

Gamma Knife plan for treatment of trigeminal neuralgia

Surgical Options for Treating Facial Pain

Facial pain comprises a group of complex and often poorly understood disorders that are severely debilitating and often refractory to medical therapy. The source of the pain can vary depending on the syndrome, but symptoms are often similar, making correct diagnoses for facial pain especially challenging. Professor of Neurological Surgery, Nicholas Barbaro MD, is an expert in treating severe facial pain, including trigeminal neuralgia and other neuropathic facial pain syndromes. “Occasionally patients are misdiagnosed,” says Barbaro. “Some physicians group all facial pain under the umbrella of trigeminal neuralgia, but trigeminal neuralgia is a specific condition that has highly effective and specific treatments.” Some treatments that are effective for trigeminal neuralgia can actually worsen trigeminal neuropathic pain. The Department of Neurological Surgery treats patients from all over the Western United States, and Barbaro and his team review records and, if necessary, conduct telephone interviews to determine if patients can be helped before they travel to San Francisco for treatment.

Trigeminal Neuralgia

The first line of treatment for patients with trigeminal neuralgia is always medication. The drugs most commonly used for treating trigeminal neuralgia are medications that were originally developed for the treatment of epilepsy. However, carbamazepine and other drugs prescribed for trigeminal neuralgia do not always remain effective over time, requiring higher and higher doses or a greater number of medications taken concurrently, and some patients experience side effects serious enough to warrant discontinuation. These patients may be candidates for surgical pain intervention. UCSF offers multimodality surgical treatments chosen for the needs of each patient.

Microvascular Decompression

Microvascular decompression (MVD), also known as the Janetta procedure, is the most common surgical procedure for the treatment of trigeminal neuralgia. In most cases, there is a blood vessel (typically an artery, but sometimes a vein) compressing the trigeminal nerve. By moving this blood vessel away from the nerve and interposing a padding made of Teflon felt, the pain

is nearly always relieved. While MVD is considered to be the most invasive surgery for trigeminal neuralgia, it is also the best procedure for correcting the underlying problem that usually causes trigeminal neuralgia: vascular compression. MVD also causes the least damage to the trigeminal nerve and provides, on average, the longest pain-free periods and the best chance for a patient to be permanently off medication. MVD has a long-term success rate of approximately 80% as a stand-alone treatment. The procedure requires an average hospital stay of two to three days, and four to six weeks to return to normal daily activities.

Gamma Knife® Radiosurgery

Radiosurgical treatment for trigeminal neuralgia is the least invasive surgical option. The Gamma Knife is a device that delivers precise, controlled beams of radiation to targets inside the skull, including the brain or associated nerves. For trigeminal neuralgia treatment, the radiation beams are aimed at the trigeminal nerve where it enters the brainstem. Gamma Knife treatment does not target the root cause of trigeminal neuralgia, but instead damages the trigeminal nerve in a controlled way to stop the transmission of pain signals. The procedure requires little or no anesthesia, and is performed on an outpatient basis. This procedure provides significant pain control or reduction in approximately 80% of patients, but response is usually slower than for other

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Branch of superior cerebellar artery compressing the trigeminal nerve in a patient with trigeminal neuralgia



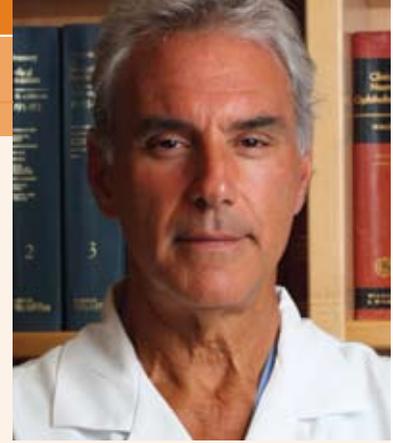
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Pain is one of the most universal experiences and a condition that all of us as medical professionals come up against, regardless of our specialty. While many types of pain can be managed with medications, debilitating pain refractory to medical treatment can be complex and especially difficult to diagnose and treat. Many patients will need life-long care by a multidisciplinary group able to offer ongoing therapies, ranging from psychological to surgical. The relevance of neurological surgery in pain management is inherent in the way transmission of pain signals occur through the central nervous system. Through the development of specialized surgical procedures, from intrathecal opiate pumps to spinal cord stimulators, neurosurgeons have long played a major role in delivering pain control.

At UCSF, the history of breakthroughs in pain treatment began in 1958 with John Adams MD, then chair of the Department of Neurological Surgery, who used hypophysectomy to treat pain resulting from metastatic breast cancer and prostate cancer. In 1971, another chair, Charles Wilson MD, also found that hypophysectomy gave significant relief of pain to two thirds of patients with metastatic breast cancer. Other types of surgeries for intractable pain performed during the 1960s and 1970s included thalamotomy and radiofrequency electrode implantation, and research explored stimulating the brain's own endorphin-mediated analgesia system, which modulates pain and can be activated by external manipulations. In July 1969, Yoshio Hosobuchi from the University of Chicago joined the faculty, starting a program for the

treatment of chronic pain that included percutaneous cordotomy, medullary tractotomy, dorsal-column stimulation, and thalamic and internal-capsule stimulation for thalamic and paraplegia pain. By 1978, percutaneous dorsal-column stimulation was largely abandoned as ineffective in 70% of cases, and deep brain stimulation was used for relieving thalamic pain, anesthesia dolorosa, and intractable low back pain.

Deep brain stimulation continues to be explored as a treatment for pain, and investigators at UCSF, led by Philip Starr MD, PhD, have published one of four open-label series of deep brain stimulation for cluster headache – the most severe form of primary headache, in which 10 to 20% of cases are unresponsive to medical therapy. The results of these four series indicate that 50 to 70% of patients experience substantial relief of their headache symptoms one to four years following surgery. While cluster headache is not yet an approved indication for deep brain stimulation, the initial results are promising and warrant further investigation in controlled clinical trials. As many, but not all, patients with cluster headaches respond to deep brain stimulation, it will also be important to develop a method to prospectively identify those patients most likely to benefit. It has also recently been found that occipital nerve stimulation provides results similar to deep brain stimulation, and our functional neurosurgery group currently suggests offering this approach prior to treatment with deep brain stimulation.

Although neurosurgeons have an important role in pain management, fewer neurosurgical residents are entering this subspecialty.

Our colleagues in the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Pain have expressed concern over the waning interest in pain medicine due to lower level reimbursements and the difficulty in managing this patient population. But it is important to note that this can also be one of the most rewarding patient populations; one in which it is possible to dramatically improve quality of life and relieve suffering. At the Department of Neurological Surgery, our faculty work with a variety of other pain specialists at the UCSF Pain Management Center to design a therapeutic course for pain control that is tailored to each case. It is our mission to ensure that no patient lives with uncontrolled pain.

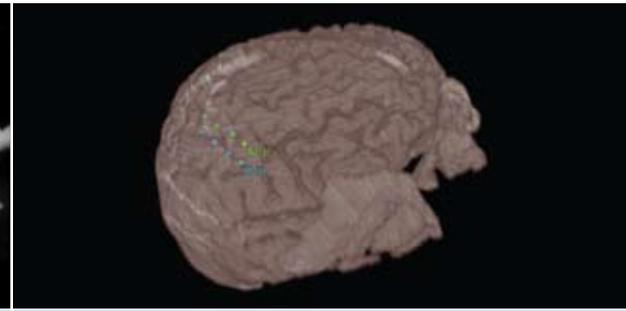
Mitchel S. Berger MD,
Kathleen M. Plant
Distinguished Professor & Chairman

Director, Brain Tumor
Research Center

Department of
Neurological Surgery, UCSF



Fluoroscopic image of radiofrequency needle inserted into the trigeminal cistern



Frameless stereotactic magnetic resonance image with superimposed position of motor cortex stimulation electrodes

Surgical Options for Treating Facial Pain

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treatments. Patients usually respond within four to six weeks following treatment; however, some patients require as long as three to eight months for the full response. Most patients remain on full doses of medication for at least three months after treatment.

Radiofrequency Lesion

Radiofrequency lesion (RFL) is a good option for treating severe pain in high-risk patients, such as those with concurrent illness that would make an open surgical procedure too dangerous. It is also a good option for patients with multiple sclerosis, whose trigeminal neuralgia is often not caused by vascular compression. Like Gamma Knife treatment, RFL damages the trigeminal nerve to stop the transmission of pain signals. In RFL an electrode inserted through the cheek is used to heat the nerve and cause selective damage to stop pain signals from traveling to the brain. The treatment provides immediate pain relief in up to 90% of patients, but can cause more facial numbness than the other procedures and has a pain recurrence rate of 40% at two to three years after surgery. If necessary, the procedure can be repeated.

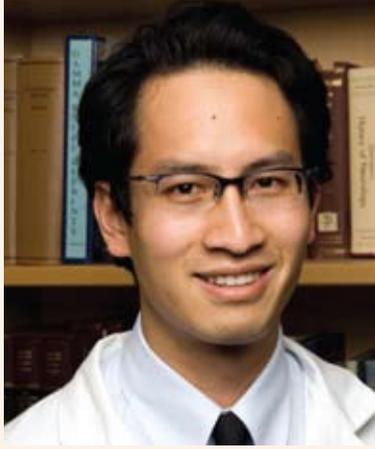
Neuropathic Facial Pain

Non-trigeminal neuralgia neuropathic facial pain may be caused by trigeminal nerve injuries occurring during dental procedures or following trauma to the skull or face, or it may be idiopathic. A variety of medications may be used, and some patients may respond sufficiently to avoid invasive procedures. In many cases, the injured nerves will heal over time, although this may take several years. Patients with facial pain that is not sufficiently reduced by medications may be candidates for treatment with motor cortex stimulation, which uses an electrode placed over the face motor cortex through a small craniotomy.

Motor cortex stimulation works in a way similar to spinal cord stimulation, which uses electrodes placed onto the lower spine to stimulate nerve fibers and block the transmission of pain signals resulting in back or leg pain. The original testing was to be done over the sensory cortex to see if the same result could be obtained. However, the investigators discovered that stimulation of the electrodes over the motor cortex was more effective at reducing

neuropathic pain. More widespread use of motor cortex stimulation began in the early 1990s after a series of clinical experiments by Tsubokawa et al. demonstrated its long-term efficacy in controlling pain.

In motor cortex stimulation surgery for neuropathic facial pain, the electrode's power source is kept externally for up to three days and is hooked up to a pulse generator. There is a 50 to 70% success rate with this procedure. If the trial electrode is successful, the pulse generator is implanted under the patient's skin to provide long-term pain relief. Improvements in frameless stereotactic navigation techniques ensure that the electrode is placed very accurately under general anesthesia with a relatively small craniotomy. Although the scientific basis for pain relief with motor cortex stimulation is not well understood, the results represent a remarkable advance in treatment for specific types of facial pain that are not helped by other modalities.



selected publications

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Edward Chang MD is currently chief resident of neurological surgery. He received his undergraduate degree from Amherst College in Massachusetts, and attended medical school at UCSF where he graduated with AOA honors. In 2001, he was awarded a Howard Hughes Medical Institute fellowship.

As a neurosurgical resident, with Nicholas Barbaro MD, Chang characterized the predictors of seizure remission after stereotactic radiosurgery for epilepsy, and examined the outcomes of resective surgery for epilepsy from tumors and cortical malformations. With Philip Starr MD, PhD, he detailed the functional somatotopic organization of the human globus pallidus internus in patients with dystonia. With Mitchel Berger MD, Chang documented the long-term survival benefits of intraoperative stimulation mapping and extent of resection for low-grade gliomas. With Michael McDermott MD, he devised a powerful prognostic scoring system for low-grade gliomas, and later validated it in a multi-institutional collaborative cohort. With Michael Lawton MD, Chang reported seizure control

outcomes and also microsurgical approaches to eloquent and deep cavernous malformations.

Chang's principal research goals are to understand the basic cortical mechanisms underlying speech perception and production. In 2008, he began a postdoctoral research fellowship with Robert Knight MD at the Helen Wills Neuroscience Institute at UC Berkeley. With support from a NIH National Research Service Award fellowship, he used electrocorticography to study the emergent representation of categorical speech perception in the human superior temporal gyrus. Chang was awarded the Wilder Penfield Fellowship from the Congress of Neurological Surgeons to develop a novel method of mapping brain dynamics using electrocorticography.

Chang intends to pursue a career in functional and epilepsy neurosurgery. His long-term research priorities are to discover the neurophysiologic substrates of higher brain function in humans, to elucidate their abnormalities in cognitive and motor disorders, and to develop novel restorative strategies towards their remediation.

residents' publications

Bloch OG, Jian BJ, Yang I, Han SJ, Aranda D, Ahn BJ, Parsa AT. A systematic review of intracranial chondrosarcoma and survival [published online ahead of print September 29, 2009]. *J Clin Neurosci*. doi:10.1016/j.jocn.2009.05.003.

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Clark AJ, Lee K, Broadus WC, Martin MJ, Ghatak NR, Grossman CE, Baker S Jr, Baykal A. Primary brain T-cell lymphoma of the lymphoblastic type presenting as altered mental status [published online ahead of print July 4, 2009]. *Acta Neurochir (Wien)*. doi: 10.1007/s00701-009-0433-z.

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Potts MB, Adwanikar H, Noble-Haesuslein LJ. Models of traumatic cerebellar injury. *Cerebellum* 2009;8(3):211-221.

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Vincent Wang MD, PhD was born in the United Kingdom and was raised in Hong Kong. He moved to Houston, TX when he was thirteen years old and subsequently attended the University of Houston, where he studied Biology. After working as a research assistant at M.D. Anderson Cancer Center, he entered the MD/PhD program at Baylor College of Medicine in 1996. At Baylor, Wang joined the Pediatrics laboratory of Huda Zoghbi MD and studied mouse cerebellar development. He was supported by an individual National Research Service Award from the NIH. At Baylor, he also worked with Claudia Robertson MD and developed an interest in traumatic brain injury and neurocritical care.

Wang started his neurological surgery residency in 2005 at UCSF. He joined the laboratory of Geoffrey Manley MD, PhD and studied the function of aquaporin 4 in the control of water efflux in mice during a hyperosmotic state. Through this project, he developed an interest in the cellular adaptive response to a hypertonic condition. He plans to continue studying this area in the future.



In addition to his clinical interest in neurosurgery, Wang has also developed an interest in the socio-economic issues in healthcare. He has recently been selected as a resident fellow of the Council State of Neurological Surgery and will participate in organized neurosurgery committees to address various socio-economic issues in neurosurgery. He is also a member of the UCSF Medical Center's Utilization Management Committee. In addition to clinical practice, Wang is also interested in using his experience in a hospital administration role in the future.

selected publications

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Chou D, Lu D, Chi J, Wang V. Rib-head osteotomies for posterior placement of expandable cages in the treatment of metastatic thoracic spine tumors. *J Clin Neurosci* 2008;15(9):1043-7.



Nicholas M. Barbaro MD, professor of neurological surgery, has extensive expertise in the treatment of disorders that are manageable by stereotactic and functional neurosurgical techniques, including epilepsy and

chronic intractable pain syndromes. He is co-director of the Functional Neurosurgery Program and is recognized internationally for his work in epilepsy surgery. Barbaro also has a special interest in surgical management of trigeminal neuralgia, which may offer relief for many patients who are not helped by medical therapy. He is director

of the UCSF Nerve Injury Clinic, a multidisciplinary clinic where patients with various types of injuries to peripheral nerves are evaluated for possible surgical treatment. As a member of the Neurospinal Disorders Program, Barbaro performs surgery for adult Chiari malformations and for pain resulting from compression syndromes, such as thoracic outlet and piriformis syndrome (extraspinal sciatica), previous trauma, tumor, infection, or inflammation.

Barbaro also serves as the Neurological Surgery Residency Program Director and has received several teaching awards for his dedication in training future academic neurosurgeons. He has lectured widely about epilepsy, movement disorders, surgical management of pain, and surgical management of peripheral nerve disorders throughout the United States and in Canada and Europe.

selected publications

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Brown JA, Barbaro NM. Motor cortex stimulation for central and neuropathic pain: current status [review]. *Pain* 2003;104(3):431-5.

Manish Aghi MD, PhD, assistant professor of neurological surgery, has been awarded an American Brain Tumor Association Young Investigator Award and a Translational Research Grant for the project “Understanding distinct mechanisms of response to anti-angiogenic therapy in glioblastoma”; an NIH/NINDS Independent Scientist Award (K02) for the project “Characterizing and targeting tumoral factors recruiting perivascular progenitors”; and an American Cancer Society Research Scholar Grant for the project “Defining and targeting mechanisms of Avastin resistance in glioblastoma.”

Mitchel S. Berger MD, Kathleen M. Plant distinguished professor and chair of neurological surgery, delivered a keynote address on low-grade gliomas at the 2009 meeting of the World Federation of Neurosurgical Societies, held in Boston, Massachusetts.

Krystof Bankiewicz MD, PhD, professor of neurological surgery and Kinetics Foundation chair in translational research, **John Forsayeth PhD**, adjunct professor of neurological surgery, and their colleagues have recently published a landmark article in *Neuroimage* on optimizing cannula placement for infusions into the primate putamen. Their image-guided system allows real-time visualization of infusions into the brain, which enables neurosurgeons to carefully monitor infusions of therapeutic agents and, if necessary, alter the parameters or terminate the infusion.

The Bankiewicz laboratory has also received a \$6 million grant from the NIH as part of a consortium of leading investigators to develop a new model of Parkinson’s disease in monkeys. The work will deliver a virus encoding a mutant kinase, LRRK2, which is a common cause of familial Parkinson’s disease, in order to precipitate the disease. A small-molecule inhibitor of the LRRK2 will then be delivered to test its effectiveness in blocking

the appearance of the disease. The goal of this work is to pave the way for clinical testing of the inhibitor and to develop a new model of Parkinson’s disease that is not based on neurotoxins.

Edward Chang MD, chief resident in the Department of Neurological Surgery, has been awarded a K99/R00 Pathway to Independence Award by the National Institute of Neurological Disorders and Stroke. This highly competitive funding mechanism awards the most promising researchers with up to five years of substantial early career NIH support. His research seeks to reveal the cortical circuitry underlying higher cognitive behavior in humans, including language and decision making.

John R. Fike PhD, professor of neurological surgery, recently collaborated with a group of investigators at UC Irvine to transplant stem cells into the brains of rats that had undergone radiation treatment. The study found that transplanted stem cells restored learning and memory to normal levels four months after radiotherapy. In contrast, irradiated rats that did not receive stem cells experienced a more than 50 percent drop in cognitive function.

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Daniel Lim MD, PhD, assistant professor of neurological surgery and director of restorative surgery, has been awarded a \$600,000 Sontag Foundation Distinguished Scientist Award to study how neural stem cells can become cancerous. He was also given a \$1.5 million New Innovator Award by the NIH to study the gene expression “switches” in developing neural stem cells. These switches progressively control the specialization of the cells into the multitude of cell types that form the brain. New Innovator awards

are designed to support promising new investigators, with the goal of advancing exceptionally innovative research ideas.

Geoffrey Manley MD, PhD, professor of neurological surgery, has been awarded a \$4 million GO grant by the NIH to build on a proposal to standardize data collection across traumatic brain injury (TBI) studies, referred to as the TBI Common Data Elements (TBI-CDE). The TBI-CDE emphasizes demographics, neuroimaging, outcome measures, biomarkers, and psychological health. With funding from the GO grant, a multi-center effort to validate the TBI-CDE will be performed at six medical centers. By developing infrastructure, refining standards for data collection, and improving TBI classification schemes, the project is designed to tackle the major issues that have hampered opportunities for translating research into new treatments.

The laboratory of **S. Scott Panter PhD**, assistant adjunct professor of neurological surgery, recently collaborated with the Alzheimer’s Research Center at Regions Hospital to examine the effects of deferoxamine, a high-affinity iron chelator, on ischemic stroke damage. They found that pretreatment with deferoxamine administered intranasally could protect rats from stroke induced 48 hours later. Drug given after the stroke significantly reduced tissue damage. Intranasal delivery allows the drug to bypass the blood-brain barrier and enter the brain within minutes. The pretreatment paradigm is relevant to patients undergoing bypass or any other vascular surgery, and the post-treatment may be useful for stroke patients.

Hanson LR, Roeytenberg A, Martinez PM, Coppes VG, Sweet DC, Rao RJ, Marti DL, Hoekman JD, Matthews RB, Frey WH 2nd, Panter SS. Intranasal deferoxamine provides increased brain exposure and significant protection in rat ischemic stroke. *J Pharmacol Exp Ther* 2009;330(3):679-686.

UCSF Brain Tumor Research Center Receives Major Grant for Stem Cell Therapy

The California Institute for Regenerative Medicine has awarded five California-based institutions \$19,162,435 to advance stem cell based strategies for treating brain tumors. The objective of the grant is to file a new drug application with the U.S. Food and Drug Administration within four years, driving a stem cell-associated therapy towards clinical trial. The studies will be led by **Mitchel Berger MD**, chair of the UCSF Department of Neurological Surgery, and includes collaborators at the Ludwig Institute for Cancer Research at UCSD, UCLA, the Burnham Institute for Medical Research, and the Salk Institute. The overall goal of the project is to genetically engineer stem cells that home to and deliver therapeutic agents that specifically kill glioblastoma cells. The concept is based on the research team's discovery that neural stem cells naturally seek out brain tumor cells. If the product of this research is approved by the FDA, it would be tested first in patients with recurrent glioblastoma.

Mei-Yin Polley PhD, assistant adjunct professor of neurological surgery, was honored with the Award for Excellence in Adult Clinical Research at the 2009 joint meeting of the Society for Neuro-Oncology and the AANS/CNS Section on Tumors for her paper entitled "Six-Month Progression-Free Survival as an Alternative Primary Efficacy Endpoint to Overall Survival in Newly-Diagnosed Glioblastoma Patients Receiving Temozolomide."

Isaac Yang MD, chief resident in the Department of Neurological Surgery, was given the Kaiser Resident Research Award at the 2009 meeting of the San Francisco Neurological Society as well as the Resident Research Award from the American Academy of Neurological and Orthopedic Surgeons. He has also earned a 2009 UCSF School of Medicine Teaching Award.

New Faculty

Clinical neuropsychologist **Caroline Racine PhD** has recently joined the Department, specializing in the assessment of cognition and mood in patients with neurological disorders. She serves as part of the multidisciplinary team for three main patient groups: neuro-oncology, radiation oncology, and surgical movement disorders. Specifically, she provides neuropsychological assessment for patients prior to surgery or intervention (baseline evaluations) and also provides ongoing assessment in order to monitor cognitive function over time. The results of these evaluations are used to assist with treatment planning and return-to-work strategies. Dr. Racine also takes a limited number of referrals to evaluate other individuals with cognitive complaint secondary to neurosurgical and/or neurological conditions.

New Skull Base Tumor Board

The Departments of Neurological Surgery and Otolaryngology – Head and Neck Surgery are pleased to announce a new format for a multidisciplinary skull base tumor board the first Thursday of each month in L-34 in the Department of Radiation Oncology. Physicians

are invited to submit cases for discussion to Judi Chesler at CheslerJ@neurosurg.ucsf.edu.

Clinical Trial Highlights

- The Department of Neurological Surgery has launched a phase II trial of the HSPPC-96 vaccine with concurrent temozolomide in patients with newly diagnosed glioblastoma multiforme. Funded entirely through a Specialized Program of Research Excellence grant from the NCI and patient advocacy groups, this will be the first study of this brain tumor vaccine in patients with primary tumors, after initial trials in recurrent patients have demonstrated safety and a tumor-specific immune response. By refining the patient population and obtaining a better understanding of the immune response evoked during different stages of the cancer, we have the potential to transform brain cancer from a life-threatening illness into a chronic disease. Contact Andrew Parsa MD, PhD by e-mail at ParsaA@neurosurg.ucsf.edu.
- The UCSF Division of Cerebrovascular Surgery is participating in the Carotid Occlusion Surgery Study (COSS), an NIH-funded, randomized clinical trial. In this study, we will



Caroline Racine PhD

determine if extracranial-intracranial (EC/IC) bypass surgery combined with best medical therapy can reduce subsequent ipsilateral ischemic stroke (fatal and non-fatal) at two years by 40%, despite perioperative stroke and death. Eligible participants must have internal carotid artery occlusion producing hemispheric symptoms within the previous 120 days and ipsilateral increased oxygen extraction fraction (OEF) measured by positron emission tomography (PET). Clinically eligible subjects will undergo PET. Those with increased OEF will be randomized equally to undergo EC/IC bypass or not. Follow-up is at one month and every three months for two years. For those with normal OEF, PET provides evidence of good prognosis on medical therapy alone. The study will pay for PET and for EC/IC bypass surgery. Contact Lisa Hannegan MS, CNS, ACNP at (415) 476-2180 or by e-mail at HanneganL@neurosurg.ucsf.edu.

selected recent publications from the department of neurological surgery

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