Progressive Neuroscience

A publication for physicians produced by the Institute for Neurosciences at Winthrop-University Hospital

• The Latest MS Therapies & Controversies
• qMRA Measures Cranial Blood Flow Noninvasively
• Epilepsy Localization & Extraoperative Brain Mapping
Message from the Chiefs

To Our Colleagues

Despite the indisputable value of evidence-based medicine, debates about the most effective treatment approaches continue to have a critical and profound impact on clinical judgment and management.

At Winthrop-University Hospital’s Institute for Neurosciences, discussions of the many recent advances in neurology and neurosurgery are ongoing, generating impressive practice changes. We are constantly upgrading and setting new standards for patient care. Inaction is not an option; our progress is fueled by persistent treatment assessments, re-evaluations and appropriate modifications tailored to individual needs.

This issue of Progressive Neuroscience examines:

- The latest MS Therapies and Tysabri® rebound
- CyberKnife® treatment for spine and brain tumors: 1 vs 3 vs 5 fractions
- The use of qMRA before and after treatment of cerebrovascular pathology
- Epilepsy localization and extraoperative brain mapping

Additionally, we have included an overview of the vital role of physician assistants in neurocritical care.

Our charge is to obtain superior outcomes through the provision of leading-edge, compassionate care that focuses on healing and improved quality of life for each patient. Fundamental to this mission are the strong collaborative relationships we share with you — our referring physicians.

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**Progressive Neuroscience** is produced by the Institute for Neurosciences at Winthrop-University Hospital, 259 First St., Mineola, NY 11501, 516-663-0333. www.winthrop.org.

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*Progressive Neuroscience* Winter 2011-12
### Fractionation in the Treatment of Brain & Spine Tumors with CyberKnife®

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CyberKnife — the gold standard for frameless stereotactic radiosurgery (SRS) — provides hope to thousands of patients struggling with tumors once considered unresectable and/or inoperable.

A complex system that demands exceptional skill and attention to detail, CyberKnife requires a team of highly trained physicians, physicists and technologists for operation, which rests on two fundamental principles:

- If a lesion can be imaged, it can be targeted with extreme accuracy using stereotactic localization.
- By utilizing cross-fired beams to administer ablative doses of high-energy radiation, a targeted lesion can be destroyed without injuring the normal surrounding tissue and anatomy.

Providing unprecedented access to small, deeply imbedded, complex masses non-invasively, the frameless system brings highly conformal radiation doses to targeted lesions in the brain, spine, chest, abdomen and pelvis from multiple positions and angles with pinpoint accuracy.

The device’s powerful irradiation and precision can shrink or obliterate tumors in a few outpatient visits, rendering it effective for individuals who have had the maximum allowable conventional radiation therapy and those who are not candidates for open surgery.

### Fractionation

Earlier SRS systems required immobilizing patients in restrictive, uncomfortable frames to ensure radiosurgical targeting. This not only made fractionation (staged treatments over time) for larger tumors near radiosensitive critical structures impossible, but it also made it very difficult to treat extracranial tumors or lesions at the extreme sides of the brain.

CyberKnife’s frameless system obviates the need for neurosurgical halos. The advanced technology places a linear accelerator on a robotic arm with 6º of movement and positioning accuracy of 0.2 mm. The robot constantly updates the patient’s position, compensating for any minor movement to ensure precise treatment with maximum flexibility.

Essentially, fractionation buys time for patients — time between treatments that enables their bodies to repair sublethal cell damage and repopulate cells. The technique allows the neurosurgeon and radiation oncologist to target lesions with from two-to-five treatments — as opposed to prescribing prolonged courses of radiation — effectively and safely even when the tumors are adjacent to radiosensitive critical organs, such as the spinal cord, optic structures and cranial nerves.

The number of fractions prescribed for each patient depends on several factors, including lesion size, location and histology; surrounding dose-sensitive structures; prior treatment; expected treatment duration; and comorbidities.

### Cranial Tumors

Pituitary adenomas, meningiomas and cranioopharyngiomas near the optic chiasm and anterior visual pathways are especially challenging, and in these cases, staged SRS has proven particularly useful. For metastatic cranial lesions, CyberKnife affords symptom palliation and extended survival time. Patient selection criteria include: a limited number of metastases, tumor diameter <3.5 cm for solitary treatments (larger lesions are amenable to fractionated treatments), and stable or non-existent disease at the primary and extracranial sites. Additionally, candidates for cranial CyberKnife treatments should have a post-treatment estimated survival period of six months or more, the ability to tolerate treatment and well-defined masses on radiographic images.

### Spine Tumors

Criteria for spine-tumor patients considering fractionated CyberKnife include well circumscribed lesions, minimal spinal cord compromise, lesions difficult to resect via open surgery and significant medical comorbidities that rule out surgical intervention.

CyberKnife can track intracranial lesions relative to bony landmarks in the skull, and with new X-Sight spine technology for spine tumors, neurosurgeons and radiation oncologists can track off spine anatomy as opposed to implanting fiducial markers — tiny, point-like visual landmarks in the bone adjacent to the lesion that provide clear radiographic tracking landmarks during treatment.

CyberKnife spine tumor treatment plans are based upon shape, proximity to spinal cord, location, histology, spinal cord tolerance and previous radiation to nearby normal tissue. Since CyberKnife target doses have a steep fall off gradient, the possibility of radiation-induced myelopathy is reduced, and treatments can be provided early in the postoperative period. In most cases, the treatment goal is to palliate pain, prevent pathologic fractures and reverse or halt progression of neurological deficits.

At Winthrop, CyberKnife SRS — with Jeffrey Brown, MD, the CyberKnife Center’s Neurosurgical Director — is a leading-edge therapeutic modality for patients with cranial and spinal masses that are inoperable or have been previously irradiated. Additionally, with the power to improve control of brain and spine tumors, it is employed as an adjunct to surgery.

For more information, call the Institute for Neurosciences at 1-866-NEURO-RX or visit www.winthrop.org.
The Power of Neurocritical Care: A PA’s Perspective

By Colleen M. Christiansen, MPAS, RPAC
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The challenges of caring for patients with life-threatening and severely disabling neurological conditions can be at once daunting and exhilarating. But, the rewards are beyond measure. Little can match the satisfaction we experience with even the smallest sign of progress.

Working in Winthrop-University Hospital’s Neuroscience Intensive Care Unit (NeuroICU) is especially stimulating. In this state-of-the-art facility — the first unit of its kind on Long Island — our multidisciplinary team of neurosurgeons, neurointensivists, neurologists, nurse practitioners, physician assistants and nurses treats patients recovering from complex neurosurgical procedures and those with acute and often grave neurological illnesses.

The Unit

Led by Elzbieta Wirkowski, MD — Medical Director of the NeuroICU, and Director of Winthrop’s Cerebrovascular Disorders Program, and Michael Brisman, MD, Chief of Neurosurgery — the highly cohesive NeuroICU team coordinates and implements the complex testing and interventions required to minimize or delay brain damage, promote healing and maximize recovery.

Along with the most advanced technology used to monitor intracranial pressure, cerebral perfusion pressure, brain oxygenation levels and core body temperature, the Unit houses 14 fully equipped ICU beds wired for remote EEG monitoring in order to meet the needs of patients whose care demands continuous EEG supervision by epileptologists.

The staff’s specialized skills — including the ability to perform vigilant neurological monitoring, formulate neurological differential diagnoses and execute timely interventions — distinguish the NeuroICU from standard medical-surgical ICUs and underscore Winthrop’s distinctive position as a leader in neurological care.

The PA Team

The PA team of 23 full-time professionals provides on-site, 24/7 coverage, conducting crucial evaluations, consulting with physicians and participating in daily, multidisciplinary teaching rounds, where interventional neuroradiologists, neurologists and neurosurgeons develop new treatment strategies based on even the smallest changes in patients’ conditions. For neuro PAs, nothing is more important than the ongoing neurologic assessments and evaluations provided at bedside for patients suffering from the broad array of neurologic and neurosurgical conditions, including subarachnoid hemorrhage, ischemic stroke, status epilepticus, traumatic brain injury, serious neuromuscular disorders and tumors or infections of the brain or spinal cord. Our training has sharpened our ability to detect and evaluate even the most subtle and early changes in patient status. We can assess patients in coma, with paralysis or with debilitating strokes that render them unable to communicate verbally.

What’s more, we are also equipped to manage our patients’ serious and sometimes life-threatening comorbidities, including arrhythmias, hypertension, respiratory failure requiring mechanical ventilation and infections, which are superimposed over their acute neurologic conditions. Even ICU psychosis, so common in conventional critical care units, presents slightly differently in the NeuroICU, and it is our job to understand the subtle dynamics before situations escalate.

Neuro PAs also assist in obtaining and analyzing radiographic images, frequently providing the on-call neuroscience specialists with vital information so that crucial treatments can be implemented as rapidly as possible. Additionally, with supervision from neuroscience physicians, we perform a wide range of invasive and noninvasive, high-tech bedside procedures, including therapeutic hypothermia, Cheetah non-invasive cardiac output monitoring, LycoX brain tissue oxygenation, intracranial pressure monitoring and management of external ventricular catheters, as well as the implantation of lumbar drains used in patients needing cerebrospinal fluid diversion.

We are also actively involved in assisting with life-saving strategies on the Unit or in the operating room, including craniectomy, laminectomy, discectomy, decompressive hemicraniectomies, intra-arterial TPA, intra-arterial verapamil (in patients suffering from cerebral vasospasm), MERCI and PENUMBRA clot retrieval.

Typical Day

Typically, the day of a neuro PA begins with receiving sign-out from the previous shift and progresses to patient assessments and collection of the 24-hour patterns, vitals and neurologic changes. Daily formal bedside rounds include discussions of active issues and teaching opportunities. Each patient has a daily care plan, which is followed diligently with allowances made for even the slight changes in condition. And at the end of the day, during “exit rounds,” those individualized care plans are further customized to meet changes in patient needs.

Underscoring our involvement in the mechanics of caring for patients in the ICU is a sense of urgency that colors every moment in the NeuroICU. Neurocritical care has the power literally to turn lives around. Every patient — whether it’s the youngster critically injured in an auto accident, the 45-year-old man recovering from brain surgery that excised a life-altering tumor or the elderly woman whose life will never be the same since her massive brain hemorrhage — gets our focused, intense attention.

For more information, call the Institute for Neurosciences at 1-866-NEURO-RX or visit www.winthrop.org.
Combining unique, relatively new software with conventional magnetic resonance imaging (MRI), quantitative magnetic resonance angiography (qMRA) is an innovative blood flow analysis system that quantifies cerebral blood flow — measuring cc/min — noninvasively and without contrast.

The technology uses traditional time-of-flight and phase-contrast MRI to produce a 3D model of the vasculature that rotates 360°, allowing visualization of extracranial and intracranial vascular anatomy from all angles, and enabling the precise evaluation of entire vasculatures or specific areas within a vessel.

“In addition to identifying each vessel during the course of a single MR examination, qMRA provides us with significant physiologic information from arterial waveform analysis in patients with a range of cerebrovascular diseases,” said Jonathan Brisman, MD, Winthrop-University Hospital’s Director of Cerebrovascular and Endovascular Neurosurgery, and one of the nation’s few neurosurgeons with dual training in microneurosurgery and endovascular techniques.

“Winthrop was the first Long Island hospital to acquire this technology,” added Dr. Brisman. “In addition to showing volumetric flow rates, the detailed and accurate reports also indicate velocity, waveforms and flow direction. With such data we can stratify stroke risk, evaluate vertebrobasilar flow, screen for intracranial in-stent stenosis and assess blood flow after extracranial arterial stent placement.”

The technology accurately predicted the effects on cerebral blood flow in 10 out of 10 patients who underwent qMRA studies before and after endovascular or neurosurgical interventions.
Collaborating with endovascular neuroradiologist John Pile-Spellman, MD, and stroke neurologist Angelos Konstas, MD, PhD, Dr. Brisman recently conducted and published a study of the clinical utility of qMRA to assess the hypothesized pathophysiology (HP) in a variety of cerebrovascular disorders.1 The technology accurately predicted the effects on cerebral blood flow in 10 out of 10 patients who underwent qMRA studies before and after endovascular or neurosurgical interventions. Additionally, they confirmed that qMRA evaluation of arterial waveforms can improve the assessment of the HP.

Of the 10 patients, two had vertebral artery stenosis, three were diagnosed with arteriovenous malformations and the others had common carotid artery (CCA) occlusion, internal carotid artery (ICA) occlusion, fibromuscular dysplasia and stenosis of the ICA, subclavian steal syndrome, and intracranial vasospasm following rupture of an anterior communicating arterial aneurysm.

The qMRA studies were reviewed before and after treatment. Anatomy, volumetric flow rates and arterial waveforms for each sampled vessel were assessed, and a consensus was formed as to whether the parameters supported the clinical diagnosis/HP and subsequent disease management.

In all patients, the HP was supported, based on the abnormal volumetric blood flow values in the affected vessels before treatment and after successful therapy. Each of the five patients with occlusive disease/vasoconstriction demonstrated evidence of dampening of the arterial waveforms distally to the narrowed artery (parvus-tardus phenomenon). The parvus-tardus effect disappeared after treatment.

“With qMRA, during a single MR examination, we can obtain critical information about vascular status in patients with a wide range of cerebrovascular diseases,” Dr. Brisman reported.

For more information, call the Institute for Neurosciences at 1-866-NEURO-RX or visit www.winthrop.org.

REFERENCE

Some of the Most Promising New Multiple Sclerosis Therapies

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The ideal therapy for multiple sclerosis (MS) would completely halt disease progression, repair the nervous system, and affect all phases of the disease. While we have not yet reached that goal, the latest medications are proving to be powerful and valuable in the inflammatory stage.

With different mechanisms of action targeting the immune system, the new agents decrease the number of MS relapses and progression of disability significantly. Although “partially effective,” they, nevertheless, provide an unprecedented number of therapeutic options.

Alemtuzumab (CAMPATH®) — a humanized monoclonal antibody directed against the cell surface protein CD52 — depletes B and T cells in the immune system, the new agents decrease the number of therapeutic options. Alemtuzumab reduces the relapse rate and risk of developing disability. The Phase II CAMMS223 study, which involved 334 patients and compared CAMPATH with standard therapy interferon beta-1a (Rebif®), found a 74% decreased relapse rate and a 71% decreased risk of sustained disability accumulation with alemtuzumab. Four-year data showed sustained efficacy with a 69% reduction in relapse rate and disability progression.

The study evaluated the safety of a planned treatment interruption. During the 24-week drug withdrawal period patients were started on Copaxone®, Avonex®, methylprednisolone or placebo.

Despite the proliferation of MS therapies, it is not yet possible to determine the most effective treatment for an individual prospectively.

Taking a Tysabri® Drug Holiday May Cause Rebound in MS Activity

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When the FDA approved the use of natalizumab (Tysabri) in 2004, the drug was hailed as a major breakthrough in the treatment of relapsing-remitting multiple sclerosis (RRMS). Clinical trials showed it to be nearly twice as effective as other MS disease-modifying medications in use at that time. However, it did not change the fundamental disease process, believed to be triggered when activated immune cells breach the blood-brain barrier and enter the central nervous system (CNS).

Natalizumab is a selective adhesion molecule inhibitor that hinders leukocyte migration across the blood-brain barrier. Extremely effective at blocking CNS inflammation and diminishing MS exacerbations, it is administered via infusions every 28 days.

Despite its initial success, one year later, hopes were dampened. FDA approval was temporarily withdrawn when natalizumab was linked with progressive multifocal leukoencephalopathy (PML), a potentially fatal, white matter viral infection of the brain caused by the JC virus (JCV). However, in 2006, natalizumab was reintroduced when the FDA reapproved its use with stringent safety and monitoring guidelines known as the Tysabri Outreach: Unified Commitment to Health (TOUCH) Program.

Although PML is rare in patients treated with Tysabri (approximately 1/10,000), the longer natalizumab therapy continues, the greater the risk of developing the infection. This risk appears to peak between 24 and 32 months of therapy and may decrease. Another risk factor is previous treatment with immunosuppressive therapy.

Researchers hypothesize that temporary interruptions of the therapy may decrease PML risk. However, the latest evidence — including an investigator-initiated trial conducted at Winthrop-University Hospital’s comprehensive Multiple Sclerosis Care Center — suggests that disease activity returns to pretreatment levels, peaking at about four months after natalizumab is discontinued.1

The RESTORE (Randomized Treatment Interruption of Natalizumab) Trial, which reported preliminary results in October 2011, examined the effects on disease activity of a planned 24-week pause in natalizumab therapy on 175 patients who had been relapse free with no MRI activity for at least 12 months. Although it is hoped that planned suspensions of Tysabri treatment may decrease the risk of
Winthrop-University Hospital’s comprehensive Multiple Sclerosis Care Center participated in the Phase III Care MS 2 study, which involved 849 patients and reported results in November 2011. CAMPATH showed a 49% reduction in relapse rate and a 42% reduction in sustained disability progression, compared to Rebif. These patients failed standard treatment before taking CAMPATH.

**Oral Medications**

The first FDA-approved oral medication, fingolimod, was introduced in 2010. Several more, expected in 2012 and 2013, are designed to treat RRMS. They are most notable for their route of administration, rather than clinical efficacy, which is similar to existing injectable medications. These agents include:

- **Fingolimod (Gilenya®)**, the first — and currently only available — oral agent in its class, was introduced in 2010. It is a new class of medication that blocks sphingosine-1-phosphate receptors, and has been shown to slow progression of disability and reduce frequency of MS relapses. The medication binds to sphingosine-1-phosphate receptors and sequesters activated immune cells in lymph nodes, preventing them from crossing the blood-brain barrier and entering the central nervous system, where they can trigger an autoimmune reaction to the myelin.

In the two-year, Phase III FREEDOMS study, which compared two doses of fingolimod to placebo, relapses were reduced by approximately 50%, and risk of disability progression dropped 30% compared to placebo.

The one-year TRANSFORMS study compared two doses of fingolimod to interferon beta-1a (Avonex®). Fingolimod reduced relapses by about 50%, and MRI findings showed significant improvement (the number of new T2 lesions on MRI scans, compared to interferon beta-1a was 1.6 vs. 2.6). However, there was no change in disability status, which was attributed to the trial’s short duration.

- **Teriflunomide** — an active metabolite of leflunomide (Arava®) — inhibits active pyrimidine synthesis, reducing B- and T-cell activation and proliferation of slowly dividing cells that use the “salvage pathway.”

The multinational, randomized, Phase III, two-year TEMSO study showed a significant reduction (31%) in annualized RRMS rates with two doses (7mg and 14mg), compared to placebo. The higher dose showed delayed disability progression. Long-term data on safety and efficacy revealed that both doses were well tolerated six years after initial randomization.

- **Dimethyl fumarate (BG12)** is an anti-inflammatory considered neuroprotective. The two-year DEFINE study, comparing BG12 to placebo, showed a 49% decrease in relapses and a 38% reduction in disability progression. Results of the CONFIRM study, which compared BG12 to placebo and Copaxone®, are expected to be announced shortly.

- **Laquinimod**, a derivative of thalidomide, is an immunomodulator that enters the CNS. Several trials have demonstrated that it reduces relapse rate compared to placebo. However, a recent two-year trial, comparing laquinimod to Avonex demonstrated reduced disability progression without decrease in relapse rate. It is possible that this medication is truly neuroprotective. The dissociated result of improved disability status without diminishing relapses is unique to laquinimod.

- **Cladribine** depletes CD4 and CD8 cells. Despite encouraging clinical trial data, the manufacturer withdrew the FDA application because of safety concerns.

**Head-to-Head Trials & Ethical Concerns**

Many of the new drugs have proven effective against placebo, but not in head-to-head comparisons. The best way to evaluate and compare drugs is in head-to-head trials; comparing the relapse rate reduction from one placebo-controlled trial to another is not a valid technique. For example, the relapse-reduction rate for the same drug has differed significantly over time when compared to placebo in different trials. This may reflect changes in the trials’ patient pools; the great increase in trials has resulted in competition for patients, who now tend to have less active disease than those in the trials of the 1990s.

The use of placebo in MS trials has raised ethical concerns. Many investigators do not feel that placebo-controlled trials should be conducted on patients who suffer from RRMS, as effective therapies exist for this form of the disease.

Despite the proliferation of MS therapies, it is not yet possible to determine the most effective treatment for an individual prospectively. It is our hope that research will identify the mechanism of disease in each patient and allow us to select the most effective therapy at the time of diagnosis.

For more information, call the Institute for Neurosciences at 1-866-NEURO-RX or visit www.winthrop.org.

**REFERENCES**

PML, this study was not powered to make that determination. The study evaluated the safety of a planned treatment interruption. During the 24-week drug withdrawal period patients were started on Copaxone®, Avonex®, methylprednisolone or placebo. The incidence of MRI return of disease activity was: Copaxone 53%, Avonex 7%, methylprednisolone 40% and placebo 44%. None of the patients who continued Tysabri had MRI disease activity.

Other data, involving smaller numbers of patients, presented at the 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS) in October 2011 also indicated that patients with RRMS experience a high rate of recurrence when treatment with natalizumab is interrupted.

Winthrop's Tysabri Discontinuation Study

Winthrop’s comprehensive MS Care Center — one of only five facilities on Long Island certified to infuse natalizumab — currently treats almost 100 MS patients with the medication.

Seventy one patients taking Tysabri were tested for the JC virus (JCV IgG determined via the STRATIFY clinical trial.) Most JCV infections occur in childhood and are not clinically significant. Patients without prior exposure cannot have a reactivation of the JC virus and develop PML; those with positive titers indicating prior exposure are at risk. The patients, who had initiated treatment unaware if they had been exposed to JC virus, were tested and informed of their status and determined if they wished to continue Tysabri.

Results

Of the 71 patients who had JCV antibody testing performed, 32 were positive, and 39 were negative (45.1% vs. 54.9%). All 39 patients who tested negative for JCV continued natalizumab therapy. Nine of the 32 (28.1%), who tested positive, stopped treatment. Over the next six months after electing to continue Tysabri treatment, relapse occurred in two of the 39 JCV-negative patients vs. one of 23 JCV-positive patients. JC antibody status did not significantly affect relapse rate in patients who continued Tysabri (5.1% vs. 4.4%, p=0.89).

Among patients who were JCV positive (n=32), relapse occurred in one patient, who continued treatment vs. five of the nine patients who halted natalizumab (4.4% vs. 55.6%, p<0.01). The average duration of treatment was 34.2 months (range: 15 to 42 months). All relapses occurred within six months in patients who had several years of clinical and radiologic stability while treated with Tysabri: 80% of the patients who had discontinued Tysabri and relapsed resumed the medication despite knowing they are at risk for PML.

Conclusions

Patients receiving treatment with natalizumab were more likely to discontinue therapy, if found to be JCV IgG positive, and those who stopped treatment were more likely to relapse within six months. Those who elected to discontinue Tysabri had very active and persistent disease activity prior to initiating therapy. These patients may not have fully appreciated their potential for relapse because of their prolonged symptom-free state while taking natalizumab.

At Winthrop, we now use natalizumab in JCV antibody-positive MS patients who have failed other treatments or are at high risk for disability progression. The medication is used more liberally in JCV antibody-negative patients. The negative patients are tested on a yearly basis and appear to have a 2% annual conversion rate to antibody positivity. There is also a false negative JCV IgG antibody test rate of approximately 2%-3%.

We do not advocate intentional pauses in Tysabri treatment as the risk of relapse is very high, and this is not a proven strategy to prevent PML.

For more information, call the Institute for Neurosciences at 1-866-NEURO-RX or visit www.winthrop.org.

REFERENCE

Epilepsy, the most common, chronic neurological disorder, affects more than 2 million Americans. Although a host of antiepileptic drugs have been introduced over the past decade, many do not control seizures, making it necessary for patients with medication-resistant epilepsy to consider non-pharmacological treatment, including resective surgery.

With recent advances in neuroimaging, many patients who undergo surgery for epilepsy do not require invasive EEG studies. However, for some, particularly those whose noninvasive diagnostic evaluations reveal undefined or discordant results, intracranial EEG monitoring is necessary. Preoperative intracranial EEG studies and adjunctive electrical brain stimulation for treatment of patients with refractory epilepsy provide detailed analyses that permit extraoperative epileptogenic and functional localization when time limitations and anesthesia cannot affect functional mapping.

Epileptologists at Winthrop-University Hospital’s comprehensive Epilepsy Center — a member of the National Association of Epilepsy Centers — offer the highest level of cutting-edge care. Their decision to use intracranial EEG monitoring is carefully considered, informed by each patient’s clinical history and reached only after extensive diagnostic evaluation with extracranial video-EEG monitoring, structural and functional neuroimaging and neuropsychological assessment.

Historical Perspective

Functional localization of human motor, sensory and language-related activities in the cortex was initially determined from direct observation in the operating room with electrical stimulation during diagnosis and treatment of epilepsy. Intraoperative electrical stimulation eventually led to the development of a topographic map of motor and somatosensory function of the respective pre- and post-central gyri — better known as the motor and somatosensory homunculi. This provided preoperative knowledge of eloquent cortex and helped neurosurgeons perform resections with fewer postoperative neurological deficits.

Over the last several decades, the implantation of electrodes in portions of the epidural or subdural space in adults and children with pharmaco-resistant epilepsy has enabled both epileptogenic and functional localization, further enhancing surgical management and decreasing the risk of injury to healthy tissue.

Patient Selection

At Winthrop, before pursuing preoperative intracranial EEG monitoring, localization of the epileptogenic zone is attempted noninvasively with video-EEG monitoring, MRI, PET and SPECT. If the area of interest cannot be pinpointed with any of these technologies — or if the results of the diagnostic assessments are discordant — intracranial EEG using subdural strips, grids and depth electrodes may be employed to identify or further delineate epileptogenic regions.

Electrode placement is performed only after evaluation enables the epileptologist to develop a reasonable hypothesis regarding location of the area of epileptogenicity. The hypothesis is based on results from the aforementioned studies, as well as the patient’s clinical history and neurological examination. The strength of this hypothesis is often proportional to the likelihood of success with the invasive evaluation.
Intracranial EEG monitoring begins in the operating room, where subdural electrodes are embedded in thin sheets or strips of flexible biocompatible material, such as polyurethane, and implanted in the subdural space (Fig. 1, Fig 2). Grids are typically placed over the cortical surface through a craniotomy. They contain disc electrodes made of stainless steel or platinum alloy that measure 2-4 mm in diameter spaced at fixed 1 cm intervals. Available in a variety of sizes and shapes, grids may contain up to 64 contacts.

Subdural strips are made of similar material and contain comparable electrodes. Inserted through burr holes or at the edges of the craniotomy, they can provide coverage of areas, such as the orbitofrontal, occipital and basal surface of the temporal regions, which may not be easily accessed with a craniotomy.

Once placed, the electrodes are tested in the operating room with electrocorticography to ensure satisfactory recording. The craniotomy is then closed and the patient is transferred to the Hospital’s Neuroscience Intensive Care Unit (NeuroICU) for video-EEG monitoring, which provides continuous electroencephalography to assist in identifying the epileptogenic areas.

In addition to localizing areas of epileptogenicity, the indwelling intracranial electrodes, coupled with the video-EEG monitoring, allow for functional localization studies with cortical stimulation performed at bedside in the NeuroICU. Cortical stimulation involves introducing small currents of electricity through individual electrodes with simultaneous observation for clinical symptoms or signs of interference with cortical functioning. For instance, applying electrical stimulation over the patient’s motor cortex can produce contralateral motor signs, manifesting in involuntary movements.

**Safety & Potential Complications**

When conducting cortical stimulation, adherence to established safety parameters is essential to the patient’s well-being. Testing involves intermittent brief pulses of stimulation rather than continuous stimulation. Studies indicate that intermittent stimulation is associated with less cortical damage than continuous stimulation. While there are no reports of cortical changes in histopathology in patients undergoing subdural stimulation, there is the possibility of infection, hemorrhage or edema.

Since electrode wires are tunneled and exit through the dura, skull and scalp, there is potential for infection. Strict antiseptic techniques — in and out of the operating room — and the vigorous use of prophylactic antibiotics help reduce the possibility of infection. In the past decade, the infection rate has decreased to 1%-5%, with the low end of that range seen most recently.

Hemorrhage — namely subdural hematoma — is one of the most feared complications associated with the use of indwelling electrodes. The incidence of life-threatening hemorrhage has dropped significantly over the past years due to preoperative evaluation of coagulation and clotting parameters, as well as direct visualization of the cortex through craniectomy rather than a burr hole for electrode placement.

A recent report on invasive video-EEG monitoring with subdural electrodes indicated that complications were encountered in under 20% of patients, and most of those were transient, not requiring treatment. Complications were associated with use of a high number of electrodes, longer monitoring duration, older patient age and left-sided grid insertion. Prophylactic administration of steroids during monitoring helps reduce cerebral swelling and may reduce the risk of potential complications.

**Conclusions**

Comprehensive epilepsy centers — such as Winthrop’s — offer patients the full range of advanced treatment options, including epilepsy surgery. To provide neurologists and neurosurgeons with critical information essential to surgical planning and positive patient outcomes, epileptologists in these centers are skilled in utilizing complex, extraoperative intracranial EEG monitoring to achieve epilepsy localization and functional cortical mapping.

For more information, call the Institute for Neurosciences at 1-866-NEURO-RX or visit www.winthrop.org.

**REFERENCES**

Dr. Michael Brisman specializes in stereotactic surgery and radiosurgery for brain tumors and trigeminal neuralgia. He is Board Certified by the American Board of Neurological Surgeons and is a Fellow of the American College of Surgeons. His postgraduate training includes a neurological residency and surgical internship at The Mount Sinai Medical Center in New York, where he was Chief Resident. He received his medical degree from Columbia University’s College of Physicians and Surgeons. Dr. Brisman has published numerous articles in professional journals. He is President of the Nassau County Medical Society and is also on the Board of Directors of the New York State Neurosurgical Society.

Dr. Malcolm Gottesman specializes in the treatment of multiple sclerosis (MS), and is the founder of Winthrop’s comprehensive MS Care Center. The Center conducts original clinical research and participates in state-of-the-art clinical trials. Dr. Gottesman was also instrumental in establishing the Hospital’s Stroke Program and Neuroscience Intensive Care Unit. He is Board Certified in Psychiatry and Neurology. His postgraduate training includes a residency in neurology at Long Island Jewish Medical Center, where he was Chief Resident. He also completed an internship and residency in psychiatry at Boston University Medical Center. Dr. Gottesman received his medical degree in an accelerated BS-MR program jointly sponsored by Rensselaer Polytechnic Institute and Albany Medical College. He has published numerous articles in professional journals and presents at national and international conferences. Dr. Gottesman received an MS Leadership award from the Long Island MS Society.

Dr. Jonathan Brisman specializes in cebp vascular and endovascular surgery for diseases of the central nervous system. As one of the few neurosurgeons, nationwide, with dual training in microendoscopic surgery and endovascular techniques (and the first on Long Island), he is skilled in aneurysm clipping and endovascular coiling for brain aneurysms, as well as in advanced procedures to treat brain arteriovenous malformations (AVM), carotid stenosis and acute stroke. His postgraduate training includes an Interventional Neuroradiology Fellowship at Roosevelt Hospital in New York and a Microvascular Neurosurgical Fellowship at Swedish Hospital in Seattle. He completed a neurological residency and surgical internship at Massachusetts General Hospital, where he was Chief Neurosurgery Resident. Dr. Brisman received his medical degree from Columbia University’s College of Physicians and Surgeons. He has published numerous articles in peer-reviewed neurosurgery journals, including “Medical Progress: Cerebral Aneurysms” in the New England Journal of Medicine and one on stroke management in Lancet.

Dr. Janna Andrews is a Board-Certified Radiation Oncologist with skill and experience in a wide range of treatment modalities, including stereotactic radiosurgery, CyberKnife, brachytherapy, 3D CRT, IMRT, EPID Fiducial System and prostate seed implantation. Prior to joining Winthrop, she was in private practice and an Assistant Professor of Clinical Oncology, specializing in breast cancer, sarcoma and women’s health at the Indiana University School of Medicine in Indianapolis. Her postgraduate training includes a Radiation Oncology Genitourinary Fellowship at the University of California San Francisco and a residency in radiation oncology at Emory University in Atlanta. She earned her medical degree at Temple University School of Medicine. Dr. Andrews has presented at more than 20 professional meetings. Her current interest focuses on eliminating health care disparities.

Dr. Jeffrey Brown — a pioneer in the development and use of motor cortex stimulation (MCS) — is nationally recognized for his expertise in complex and chronic pain syndromes, especially facial pain. He is a past member of the Board of Directors of the American Association of Neurological Surgeons and chair of the Joint Section on Pain of the American Association of Neurological Surgeons and Congress of Neurological Surgeons. Currently, he is co-chair of the Medical Advisory Board of the TNA-Facial Pain Society, an international support group for patients in pain. He has published numerous peer-reviewed research articles on pain, spine and vascular, brain tumor and functional neurosurgery in addition to 20 book chapters, and has delivered more than 200 invited lectures at local, regional, national and international venues.

Ms. Denise Cheng, a Multiple Sclerosis Certified Nurse at Winthrop’s comprehensive Multiple Sclerosis Care Center, is responsible for patient and family education and counseling regarding the disease and its management. She is the coordinator of the Center’s Tysabri infusion program. Her experience includes providing in-home training for patients and families initiating drug treatment, as well as teaching MS symptom management and drug therapy to healthcare professionals. Ms. Cheng serves as a study coordinator for Winthrop’s many MS clinical trials. She is a graduate of St. Vincent’s Hospital School of Nursing in New York and received her BSN from Adelphi University in Garden City, New York.
Colleen M. Christiansen, MPAS, RPAC
Co-Chief Physician Assistant, Neuroscience
516.663.3833
Ms. Colleen Christiansen, an experienced physician assistant specializing in neuroscience for more than 15 years, supervises and trains Winthrop’s 23 neuroscience PAs in all procedures performed in the Neuroscience Intensive Care Unit. She also provides pre- and postoperative care for the Hospital’s adult and pediatric neurosurgical patients, including those in the NeuroICU, Neonatal ICU and Pediatric ICU. Her duties include conducting trauma evaluations, ordering appropriate diagnostic studies, making preliminary assessments and formulating treatment plans. As a member of Winthrop’s Stroke Team, she assesses patients for the initiation of tPA. She earned her Physician Assistant Certification at Stony Brook University Medical Center and completed a physician assistant surgical residency at Yale University-Norwalk.

David E. Friedman, MD
Director, EEG Monitoring
516.663.4965
Dr. David Friedman is Board Certified in Psychiatry, Neurology and Neuropsychology with added competency in Epilepsy Monitoring. Prior to joining Winthrop, he served as Medical Director of the Epilepsy Clinic at Baylor College of Medicine and the Epilepsy Monitoring Unit at St. Luke’s Episcopal Hospital in Houston, Texas. His postgraduate training includes a Fellowship in Clinical Epilepsy at Columbia University Medical Center, where he also completed a neurology residency. He earned his medical degree from the Sackler School of Medicine – New York State/American Program at Tel Aviv University in Israel. Focusing on epilepsy, Dr. Friedman was a principal and co-investigator in many research projects conducted at Baylor College of Medicine, and is also involved in neurology research at Winthrop. He has published in peer-reviewed journals and has co-authored book chapters, including “Extraoperative Use of Subdural Electrodes” in Clinical Brain Mapping.

Jonathan Haas, MD
Chief, Radiation Oncology
516.663.2502
Dr. Jonathan Haas is a Board Certified Radiation Oncologist who has been using radiation therapy to treat cancer patients for more than a decade. A recognized international expert in CyberKnife radiosurgery, he lectures extensively on its clinical applications. In addition to using CyberKnife for brain and spine tumors, his interests include prostate cancer, lung cancer, gynecologic cancer, pediatric radiation and brachytherapy. His postgraduate training includes a residency in radiation oncology at the University of Pennsylvania, where he was Chief Resident, and an internal medicine internship at Winthrop-University Hospital. He received his medical degree from Washington University in St. Louis. Dr. Haas publishes frequently in peer-reviewed journals, presents radiation oncology research at national and international meetings and appears regularly on radio and television as a radiation oncology expert.

John Pile-Spellman, MD
Endovascular Neuroradiologist
516.255.9031
Dr. John Pile-Spellman is an internationally known endovascular neuroradiologist, specializing in the diagnosis, management and treatment of cerebral aneurysms, strokes, tumors and vascular malformations. Dr. Pile-Spellman has many years of experience in developing high-impact, clinically relevant imaging and treatment paradigms. His postgraduate training includes Fellowships in Neuroradiology at Massachusetts General Hospital and in Interventional Neuroradiology at New York University Medical Center; he was also a visiting Fellow in Endovascular Neurosurgery at the Kiev Neurosurgical Institute, Kiev, Ukraine. Dr. Pile-Spellman completed a residency in diagnostic radiology at Massachusetts General Hospital in Boston, and earned his medical degree from Tufts University School of Medicine in Boston. Prior to joining Winthrop, he was an attending radiologist and Director of Academic Interventional Neuroradiology at New York Presbyterian Hospital. He was also Vice Chair of Research and Director of Interventional MRI at Columbia University Medical Center. He has published numerous articles in peer-reviewed journals.

Lee E. Tessler, MD
Chief, Neurotrauma
516.255.9031
Dr. Lee Tessler specializes in the multimodality treatment of malignant and benign brain tumors, which includes stereotactic surgery and radiosurgery. He is proficient in CyberKnife® Radiosurgery. His postgraduate training includes a residency in neurosurgery and internship in general surgery at New York University Medical Center and Bellevue Hospital Center, where he was Chief Resident. He earned his medical degree at The Ohio State University College of Medicine and Public Health in Columbus, Ohio, with clinical honors in neurosurgery and general surgery.

Matthew R. Witten, PhD, DABR
Director, CyberKnife Radiosurgery
516.663.3830
Dr. Matthew Witten, Chief Physician in Winthrop’s Division of Radiation Oncology, is Board Certified in Therapeutic Radiologic Physics and a Diplomate of the American Board of Radiology. His postgraduate training includes a PhD in Applied Physics, with a concentration in medical physics from Columbia University, where he also earned two Master’s Degrees in applied physics. He received his clinical training at Memorial Sloan-Kettering Cancer Center.

Shicong Ye, MD
Neurologist
516.663.4525
Dr. Shicong Ye specializes in evaluating and treating patients with epilepsy. He has a special interest in treating refractory seizure patients with vagal nerve stimulation and surgery. Dr. Ye is Board Certified in Neurology. His postgraduate training includes a Fellowship in EEG/Epilepsy at Long Island Jewish Medical Center (LIJ). He completed a neurology residency at LIJ, where he was a Chief Resident, and an internship at Kingsbrook Jewish Medical Center. Dr. Ye completed an honorary medical degree from the prestigious Shanghai Medical University in China. He has been a primary investigator in several epilepsy clinical trials and co-investigator in many others.
Winthrop-University Hospital is a 591-bed teaching hospital located on Long Island in Mineola, NY. A major regional healthcare resource, the Hospital has been a leading healthcare provider for more than a century, dedicated to the integrity, dignity and well-being of every individual. Winthrop offers a full complement of advanced inpatient and outpatient services with a deep commitment to medical education and research.

Physicians and surgeons in Winthrop’s Institute for Neurosciences are pioneering the use of technologically advanced approaches for the diagnosis and treatment of diseases of the brain and spine, including computerized imaging systems, state-of-the-art surgical interventions and the latest generation of medication therapies.

The Institute’s interdisciplinary team includes neurologists; neurosurgeons; neurointensivists; pediatric neurologists and neurosurgeons; neuroradiologists; vascular surgeons; orthopaedic spine surgeons; neuro-oncologists; neuropathologists; neurophysiologists; and specially trained nurse practitioners, physician assistants and nurses. Specialized physical and occupational therapy, social work and other supportive services are also key components of the Institute. The Institute’s experts are up to date on the latest developments in neuroscience and help pave the way for new discoveries through participation in clinical research trials, which enable them to provide patients with access to tomorrow’s most promising therapies.

Winthrop-University Hospital’s Institute for Neurosciences

Programs & Services Offered by the Institute for Neurosciences

Neuroscience Intensive Care Unit
The 14-bed acute care NeuroICU is reserved for patients with serious, complex neurological issues. The focus is on providing continuous monitoring and instantaneous results of critical values, allowing the expert staff, experienced in using advanced technology and providing neurocritical care, to employ aggressive interventions that treat neurological deterioration.

Neurology
- Epilepsy Program
- Movement Disorders Program
- Multiple Sclerosis Care Center
- Neuromuscular/Peripheral Neuropathy Program
- NYS Designated Stroke Center with AHA and ASA “Gold” Level Status

Neurosurgery
- Aneurysm Coiling & Clipping
- Disc Replacement
- Brain Aneurysm Program
- Brain Tumor Program
- Brain & Skull Base Surgery
- Carotid Stenting & Endarterectomy
- Cerebrovascular & Endovascular Surgery
- Chiari Decompression Surgery
- Complex & Minimally Invasive Spinal Surgeries
- Complex Cranial Surgery
- Computer-Assisted Resection of Brain Tumors
- CyberKnife® Radiosurgery
- Endoscopic Pituitary Surgery
- Epilepsy Surgery Program
- Facial Pain/Trigeminal Neuralgia Program
- Image-Guided Spine Surgery
- Kyphoplasty
- Merci®/Penumbra® Clot Retrieval
- Microdiscectomy
- Microneurosurgical Techniques
- Microvascular Decompression for Trigeminal Neuralgia
- Neuro-oncology
- Parkinson’s Disease Surgery Program
- Posterior Lumbar Interbody Fusion
- Prestige® Cervical Disc
- Programmable Shunt Placement
- Spinal Stimulation
- Spine Revision Surgery
- Stereotactic Radiosurgery
- Traumatic Brain & Spine Injury Diagnosis & Treatment
- X-Stop® for Spinal Stenosis

Neuroradiology
- Aneurysm Treatment
- CT Perfusion Scanning
- Interventional Neuroradiology
- Neuroangiography
- Neuro Diagnostic Lab
- Positron Emission Tomography (PET) Scanning
- Ultrafast Computed Tomography (CT) & Magnetic Resonance Imaging (MRI)

Pediatric Neurology & Neurosurgery
- Attention Disorders & Learning Disabilities Treatment
- Craniosynostosis Surgery
- Brain Tumor Treatment
- Evaluation & Treatment of Children with Headaches
- Evaluation & Treatment of Neurological Disorders
- Myelomeningocele Surgery
- Neuro Developmental Screening & Early Intervention
- Pediatric Intensive Care Unit
- Seizure Disorders Management
- Treatment for Hydrocephalus & Other CNS Anomalies

For more information, call the Institute for Neurosciences at 1-866-NEURO-RX.