas:
Changing Management Paradigms

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Introduction

Petroclival meningiomas form a fascinating and challenging subset of extra-axial central nervous system tumors due to their unique nature of location, growth, and extension into multiple cranial fossae and foraminae that makes total surgical resection cumbersome and often impossible.[1-6] Like any other skull base meningioma, these lesions are engulfed or impinged upon by the juxtaposed neurovascular structures, and the right selection of surgical corridors requires an excellent understanding of the bony and neurovascular anatomy. This includes a careful study of the dural-based venous structures, which may dictate the choice of surgical approach. Atypical and malignant meningiomas in this location may demonstrate extensive infiltration along the dura mater and invasion of adjacent brain cortex or major veins, venous sinuses, or arteries, often rendering surgical resection incomplete. Tumors in the petroclival region become symptomatic due to compression or displacement of neurovascular structures and dural extension of the tumor into the tentorial notch, cavernous sinus, clivus, and cerebellopontine angle. Nomenclature regarding these lesions is often inconsistent and complex but generally reflects lesion location relative to the clivus, tentorium, and internal acoustic meatus (IAM). These complex lesions were initially considered inoperable, and early results showed high morbidity and mortality ranging from 8–39%.[1,3,6-16] Advances in microsurgical techniques, neuroanesthesia, preoperative neuroimaging, intensive care management, and intraoperative monitoring have contributed to significantly lower complication rates. Nevertheless, just as technological advances in the surgical arena have lowered rates of complication, so have other technological advances, particularly in the realm of stereotactic radiosurgery (SRS), tempered enthusiasm in some circles for aggressive complete resection. This article reviews the literature regarding these lesions and discusses possible treatment algorithms designed to provide for the best long-term outcomes at low rates of neurological morbidity.

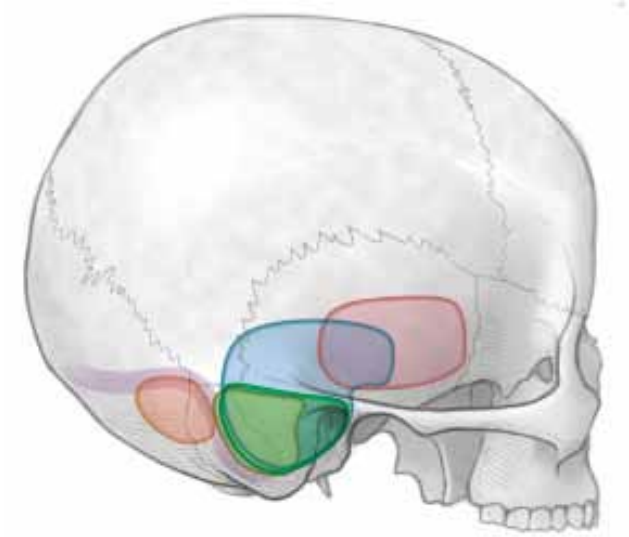
Natural History

Initially, the natural history of petroclival meningiomas was described by Cushing and Eisenhart[17] and later by Cherington and Shneck[18] as progressive and often fatal. However, in a recent series of 21 conservatively treated patients, Van Havenbergh and colleagues studied the demographic features, radiological changes, and functional changes in petroclival meningiomas. They conclude that tumor growth patterns are highly unpredictable and variable.[19] According to Olivero and colleagues, the studies on the natural history and growth rate of asymptomatic meningiomas, in general, showed approximately 35–60% of all intracranial meningiomas may spontaneously stop growing and remain dormant for varying lengths of time, though they do recommend frequent imaging follow-up.[20] It may be that tumors arising in the petroclival region represent a relatively homogeneous subset of meningiomas that have a slow growth and protracted course, indicating that the common goal of gross total resection in meningioma treatment may not be justified with all petroclival meningiomas.[21,22] Thus, it is important to recognize those petroclival lesions with favorable surgical features before planning a complex skull base approach for resection of these tumors. Little and colleagues have shown that intraoperatively defined tumor characteristics played a vital role in identifying those with a higher risk of postoperative deficits and argue that near total resection resulted in a greater reduction in morbidity than gross total resection, without increasing tumor recurrence rates.[12]

Table 1. Surgical Approaches in the Treatment of Petroclival Meningiomas

• Retromastoid suboccipital, with or without combined subtemporal, orbitozygomatic, or transcondylar approach
• Combined petrosal, with retrolabyrinthine, translabyrinthine, or transcochlear
• Frontotemporal transcavernous or pericavernous
• Anterior transpetrous (Kawase)
• Transmastoid translabyrinthine
• Preauricular and postauricular translabyrinthine, transotic, and transcochlear, with a total petrosectomy

1A



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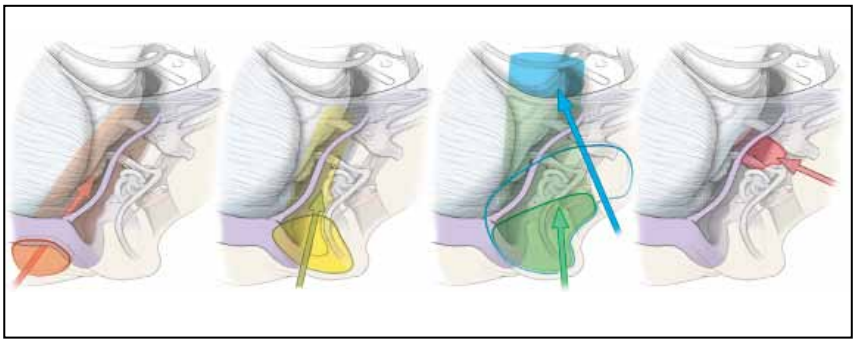

Figure 1: Schematic illustration of degree of bony resection for various approaches to the petroclival region (A) and degree of exposure afforded (B).

Surgical Treatment Risks, Outcomes, and Options

Surgical resection of petroclival meningiomas is potentially curative but often involves an integrated multidisciplinary approach of neurosurgeons, neurotologists, and interventional neuroradiologists working together. Successful resections of even large tumors with acceptable rates of morbidity and mortality have been reported in neurosurgical literature.[21,23] Numerous studies have described the different types of approaches available for accessing the skull base.[2,3,6,20,24-43] These reports usually include a wide variety of opinions about the precise and best indication for each approach, depending on the authors' unique experiences and biases. Overall, as previously noted, a major determinant of surgical outcome is the involvement of the tumor in question with surrounding neurovascular structures.

Many surgical series have reported outcomes and recurrence rates. Couldwell and colleagues reported a 13% recurrence rate with surgical management of petroclival meningiomas over a follow-up period of six years.[10] Samii and colleagues reported total removal of petroclival meningiomas in 71% of the cases in an initial series of 24 patients.[8] Hakuba and colleagues reported a series of six patients with operative mortality of 17%.[11] Yasargil and colleagues reported total resection in 35% of cases with a mortality rate of 15%.[44] Mayberg and Symon observed tumor progression after surgery in 23% of a total of 30 cases, over a follow-up period of 34 months.[7] Sekhar and colleagues noted that the cranial nerve involvement, prior treatment, and radiological features (tumor size, vessel encasement, and multiple fossa involvement) were the most significant factors that influenced postoperative clinical outcomes.[23] Because the resections are fraught with hazard of cranial nerve dysfunction, it is often argued that the quality of life is better with nonoperative management. However, some feel that the quality of life is much better with cranial neuropathies and symptoms such as diplopia than the morbidity of progressive tumor growth, repeated surgeries, and late-effects of radiotherapy.[45-47]

Between 1953 and 1980, Kallio and colleagues reported in a series of 935 patients the factors affecting the operative and excess long-term mortality after resection on intracranial meningiomas in the Department of Neurosurgery of the Helsinki University Hospital, Finland.[48] Patients were followed until death or the end of 1987. The cumulative observed survival rate was 91% at 3 months, 89% at 1 year, and 63% at 15 years. The relative survival rate (e.g., the ratio of the observed and expected rates) was 91% at 3 months, 89% at 1 year, and 78% at 15 years. Significant risk factors for operative mortality (7%) for the 652 patients operated on from 1966 to 1980 were poor preoperative clinical condition, absence of epilepsy, old age, incomplete tumor removal, pulmonary embolism, and intracranial hematoma requiring evacuation. For the 828 patients who survived the first postoperative year, the factors predicting an excess risk of death for up to 15 years

were incomplete tumor removal, poor preoperative and postoperative clinical condition, anaplasia of the tumor, and hyperostosis. Patients whose tumors were not completely removed had a 4.2-fold relative excess risk of death compared with patients whose tumors were completely removed, and patients who had malignant tumors had a 4.6-fold risk compared with those who had benign tumors.

There are multiple surgical approaches that are employed in resection of petroclival meningiomas (Table 1, Figure 1). The preoperative preparation must utilize relevant neuroimaging, which includes an initial CT scan or MR imaging to assess the lesion. CT scanning reveals the chronic effects of the growing tumor mass, such as bone erosion and remodeling, hyperostosis, and tumor calcification. MR imaging reveals the dural attachment of the lesion and typically demonstrates a tumor that is isointense with gray matter and prominent homogenous enhancement with contrast administration (> 95%) (Figure 2). In many cases, a vascular study is performed preoperatively to assess tumor, vascular encasement by tumor, and patency and dominance of dural venous sinuses. Preoperative embolization may be planned as well.[23,49,50]

The standard retrosigmoid (RS) approach is an effective and safe method of approaching the posterior fossa component of these lesions with minimal morbidity.[51,52] This approach is best used when the tumor is infratentorial, for debulking of mass in elderly patients with medical comorbidities, and as the first stage in combination approaches (Figure 3). Bricolo and colleagues emphasized this point in their use of the RS approach alone to treat 65% of 110 skull base tumors.[1] Of 28 cases treated by Goel and Muzumdar with the RS approach with a gross total resection rate of 75% in moderately sized (mean diameter of 4cm) petroclival tumors, five patients (18%) developed facial nerve deficits.[21] Advantages of the RS approach are a shorter operating time and a lower chance of cerebrospinal fluid (CSF) leak compared to other skull base approaches. Disadvantages include a narrow corridor with an inability to look across the clivus and an increased risk of fourth cranial nerve injury in patients with supratentorial extension of mass. The standard RS approach can be extended or modified with a suprameatal extension, as described by Seoane and colleagues, to suit surgical needs.[2]

A combined petrosal (CP) approach is indicated for medium and large tumors, with significant posterior fossa extension. The approach employs an anterior petrosectomy (to view posterior cavernous sinus and superior clivus) and a posterior petrosectomy (to access the petrous bone surface to the IAM), thus providing extensive supratentorial and infratentorial exposure, especially after opening the Meckel's cave and tentorial attachment. The advantages are that the seventh cranial nerve, cochlea, and labyrinth are intact. Disadvantages to this approach include

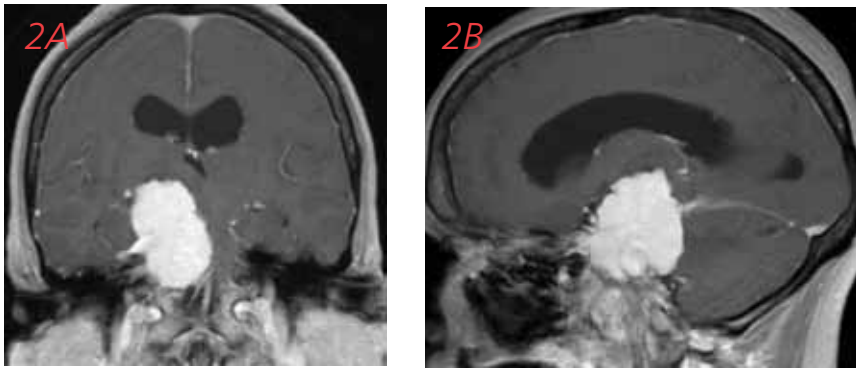

Figure 2: Large petroclival meningioma in coronal (A) and sagittal (B) views. The tumor enhances brightly on post-contrast T1 MR imaging and involves both the middle and posterior cranial fossae.

moderate risk of postoperative CSF leak and its labor-intensive nature. This approach offers cranial nerve morbidity similar to the standard RS approach. A case series by Mathiesen and colleagues reviewed 29 patients with petroclival meningiomas larger than 30mm who underwent transpetrosal approaches. The authors' data showed that Glasgow Outcome Scores improved in 14 patients, were unchanged in 11 patients, and worsened in four patients. The House-Brackmann Grade for facial nerve function was 3 or worse in six patients, including three individuals with transcochlear surgery and facial nerve rerouting.[53] In studies comparing working areas or angles of attack between the RS and CP approaches, results have been mixed. Siwanuwatn and colleagues discovered that, without the addition of a transcochlear exposure, there were no statistically significant benefits of the petrosal approaches over the RS exposure in a cadaveric study. This is likely explained by the dorsal axis of approach of the RS exposure along the plane of the petrous bone, which limits the extra exposure gained by a CP approach without a complete petrosectomy.[5,29] Similarly, in a recent cadaveric study, the quantitative assessment of the working areas and the angles of attack were studied with the amount of brain shift in an RS approach associated with inflating a balloon between the upper cranial nerves and upper clivus to mimic the effects of tumor compression. This simulation of a tumor mass in the posterior fossa and cerebellopontine angle significantly shifted neurovascular tissue and opened a surgical corridor toward the petroclival region.[13] In addition to the standard RS approach, the removal of the suprameatal tubercle has been utilized as a method by which increased exposure of the petroclival region may be gained.[2] The use of such maneuvers and the natural retraction created by tumors growing posteriorly may provide enough exposure through which adequate surgical access to the upper clivus may be obtained. Often, this may obviate the need for additional bony removal for achieving desired tumor resection.

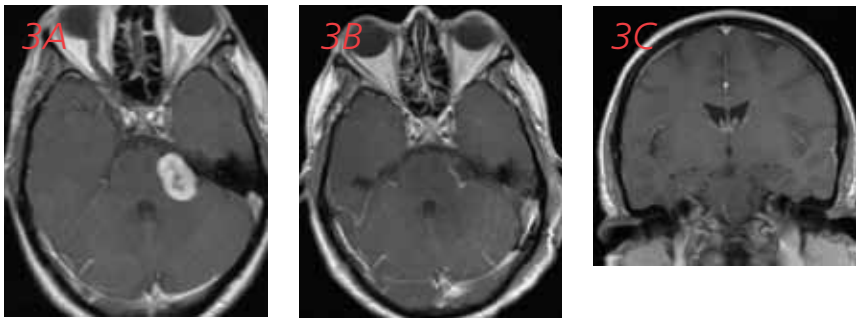

Figure 3: Medium-sized petroclival meningioma on axial view (A). This lesion was completely resected via the retrosigmoid approach without morbidity, shown on axial view (B) and coronal view (C).

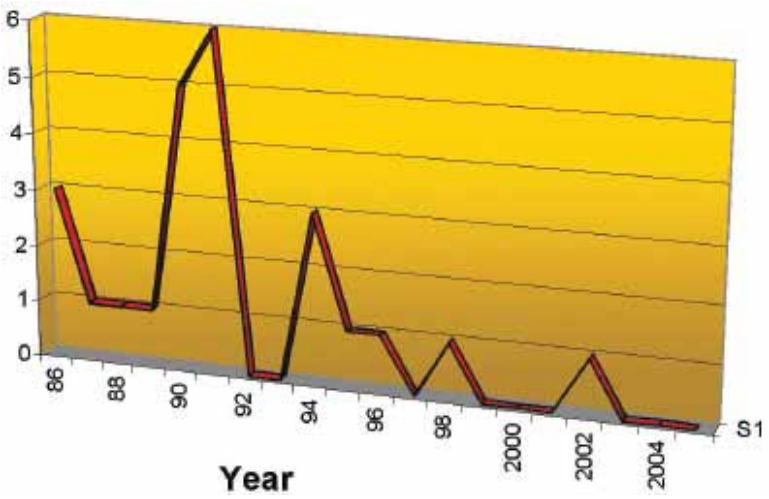

Figure 4: Graphic demonstration of combined petrosal and transcochlear procedures performed at our institution over the past 20 years in the treatment of petroclival meningiomas. A majority of these complex approaches were performed prior to 1996.[18] Image courtesy of Wolters Kluwer Health.

Erkmen and colleagues studied 97 patients with petroclival tumors and recommended an approach based on the location of the tumor along the clivus and in relation to the IAM.[54] In the treatment of 97 patients with petroclival tumors, they recommend the orbitozygomatic (OZ) approach for tumors located medial to the IAM, without extensive posterior fossa involvement, and a posterior transtentorial petrosal approach for those lateral to the IAM. The latter approach can be extended to the middle fossa and combined with an anterior petrosectomy when tumors extend into the middle cranial fossa and cavernous sinus. This variation is particularly preferable in patients with serviceable hearing. The transcochlear approach originally described by House and colleagues is reserved for use in patients with no serviceable preoperative hearing; it also involves transposition of the facial nerve for complete exposure of the lesion. Combination approaches would be indicated in lesions spanning middle and posterior fossa (for example, sphenopetroclival lesions) and to preserve seventh and eighth cranial nerve functions. Sen and colleagues described a subtemporal and preauricular infratemporal operative technique to the skull base through the anterior portion of the petrous temporal bone, used for the removal of predominantly extradural tumors in this region. The technique provided an extrapharyngeal route and exposure of the ventral aspect of the pons and medulla and related structures caudal to the trigeminal root. What is most useful about this approach is that it can easily be combined with an intradural subtemporal approach to provide additional exposure of the superior clivus rostral to the trigeminal root.[31]

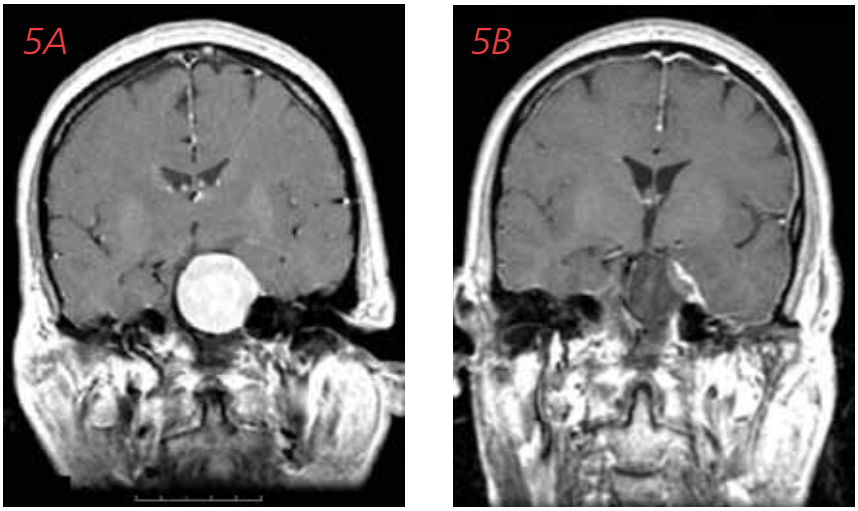

Figure 5: Coronal postcontrast MRI showing a large petroclival meningioma (A). A near complete resection was performed using a combined supratentorial and infratentorial approach via the orbitozygomatic and retrosigmoid craniotomies in a staged manner. Residual tumor (B) was treated with stereotactic radiosurgery.[72]

When reporting their results, many authors have emphasized the importance of preserving facial nerve and hearing function. Shen and colleagues described their experience with 71 meningiomas.[4] Of these, 94% were removed completely. Combined surgical approaches were used in 47% of the cases, but this proportion diminished substantially over the course of the study. This decrease coincided with an increasing priority to preserve hearing. Kaylie and colleagues[26] preserved hearing in eight of 10 patients who underwent a transcrusal approach to the petroclival region. The addition of a partial labyrinthectomy to a standard presigmoid petrosal approach has also been advocated, with the rate of hearing preservation reported to be higher than 80%.[27] A transmastoid translabyrinthine approach, pioneered by Morrison and King, is useful in elderly patients with unilateral hearing loss. The major advantages are a reduction in postoperative cerebellar retraction and swelling and early visualization of the seventh cranial nerve.[55] The approach is performed by drilling the mastoid and labyrinth, in addition to cutting the tentorium. Hakuba and colleagues modified this approach by adding a posterior fossa craniotomy in appropriate cases.[11,56] Hearing is sacrificed in translabyrinthine, transotic, and transcochlear approaches for large tumors crossing the midline.

Spetzler and colleagues used an aggressive combined approach to treat a variety of skull base tumors and vascular lesions,[5,6,29,52,57-59] but their management strategy changed significantly over time to an easier and more effective combined OZ-RS approach (Figure 4). In a retrospective analysis of 64 patients with petroclival tumors treated over 20 years, the use of CP approaches led to increased rates of gross total resection. This increase has been at the cost of higher complication rates and has led to a decrease in the use of CP approaches to limit patient morbidity. The tumor progression-free survival remained excellent for 45 patients; one of these patients developed tumor progression five years after surgery, and a second patient developed tumor progression 10 years after surgery. No patients developed tumor recurrence after gross total resection. The rate of progression-free survival in patients treated with either an RS or OZ approach was 96% at 36 months and 87% at 48 months. In cases in which supratentorial extension is significant, the use of the OZ craniotomy combined with an RS craniotomy is favored, and this method is found

Table 2. General Treatment Recommendations in the management of Petroclival Meningiomas

	SMALL (less than 3 cm in length in largest dimension)	MEDIUM (single cranial fossa)	LARGE (crosses two cranial fossae)
Symptomatic	Surgical excision *Consider SRS if patient is elderly or a surgical risk.*	Surgical excision *If GTR is not possible, follow with SRS for residual mass.*	Single-staged or two-staged surgical resection, with or without angiographic embolization *If GTR is not possible, follow with SRS for residual mass.*
Asymptomatic	SRS vs. serial follow-up, with imaging and clinical evaluation of prognostication factors, such as consistency, vascularity, cavernous sinus involvement, vessel encasement, cerebral edema, and invasive brainstem interface	Surgical excision *If GTR is not possible, follow with SRS for residual mass.*	Aggresive surgical debulking, with or without angiographic embolization, followed by radiosurgery or fractionated radiation therapy for residual tumor

* GTR: gross total resection
* SRS: stereotactic radiosurgery
* Residual petroclival meningioma: follow-up, with imaging or SRS
* Recurrent petroclival meningioma: follow-up, repeat surgery or SRS or fractionated radiation therapy (i.e., CyberKnife), depending on the prognostive factors

to be adequate in achieving an excellent resection, even of very large tumors (Figure 5). Today, with the option of SRS for backup growth control of small residual tumors, we are less aggressively pursuing gross total resection.

Al-Mefty and colleagues have used middle fossa anterior petrosal, posterior petrosal, and CP approaches and complete petrosectomy for resection of petroclival tumors, in addition to popularizing a modified retrolabyrinthine approach for these lesions.[34,60,61] Sekhar and colleagues have published extensively on petroclival meningiomas, proposing a partial labyrinthectomy and petrous apicectomy approach to treat 25 petroclival meningioma patients during a two-year period. Postoperatively, cranial nerve deficits involving cranial nerves III, IV, V, and VI occurred in 17 patients (47%), and CSF leak occurred in 12 patients (33%), four of which required only lumbar drainage.[38] Recently, Natarajan published a larger series for a 13-year period (1991–2004), using various approaches in 207 operative procedures for resection of petroclival meningiomas in 150 patients. The tumor size was large in 79% of the patients, with a mean tumor diameter of 3.44cm. One hundred patients (66%) had a single operation, 43 patients (29%) had two operations, and seven patients (5%) had three operations. Gross tumor resection was accomplished in 48 patients (32%), subtotal resection in 65 patients (43%), and partial resection in 37 patients (25%). The recurrence-free survival rate was 100% at three years, 92.7% at seven years, and 85% at 12 years; the progression-free survival rate was 96% at three years, 86.8% at seven years, and 79.5% at 12 years.[16] The complication rate gets better with increased years of surgical experience and appropriate selection of surgical approaches.

Stereotactic Radiosurgery

The technique of SRS has been increasingly used in the treatment of petroclival meningiomas.[13,22,62-69] Small tumor volumes are controlled better using this method, with a lower dose of radiation delivered to adjacent neurovascular structures.[58,62,66,68,70] Good control of larger lesions has been reported in neurosurgical and radiation oncology literature, though the patient numbers in such reports are small.[63] In one of the largest reviews, Iwai and colleagues noted in a series of 108 patients with cranial base meningiomas, treated using low-dose Gamma Knife radiosurgery, that the tumor volume decreased in 50 patients (46%), remained stable in 51 patients (47%), and increased (local failure) in seven patients (6%). In a follow-up of seven years, Iwai reported increased incidences of local failure, marginal failure, and malignant transformation.[71] Zachenhofer and colleagues[67] demonstrated a tumor growth control rate of 94% in 36 patients with a mean follow-up of 103 months in patients treated with the Gamma-Knife, while Subach and colleagues[22] described tumor control rates of 91% over 37 months in 62 patients (as primary treatment in 23 patients) with an incidence of cranial nerve deficit of 8%. In that study, tumor control rates were reported to be 100% tumor control with a follow-up period of 38 months. Other studies have confirmed these results, indicating that stereotactic radiosurgery is effective in reducing long-term tumor volume growth in small primary or residual lesions.

Conclusions

Petroclival meningiomas remain challenging lesions that are very difficult to treat adequately. We believe that the exact surgical approach chosen by the treatment team is less important than the familiarity of the team with that particular approach and the exposure provided. Tumor characteristics, such as the presence of a clear arachnoid plane and envelopment of neurovascular structures, are major determinants of the ability to achieve a safe resection, independent of the skills and experience of the treating surgeon.

The most consistent prognosticators to achieve excellent resection associated with low morbidity in petroclival meningiomas are (a) soft nonfibrous tumor consistency, (b) nonvascularity of tumor, (c) lack of cavernous sinus or brainstem invasion, (d) absence of encasement of internal carotid artery, (e) absent previous surgery or radiation therapy, and (f) absent peritumoral edema of the brain. Older age, preoperative lower cranial nerve involvement, and significant basilar artery blood supply are considered poor prognosticators in surgical management of these lesions. The ability to provide stereotactic radiation therapy to small portions of residual tumor with good short-term to medium-term control rates have affected our desire to achieve a gross total resection at the cost of increased patient morbidity. We have, therefore, modified our treatment algorithm when addressing these lesions appropriately (Table 2). Future studies investigating long-term rates of tumor control with SRS therapy, tumor biology as a predictor of recurrence, and preoperative imaging as a predictor of intraoperative consistency are important avenues actively pursued at the UH Neurological Institute.

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CEREBROVASCULAR AND SKULL BASE SURGERY PROGRAM

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Director

The Cerebrovascular and Skull Base Surgery Program provides a multidisciplinary team of specially trained and experienced surgeons to treat cerebrovascular and skull base disorders using minimally invasive, image-guided and radiosurgical techniques. Specialists from neurosurgery, radiology, otolaryngology, ophthalmology, radiology, endocrinology, neurology, oncology and radiation therapy have joined together to provide comprehensive care for complex clinical conditions, such as meningiomas, arteriovenous malformations, pituitary tumors and acoustic neuromas. The skull base surgery team meets regularly to review new cases and determine the appropriate course of treatment for every patient. Each new case is discussed by members of the team, and care is tailored to the needs of the individual patient. Clinical and basic science research efforts are underway to advance the understanding of the cause, prevention, detection and treatment of these diseases and disorders.

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Transforming the Culture of Health Care:
A Focus on Patient- and Family-Centered Care

By
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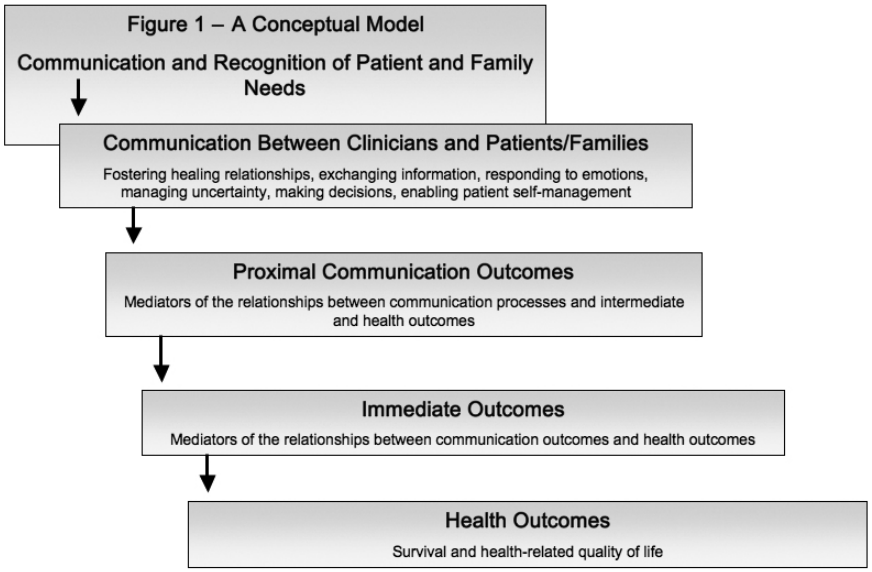
Patient- and family-centered care is an approach to the planning, collaboration, communication, and engagement of health care – key elements critical to patient outcomes, safety, and quality. Core elements of patient- and family-centered care include the following:

- People are treated with respect and dignity.
- Health care providers communicate and share information with patients and families in ways that are affirming and useful.
- Individuals and families build on their strengths through participation in experiences that enhance control and independence.
- Collaboration occurs in professional education, policy, and program development as well as delivery of care.

Founded as a nonprofit organization in 1992, the Institute of Family Centered Care (Institute) promotes leadership in advancing the evidence-based patient- and family-centered care across care settings, serving individuals of all ages and their families.[1]

In the early 1990s, the Institute's work focused primarily on family-centered approaches to pediatric care. However, within this framework, it was recommended that as a patient matured and became a young adult, he or she should be encouraged to become more involved as a decision-maker in his or her health care. As the Institute became involved in adult and geriatric care, it was important to acknowledge the patient's role more explicitly, hence patient- and family-centered care. The Institute of Family Centered Care hosted the Leadership Summit in 2006 to advance patient- and family-centered care. A broader definition emerged:



"Patient- and family-centered care places an emphasis on collaboration with patients and families of all ages, at all levels of care, and in all health care settings. Families, however they are defined, are essential to patients' health and well-being. Families are crucial allies for quality and safety within the health care system. A patient- and family-centered approach recognizes that the very young, the very old, and those with chronic conditions – the individuals most dependent on hospital care and the broader health care system – are also the most dependent on families."[1]

Physician and Patient Communication – A Conceptual Model

The National Cancer Institute notes the effects of communication with health outcomes and provides a conceptual model outlining patient and family needs (Figures 1 and 2).[2] Physician communication as well as patient and family outcomes occur throughout the continuum of cancer care: treatment, survivorship, and end of life.[2]

Perspectives Shared – Physician, Patients, and Family

William Schwab, MD, Professor and Vice Chair in the Department of Family Medicine at the University of Wisconsin, describes patient and family preferences. "What patients and families want to know from clinicians [is] 'what is the problem, and how can it be diagnosed and treated?' […] Family-centered care is not just 'being nice.' It is a direct and intentional effort to unequivocally communicate to patients that they are viewed as distinct and valuable individuals with a family and a place in the community.'"[3]

The patient and family may ask pertinent questions, including how they can contribute to the process of treatment to enhance quality and safety and when/where/how they will communicate with the physician and each other.

(Transforming the Culture of Health Care continued)

Generous philanthropic support through the annual 2009 Karen Scherr lectureship afforded an educational opportunity to provide patient- and family-centered care content to physicians and clinical staff.[3] Patient and family members shared stories describing their experience of care. Attributes consistent with
UH Ireland Cancer Center's values were spoken from the patient's and family member's perspective:

- Providing a family atmosphere
- Recognition that the more information we received, the less stress we felt
- Active listening
- Sharing in the uncertainty of cancer elicits trust
- Welcoming both patient and family as active participants of care

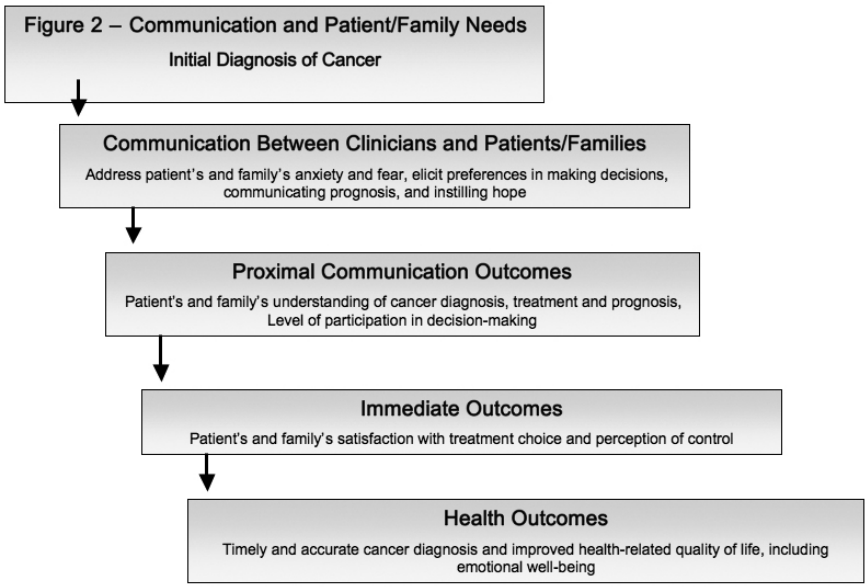
As patients and families shared their thoughts, themes emerged:

- Coordination of care is paramount in understanding what to expect, how to communicate, and with whom to communicate from one care setting to another.
- Patients and family members value choices offered, especially as the choices relate to conveying news about lab and radiology results.
- Our physician and care team have opportunities to set the tone with questions that engage the patient and family: "What questions do you have?" or "Let's review what we have covered."

Most importantly, patients and families explained that they want physicians and the team to instill hope and to have a plan.

The National Push for Patient- and Family-Centered Care

The Joint Commission's 2007 national patient safety goals declared the involvement of patients and families in identifying safety risks as crucial to health care institutions. Specifically, Goal 13 states, "Encourage patients' active involvement in their own care as a patient safety strategy." Health care institutions are required to identify ways in which the patient and/or family can report concerns about safety. In August 2008, Massachusetts' Governor Deval Patrick signed into law Chapter 305 of an Act to Promote Cost Containment, Transparency, and Efficiency in the Delivery of Quality Health Care. The law includes the establishment of patient and family councils at hospitals, thus involving patients and family members in improving the quality of care, and the establishment of rapid response methods at hospitals, allowing medical staff and patients and family members to request immediate assistance when a patient is deteriorating.



The Benefits of Patient- and Family-Centered Care

The Dana-Farber Cancer Institute has had Patient and Family Advisory Councils for both adult and pediatric oncology programs for the past 10 years, strengthening communication among patients, family members, caregivers, and staff. These advisors have helped shape efforts to improve patient safety. Patients and their families recommended a teamwork safety campaign, "You CAN," urging patients and families to Check, Ask, and Notify. While safety is the responsibility of Dana-Farber staff and faculty, patients and families CAN help ensure safe care.

The Medical College of Georgia (MCG) began its partnership with patients and families in 1993. Since that time, more than 150 patient and family advisors sit on seven councils and 45 hospital-wide committees and task forces, including the Patient Safety and Medicine Reconciliation Committees. The result of this partnership has been a marked decrease in claims and litigations at the MCG (Figure 3). The Neuroscience Center for Excellence at the MCG reported the following results in quality improvement data measured over a three-year period:

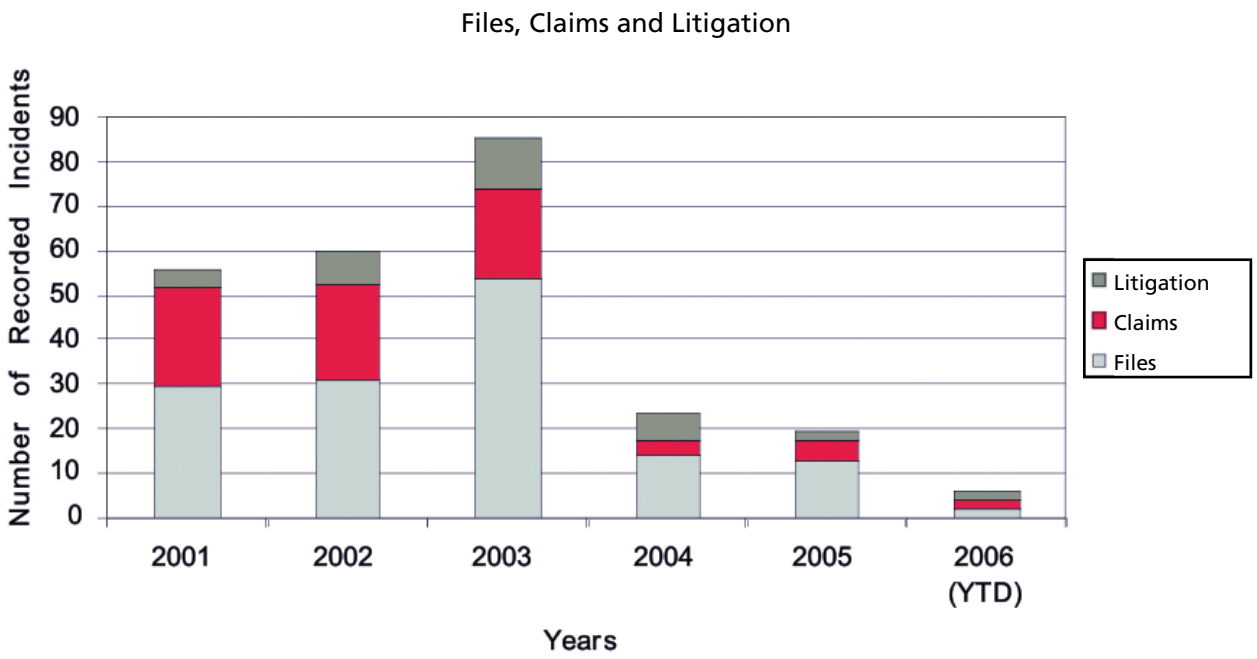
- Patient satisfaction increased from 10th to 95th percentile.
- Neurosurgical length of stay decreased 50%.
- Medical errors were reduced by 62%.
- Volume increased 15.5%.
- Staff vacancy rate decreased from 7.5% to 0% with a waiting list of five RNs.[4]

These promising results are attributed to the participation of patients and families in quality, safety, and satisfaction initiatives.

The MCG is among the top three most cost-efficient hospitals in the University Healthcare Consortium (UHC) database. Patient and family faculty teach medical students and residents and are involved with Human Resources, participating in recruitment, selection, evaluation, and recognition of staff.

Figure 3

MCG: Favorable Trends in Claims and Litigation



Source: MCG Health System prepared for the University Health System Consortium (UHC), 2007; Partnership with Patients & Families, 2008

In Summary

Patricia Sodomka, Senior Vice President of Patient and Family Centered Care at MCG Health Inc., explains the concept in these words: "Patient- and family-centered care is much more than a nice gesture. It can have a considerable impact on bottom-line issues. This model of care provides a framework and strategies for achieving your quality and safety goals, enhancing market share, lowering costs, and strengthening staff satisfaction."[5]

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CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF MEDICINE

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This continuing medical education (CME) program is provided by Case Western Reserve University School of Medicine and is intended for all physicians, particularly family practice and internal medicine physicians, neurologists and neurological surgeons interested in the latest advances in the management of neurological disorders.

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Upon completion of this educational activity, the participant should be able to:

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- Identify the recent advances in neuro-ophthalmology.
- Explain the role of the Ohio Brain Tumor Study in developing better patient prognosis.
- Discuss the changing management techniques and approaches for the treatment of petroclival meningiomas.
- Describe the key elements and benefits of patient- and family-centered care.

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