

Leksell Stereotactic Radiosurgery for Vestibular Schwannomas: Tumor Control and Cranial Nerve Outcomes Up to 20 Years

by **Stephen Johnson, MD; Hideyuki Kano, MD, PhD; Andrew Faramand, MD;
Ajay Niranjana, MD, MBA; and L. Dade Lunsford, MD**

Vestibular schwannomas (VS), also known as acoustic neuromas, are primary brain tumors that account for 10% of newly diagnosed intracranial tumors and 80% of cerebellopontine angle tumors. Management options have evolved over the years, including microsurgical resection, fractionated radiation therapy, observation, and stereotactic radiosurgery (SRS). SRS is now the most common index treatment for newly diagnosed VS, as data noting safety, tumor control, and cranial nerve preservation have proliferated in recent years. The UPMC Gamma Knife® VS experience includes 1,951 patients over 30 years. Over this time, UPMC has updated its Leksell Gamma Knife technology five times and now uses both the Perfexion and Icon models. Dose parameters have also evolved over the years, with most patients now receiving 11.5-12.5 Gy to the tumor margin, which is a downward adjustment from our early experience. This has not been associated with any decrease in tumor control.

We performed a retrospective review of this database to evaluate long-term tumor control, cranial nerve functional outcomes, and hearing preservation. Eight hundred seventy-five patients underwent Gamma Knife Surgery (GKS) as a primary treatment for VS and had sufficient follow-up data for inclusion in this study. Mean follow-up was 5.2 years. Progression-free survival (PFS) 3, 5, 7, and 10 years after GKS was 97%, 95%, 95%, and 94%, respectively. Only larger tumor volumes were associated with progression. The median time to progression was 32 months, with most instances occurring between two and three years. Trigeminal neuropathy developed in 5.8% of patients and there were no instances of facial neuropathy with the current dosing protocol.

(Continued on Page 7)

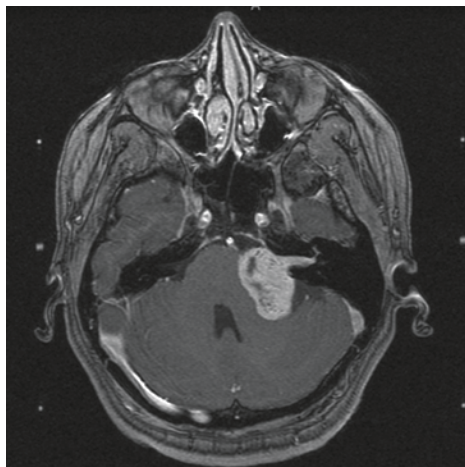


Figure 1: (Left) Axial MRI of VS patient in Leksell head frame on the day of GKS.

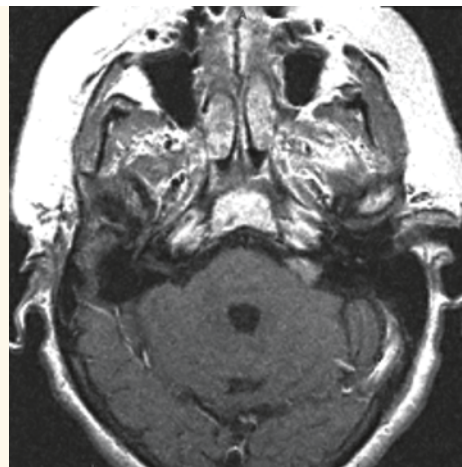


Figure 2: (Right) Follow-up MRI 10 years after GKS demonstrating tumor regression.

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Chairman's Message

Fresh, Innovative Ideas Redefine Our Field



At our recent chief resident graduation ceremony, it was remarked that, without innovation, we simply do the same thing over and over again. Without fresh approaches, we don't evolve.

Our main goal as neurosurgeons is to provide the best care for our patients. But as academic neurosurgeons, an equally important goal is to provide the means for young, brilliant medical minds to grow and stretch the boundaries of medical care for our patients.

We ask a great deal of our residents as they train to not only become the neurosurgeons of tomorrow, but more importantly, become the neurosurgical leaders of tomorrow. We ask these young neurosurgeons to take us to the next level.

Steve Jobs once famously said, "It doesn't make much sense to hire smart people and then tell them what to do; we hire smart people so they can tell us what to do." In the same sense, we train smart residents so they will eventually have the skills and mindset to innovatively tell us what to do.

The UPMC Department of Neurological Surgery has a proud 80+ year history of guiding bright, energetic medical minds. Scores of

graduates of our program are spread across the country — and the world — applying fresh approaches, and evolving practically every aspect of neurological care.

"Thinking outside the box" is not so much a saying, but a necessary approach to providing answers to old and new medical questions. We understand the how and why of neurosurgical care, but we must ask ourselves the "what else is there?" question. More often than not, this question leads to new avenues of care.

Whether it's through the innovative approach of a new mouthguard to better detect trauma in athletes as explored by Vincent Miele, the inquisitive look into the neurological benefits of medical marijuana as posed by Joe Maroon, or the continued building on the works of Jannetta, Lunsford, Gardner, Richardson, Pollack, Amankulor, Tyler-Kabara, Gerszten, Okonkwo, Sekula, Kanter, and others, the UPMC Department of Neurological Surgery has and will continue to redefine our field.

*Robert M. Friedlander, MD, MA
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Intraoperative Monitoring Changes in Somatosensory Evoked Potentials as Predictors of Perioperative Stroke in Carotid Endarterectomy

by Justin Meinert; Eyad Saca, MD; Partha Thirumala, MD; and Jeff Balzer, PhD

Significant changes in intraoperative neurophysiological monitoring reflected using somatosensory evoked potentials (SSEPs) is utilized to warn surgical teams of impending neurological complications during surgical procedures. Current alarm criteria used to identify significant changes suggest using a 50% decrease in SSEP amplitude or a 10% increase in latency as a threshold. In spine cases, the usefulness of this modality has been evaluated extensively and has become integral to the progression of the surgery. SSEP monitoring during vascular surgeries, specifically during carotid endarterectomy (CEA), is utilized but its implications need a more robust assessment in terms of alarm criteria.

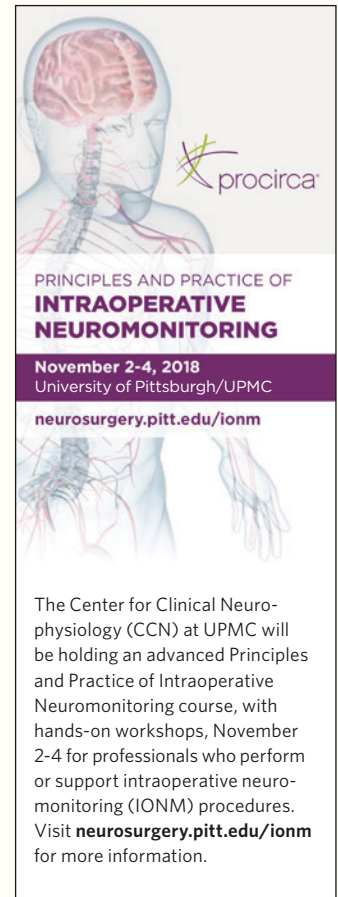
Perioperative stroke is a major complication after CEA. To date, our research at UPMC Center for Clinical Neurophysiology has shown that significant SSEP changes predict early and late stroke after CEA in both symptomatic and asymptomatic patients. With this study, we aimed to quantitatively evaluate the diagnostic value of SSEP changes in predicting stroke after CEA as it relates to alarm criteria for significant change.

We identified all perioperative strokes in patients who underwent CEA from 2010 to 2015 and paired them with a random control group. To quantitatively assess SSEP changes, amplitudes and latencies of the cortical SSEPs were measured at various critical and consistent times during the surgery (Figure 1). SSEP percentage changes were calculated from a pre-incision, post-induction baseline. Receiver operating characteristic (ROC) curves were utilized to assess the diagnostic accuracy of SSEP percentage changes in predicting perioperative stroke.

Amplitude percentage changes were significantly higher in the stroke group as compared to the control group. ROC curve analysis illustrated that SSEP amplitude changes strongly correlated with perioperative stroke status.

The current alarm criteria of a 50% decrease of amplitude had a sensitivity of 74.5% and a specificity of 62.4% for predicting stroke. Latency changes were also predictive; however, the alarm criteria of 10% prolongation proved to be a poor alarm.

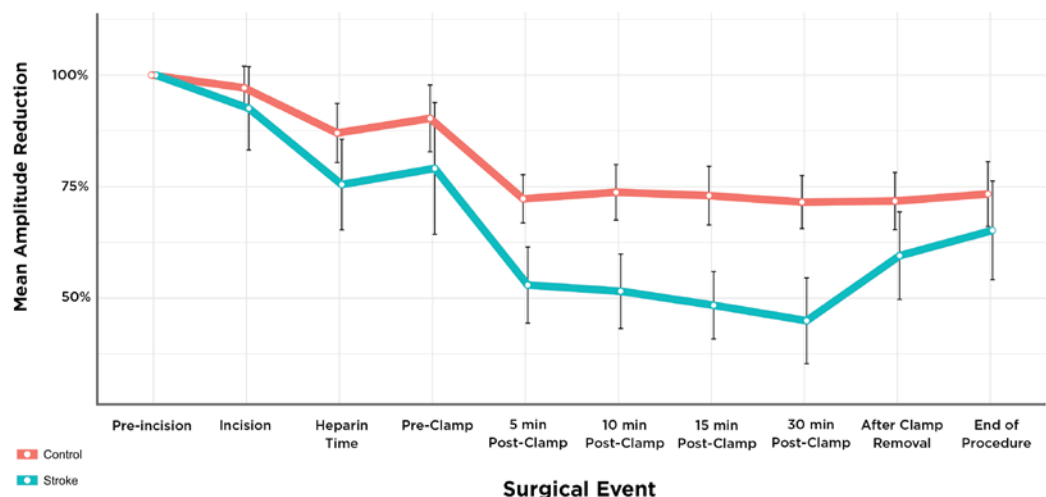
The results of this study support previous findings that SSEPs are useful in predicting perioperative strokes after CEA. It should be considered that the purpose of an alarm is to guide the surgical team and present a warning in a timeframe where intervention can still be effective. Latency changes do not appear to be very useful, especially at the current alarm of 10% prolongation. Since the current SSEP amplitude alarm criteria of a 50% decrease in amplitude is predictive of stroke, it may not be an effective alarm. We are currently conducting studies to determine what criteria indicates reversible ischemia in CEA to better guide intervention and further improve surgical outcomes.



PRINCIPLES AND PRACTICE OF INTRAOPERATIVE NEUROMONITORING
 November 2-4, 2018
 University of Pittsburgh/UPMC
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The Center for Clinical Neurophysiology (CCN) at UPMC will be holding an advanced Principles and Practice of Intraoperative Neuromonitoring course, with hands-on workshops, November 2-4 for professionals who perform or support intraoperative neuro-monitoring (IONM) procedures. Visit neurosurgery.pitt.edu/ionm for more information.

Figure 1: Mean percentage SSEP amplitude reduction at key surgical points. Error bars represent the 95% confidence interval. The x-axis represents each measured time point. The y-axis is the average percentage decrease from pre-incision. Amplitude changes are statistically different at each time point except pre-incision and end of procedure.



Intelligent Mouthguard Quantifies Head Impacts

by Joe Lemire

Vincent Miele was an amateur boxer as a teenager, who later became a ringside physician as a medical resident while training to be a neurosurgeon at West Virginia University. Along with the renowned Dr. Julian Bailes, the two conducted a video analysis comparing a control group of typical professional boxing matches with a set of highly competitive classic bouts and a set that ended with a fatality.

Their published research showed that there were no evident differences between the latter two cohorts with regard to the quantity of punches landed and the perceived force of those punches. It was not apparent from reviewing the matches with the assistance of the Punchstat computer program that one (the competitive match) or the other (the fatal match) would result in lethal damage to the competitors.

"It's really hard to tell," Miele, now a neurosurgeon at UPMC, told SportTechie. "Are they just tough? Are they getting hurt? Are the tough ones the ones who are going to get hurt? It's hard to say when to stop a fight. I wanted to come up with something objective to stop these fights."

The ambiguity gnawed at Miele. Around that time, he operated on a female boxer who had developed a subdural hematoma. She nearly died. He knew something had to be done.

While at West Virginia, Miele began tinkering with a mouthguard-based solution, but only after beginning his fellowship at Cleveland Clinic was the idea realized over years of painstaking work by a team that included neurosurgery chairman Ed Benzel, biomechanics engineering PhD Adam Bartsch, spine clinic director Lars Gilbertson, biomedical engineer Barry Kuban, and mechanical research engineer Sergey Samorezov.

The product of their work has been spun off into Prevent Biometrics' intelligent mouthguard that uses a flex circuit embedded with four accelerometers, each producing three channels of data, and an advanced algorithm that triangulates those 12 data points to measure head impacts in real-time. Among the metrics tabulated: linear acceleration, rotational acceleration, location on head, direction of impact and total number of impacts.

In a study published in the peer-reviewed *Stapp Journal*, the team reported that the mouthguard's precision in quantifying the force of blows was within five percent. Bartsch, now Prevent Biometrics' chief science officer, has called this accurate measurement of head impacts "the holy grail of concussion research."

When certain thresholds are crossed, the mouthguard lights up red and the Bluetooth technology alerts coaches and trainers on the sideline, so they can evaluate for a concussion or other impairment.



Figure 1: Intelligent mouthguard and smartphone user interface.

"If your exposure hits the red line, you're out of the fight — it's an electronic knockout, basically," Miele said. "That would save some of the tougher guys that can fight through those hits. It would save their brains."

The mouthguard was originally designed for boxing, where fighters don't wear helmets the way football players do. But in many cases helmet-based systems aren't reliable because the headwear moves too much. As Bartsch has written, "Although a number of published head impact studies have captured impressive-looking data using helmet- or skin-mounted sensors, these approaches yield erroneous head impact measures."

Miele said one's back teeth are about as close to the brain stem as one can get, calling the mouthguard "the next best thing to actually screwing an accelerometer to the skull to get readings."

"The reason a mouthguard works is because the mouthguard can securely couple to the upper arch of teeth, which is part of your skull, so it's a way of getting a coupling to the skull by proxy," Prevent Biometrics chief marketing officer David Sigel said. "It has nothing to do with the teeth. The only thing the teeth are doing are allowing you to connect to the head."

Research into neurological impairment has shown that concussions themselves aren't always the problem, and that the accumulation of sub-concussive hits are problematic. Miele likened the tallying of these hits to the old Nintendo game Mike Tyson's "Punch-Out!!" in which a bar on the top of the screen tracked the totality of blows. "It's not just the heavy punches, it's the accumulation," he said.

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Does Medical Marijuana Have Neurological Benefits?

by Joseph C. Maroon, MD, and Jeff Bost, PA-C

Numerous physical, psychological, and emotional benefits have been attributed to marijuana since its first reported use in 2,600 B.C. in a Chinese pharmacopoeia. The phytocannabinoids, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ 9-THC), are the most studied extracts from the cannabis sativa subspecies hemp, the primary source of CBD, and marijuana, the source of THC. CBD and Δ 9-THC interact uniquely with the endocannabinoid system (ECS) through direct and indirect actions and modulate and influence a variety of physiologic systems.

Neurological applications are now the major focus of renewed research using medical marijuana and phytocannabinoid extracts. Recent neurological uses include adjunctive treatment for malignant brain tumors, Parkinson's disease, Alzheimer's disease, multiple sclerosis, neuropathic pain, and the childhood seizure disorders Lennox-Gastaut and Dravet syndromes. In addition, their use in psychiatric and mood disorders, such as schizophrenia, anxiety, depression, addiction, post-concussion syndrome, and post-traumatic stress disorder are being studied.

Cannabinoid receptor pharmacology began in the late 1960s when Δ 9-THC was isolated and synthesized and found to be the primary psychoactive constituent of marijuana. The discovery in the early 1990s of specific membrane receptors for Δ 9-THC led to identification of the endogenous signaling system now known as ECS. Shortly after, the endogenous cannabinoids, N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were identified. The ECS consists of two major types of endogenous cannabinoid receptors (CB1 and CB2) located in the mammalian brain and throughout the central and peripheral nervous systems, including tissues associated with the immune system. The ECS is known to influence neuroplasticity, apoptosis, excitotoxicity, neuroinflammation, and cerebrovascular breakdown associated with degenerative disease, stroke, and brain trauma.

In 2014, the American Academy of Neurology published a review of 34 studies investigating the use of medical marijuana (as extracts, whole plants, and synthetic phytocannabinoids) for possible neurological clinical benefits. They found strong support for symptoms of spasticity and spasticity-related pain, excluding neuropathic pain, in the research using oral cannabis extracts. They reported inconclusive support for symptoms of urinary dysfunction, tremor, and dyskinesia.

Some of the most compelling medical marijuana research is in the areas of joint and spine pain relief and as a possible use to address the opioid addiction epidemic. Both THC and CBD alone

(which has no psychotropic effect like THC) provide analgesia through direct effect on the ECS. In addition, both have anti-inflammatory and anxiolytic properties that can benefit patients with acute and chronic spinal pain. We have used CBD clinically for osteoarthritic and discogenic pain syndromes with anecdotal good results.

Multiple studies have now shown that in pro-medical marijuana states there are fewer reported deaths from opioids, and there are no deaths related to marijuana overdose on record. Large randomized studies directly assessing chronic pain, reduced addiction, and the use of medical marijuana are under way.



A comprehensive safety and side effect review of CBD in 2016 in both animal and human studies described an excellent safety profile of CBD in humans at a wide variety of doses. The most commonly reported side effects were tiredness, diarrhea, and changes in appetite and weight. In studies comparing other medicinal drugs used for the treatment of these medical conditions, CBD also had a very favorable side effect profile. CBD does have interactions with common hepatic (drug)-metabolizing enzymes, belonging to the cytochrome P450 family. Therefore, interactions with drug transporters and interactions with some drugs must be considered.

THC, in contrast to CBD, can alter heart rate, blood pressure, or body temperature; induce catalepsy; and alter psychomotor and psychological functions. Impaired memory, weight gain, and gynecomastia have also been reported with chronic THC use. Adolescent use of marijuana has also been associated with impaired psychomotor development. Repeated use may result in long-lasting changes in brain function that can jeopardize educational, professional, and social development. Because of concerns regarding impaired neurodevelopment, as well as maternal and fetal exposure to the adverse effects of smoking, the American College of Obstetricians and Gynecologists recommends women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use.

Although federal and state laws are inconsistent about the legality of cannabis prescribing and use, its increasingly documented health benefits make it once again relevant in medicine. Current research indicates the phytocannabinoids have a powerful therapeutic potential in a variety of ailments primarily through their interaction with the ECS. CBD is of particular interest due to its wide-ranging capabilities and lack of side effects in a variety of neurological conditions and diseases.

Can Neurosurgery Residency Be Shorter Than Seven Years?

by **L. Dade Lunsford, MD**



In the United States, neurosurgery residency training takes seven years after medical school. It is longer than any other medical or surgical specialty. To answer the question, "Can neurosurgery residency be shorter than seven years?" we must ask what is the type of product we want to create at the end of residency training.

Neurosurgeons are bright, energetic, creative, focused, and often innovative. They enjoy the complexity of both

diagnosis and intervention in a wide variety of brain, spine, and peripheral nerve disorders. In more recent years, neurosurgery resident graduates have become increasingly subspecialized. During or, on occasion, immediately after residency, they gain special competence in various high technology fields. Endovascular, neuro-oncology, pediatrics, radiosurgery, and complex spine are examples of such focus. Even the American Board of Neurological Surgery has recognized this shift and begun to examine candidates for oral board certification, in part, related to their areas of subspecialty competence.

Most neurosurgeons either are, or will be, employees of medical centers or academic institutions. They may be part of a large neuroscience center, or a larger, multidisciplinary group practice. They will be recruited based on their general knowledge of neurosurgery so they can cover the most urgent or emergent neurosurgical care needs, plus a subspecialty focus that gives them a special niche at that center. Some trainees are destined for academic life, which still requires an investigative mind, a pedagogic ability, and the willingness to do research in some form (clinical or bench) and write about it. To advance up the academic ladder, they will need to demonstrate these aspects of their career and meet the perceived requirements of their employer.

We recently completed a 50-year assessment of our trainees at the University of Pittsburgh/UPMC. One of the goals was to assess whether the current generation of trainees (loosely speaking, the millennials) are, in fact, any different than prior trainees. We compared decade to decade. It was reassuring to note that the incidence of serious performance or professionalism issues has not changed over these past 50 years. The breed remains intact. What was found was that the reporting of resident-related concerns has increased significantly over the past ten years, which we relate to the ease with which complaints can be lodged via the ubiquitous electronic medical record.

To gain a niche, generally two additional years of training beyond core neurosurgery are needed. The answer to the question of shorter versus longer training needs to be couched in the question of whether or not our communities want generalists (basic neurosurgery of spine, trauma, routine intracranial tumors such as meningiomas and gliomas, and simple peripheral nerve disorders), or want neurosurgeons who are both generalists and subspecialists. I believe that competent general neurosurgeons can be trained in five years.

It is clear that the neurosurgery residency review committee has responded over the last 10 years to the increasing need for neurosurgeons. There are now 110 training programs, with the number of postgraduate year-one residents steadily increasing. It is less clear if this increased number of trainees is sufficient to meet a growing demand for neurosurgical services. Couple this trainee increase with the fact that older neurosurgeons are closing practices at younger ages, whether related to burnout or other factors that affect job satisfaction. In general, the survey of our trainees found recent graduates were just as satisfied as older graduates, although many reflected that our families sometimes pay a price.

Neurosurgeons who wish to subspecialize or are filling a job requiring special skills will need to train two additional years after reaching the generalist criteria. To change the current system, organized neurosurgery will need to answer many questions. If basic training is reduced to five years, who will pay for subsequent subspecialty training? Perhaps future employers will need to subsidize training with a stipend in return for a designated commitment. In a compensation system that seems to be based only on easily measured productivity (the RVU system is perhaps the worst perpetrated crime against U.S. medical care), why would a generalist refer to the specialist?

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News & Notes

UPMC Neurosurgeons Named Best Doctors

Seventeen UPMC neurosurgeons were named among this area's "Best Doctors" as part of the Best Doctors in America® list, published locally in *Pittsburgh Magazine*.

The list includes **Matt El-Kadi, MD, PhD; Robert M. Friedlander, MD; Paul A. Gardner, MD; Peter C. Gerszten, MD; D. Kojo Hamilton, MD; Brian T. Jankowitz, MD; Adam S. Kanter, MD; L. Dade Lunsford, MD; Joseph C. Maroon, MD; Edward A. Monaco, MD, PhD; John J. Moossy, MD; Ajay Niranjani, MD; David O. Okonkwo, MD, PhD; Ian Pollack, MD; R. Mark Richardson, MD, PhD; Raymond F. Sekula Jr., MD; and Elizabeth Tyler-Kabara, MD, PhD.**

These physicians are part of the Best Doctors in America® list, which is compiled by Best Doctors, Inc. An exhaustive peer review determines the physicians included in the list. Doctors cannot buy listings. Only those who earn the consensus support of their peers and meet additional qualification criteria are included.

Special Lectures and Appearances

L. Dade Lunsford, MD, presented the prestigious 2018 Van Wagenen Lecture at the American Association of Neurological Surgeons annual meeting in New Orleans on May 2.

Partha Thirumala, MD, was a visiting professor at the Christian Medical College in Vellore, India on March 3.

Congratulations

Partha Thirumala, MD, received the Top 10 Advances in Cranial Nerve Disorder Surgery recognition at the World Neurosurgeon Federation of Cranial Nerve Disorders conference in Shanghai.

Nitin Agarwal, MD, was the 2018 recipient of the AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves' Journalistic and Academic Neurosurgical Excellence (JANE) award for his paper titled, "Lateral Lumbar Interbody Fusion in the Elderly: A 10-Year Experience."

Kamil Nowicki, MD, PhD, tied for first place in the American Association of Neurological Surgeons (AANS) Neurosurgical Top Gun competition.

PGY-2 residents **Edward Andrews, MD**, and **Xiaoran Zhang, MD**, were nominees for the UPMC Physician Champion of Nursing Award. Physicians considered for this award are nominated by nurses for their care and support of nursing staff. Residents rarely receive nominations for this award.

Abstracts submitted by residents **Ezequiel Goldschmidt, MD, PhD**, and **Nitin Agarwal, MD**, were among the highest-scored abstracts of nearly 1,500 submitted to the Congress of Neurological Society (CNS) Scientific Program Committee. Both will share their work at the 2018 CNS Annual Meeting in Houston.

Leksell SRS for Vestibular Schwannomas *(Continued from Page 1)*

Serviceable hearing (Gardner Robertson Grade 1 or 2) preservation rates 3, 5, 7, and 10 years after GKS were 76.9%, 68.4%, 62.5%, and 51.4%, respectively. Multivariate analysis revealed that younger age, smaller tumor volume, and normal hearing (Gardner Robinson grade 1) at presentation were associated with higher rates of serviceable hearing preservation. Vertigo symptoms prior to SRS were associated with higher rates of hearing deterioration. This analysis was utilized to create a five-tier customized classification scheme according to age, tumor volume, and hearing status to better predict hearing outcomes for individual patients. A patient younger than 45 with grade 1 hearing and a small tumor has a greater than 90% chance of preservation of serviceable hearing 10 years after GKS.

In summary, GKS is safe and effective as a primary treatment for VS. There is extensive data supporting the goals of tumor growth control, cranial nerve functional preservation, and hearing preservation. Long-term data with extended 10-20 year follow-up continues to support this hypothesis. Our data supports the belief that patients should be treated within two years of diagnosis and before their hearing begins to worsen as the tumor grows.

Others contributing to this article include Edward Monaco III, MD, PhD; Matthew Pease, MD; Mohab Hassib, BA; David Spencer, BA; Nathaniel Sisterson, BA; Yoshio Arai, MD; and John C. Flickinger, MD.

Intelligent Mouthguard Quantifies Head Impacts *(Continued from Page 4)*

The way Little League has a strict pitch count for pitchers, Miele envisions football potentially incorporating some sort of hit count for players, especially linemen who inherently are involved in contact on every play. Syncing the mouthguard readings with video analysis can inform players and coaches of what situations and techniques lead to greater forces.

"It also can be used as a teaching tool for them," Miele said. "How can you lower your impacts? And there's an impetus for them to lower their impacts because they don't want to get pulled."

Miele is also an independent neurosurgical consultant for the NFL and the Pittsburgh Steelers. An objective head-impact measure

would alleviate the pressure of making subjective decisions regarding when to remove a player with a possible concussion — but that's not the ultimate goal.

"The NFL is nice, but again, the NFL is not the main focus of this mouthpiece, either," he said. "If the NFL adopts something, then everybody wants to do it. But the NFL is a very small number of players — the big thing is the high school kids and even the kids younger than high school age. If we can get it to them, that's where we're really going to help people."

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A \$16 billion world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC provides more than \$900 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates 80,000 employees, more than 30 hospitals, 600 doctors' offices and outpatient sites, and a 3.4 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. As UPMC works in close collaboration with the University of Pittsburgh Schools of the Health Sciences, *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside on its annual Honor Roll of America's Best Hospitals. UPMC Enterprises functions as the innovation and commercialization arm of UPMC, and UPMC International provides hands-on health care and management services with partners around the world. For more information, go to UPMC.com.

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