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Frameless Radiosurgery Ushers in New Era of Brain Tumor Treatment

In October, NewYork-Presbyterian/Weill Cornell Medical Center completed its conversion to frameless, non-invasive stereotactic radiosurgery for its Novalis radiosurgery program.

“Weill Cornell is at the forefront of the field for treating benign and malignant pathologies of the central nervous system using stereotactic radiosurgery,” says **Philip E. Stieg, MD, PhD**, Neurosurgeon-in-Chief, NewYork-Presbyterian/Weill Cornell and Chairman of the Weill Cornell Brain and Spine Center. “Frameless stereotactic radiosurgery eliminates the need to attach a frame to a patient’s skull, and the beauty of this approach is that it is equally as precise as all of the other radiation devices, it’s faster, less complex, pain free, and more comfortable for the patient.”



Dr. Susan C. Pannullo and Dr. A. Gabriella Wernicke

Radiosurgery stands as a unique field in medicine, drawing on the disciplines of neurosurgery, radiation oncology, and medical physics. At Weill Cornell, **Susan C. Pannullo, MD**, Director of Neuro-Oncology and Neurosurgical Radiosurgery, and **A. Gabriella Wernicke, MD, MSc**, a radiation oncologist who leads the

Cancer Therapy Program in the Department of Radiation Oncology and is a member of the Weill Cornell Brain and Spine Center, work in concert to plan and execute their patients’ treatment plans.

“Susan and I have a perfect marriage of two specialties – neurosurgery and radiation oncology – with a specific focus on the delivery of stereotactic radiosurgery treatments,” says Dr. Wernicke, whose

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Applying Deep Brain Stimulation to the Treatment of OCD

For patients with severe, refractory obsessive-compulsive disorder (OCD), deep brain stimulation (DBS) research and clinical trials are crucial to better understanding and treating this often debilitating disorder. Symptoms of OCD persist in 20 to 40 percent of patients despite therapeutic interventions of serotonin reuptake inhibitors (SRIs) and cognitive behavioral therapy (CBT), and as a result, emphasis on the importance of alternative treatments at NewYork-Presbyterian/Columbia University Medical Center is growing.

“We have two good first-line treatments,” says **Helen Blair Simpson, MD, PhD**, Director of the Anxiety Disorders Clinic at the New York State Psychiatric Institute. “With medications, many respond but the response is usually partial. With CBT, many respond but access is limited and

adherence varies. The good news is that maybe half will really be better, but that also means that half will continue to suffer.”

Dr. Simpson adds, “A patient would first go through treatment including SRIs and CBT, and the combination of the two. There are people who have gone through all of that and there’s still nothing that helps, and that is where DBS comes in. DBS is for a subset of OCD patients; not the majority.”

“Within the realm of psychiatry, DBS has seen the most progress in the treatment of OCD,” says **Sameer A. Sheth, MD, PhD**, Director and Founder of the Functional and Cognitive Neurophysiology Laboratory, Department of Neurosurgery at NewYork-Presbyterian/Columbia University Medical Center. “OCD is the only psychiatric disorder that

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academic and clinical interests have contributed new insights into the approach, delivery, and outcomes of radiotherapy. “Our combined efforts in building the stereotactic radiosurgery program began in 2010, and since its inception, we have introduced a number of novel treatment options for patients with a wide variety of tumors.”

Their pioneering collaborations, along with Weill Cornell colleagues, have addressed a number of hypofractionated stereotactic protocols for patients with meningioma, including a National Cancer Institute’s SEER (Surveillance, Epidemiology, and End Results) analysis of adjuvant external-beam radiotherapy (EBRT) outcomes for nonbenign meningiomas published in the *Journal of Neurosurgery* in 2012. This was the first population-based analysis examining the effect of adjuvant EBRT on outcomes in patients with nonbenign meningiomas. The study underscored the need for randomized prospective clinical trials to assess the usefulness of adjuvant EBRT and to define more precisely the subset of patients who may benefit from the addition of adjuvant radiation treatment in Grade II/III meningiomas.

In the last decade, improvements in imaging and computing have led to the development of image-guided frameless radiosurgery, a precise noninvasive variant offering improved patient comfort and treatment flexibility in addition to radiosurgical accuracy.

Today radiosurgery has become a key component in the neurosurgical armamentarium. In the last decade, improvements in imaging and computing have led to the development of image-guided frameless radiosurgery, a precise noninvasive variant offering improved patient comfort and treatment flexibility in addition to radiosurgical accuracy. It is used for patients with diagnoses that include brain metastases, glioblastomas, meningiomas, acoustic neuromas, and a variety of benign and malignant spinal tumors.

Transitioning to Frameless SRS

“We are entering a new phase of brain tumor treatment,” notes Dr. Pannullo, a neurosurgeon and a neuro-oncologist and one of the few neurosurgeons in the world with a neurosurgical practice focused only on stereotactic radiosurgery. “The transition to frameless radiosurgery marks the end of an era for our frame-based stereotactic radiosurgery program. The Novalis system enables us to treat tumors of the brain and spine, as well as other conditions, with highly focused beams of radiation that minimize exposure of normal brain and spine structures and achieve a level of accuracy comparable to frame-based radiosurgery. ExacTrac® technology, a component of Novalis, is a monitoring system that provides miniature images during the course of treatment that track any patient movement and allow for the machine to compensate by repositioning its beams.”

In conventional frame-based radiosurgical approaches, the

patient is immobilized with a head frame affixed to the skull and positioned before treatment by inferring the location of internal anatomy from external coordinates provided during the localization process. “In the past, a patient was bolted into a head-holder that was screwed into the skull to prevent movement,” says Dr. Pannullo.

“The frameless approach utilizes a head-to-shoulder immobilizing, removable mask that is extremely patient friendly,” says Dr. Wernicke. “We achieve absolute precision with targeting while delivering high doses, and at the same time sparing the normal structures. Precision-driven software, which makes adjustments based on the bony anatomy on the order of submillimeters automatically, detects intra-fractional tumor motion during the treatment delivery. This allows us to deliver single or multi-fraction treatment in the most precise manner possible and to identify the tumor target live in real-time with real-time verification.”

“If there is any small movement within the breathable, plastic face mask, it is detected,” notes Dr. Pannullo. “The beams, which come from multiple angles, reposition to account for any movement.”

“Efficiency is an important attribute for any image-guided radiotherapy system, especially given the growing patient demand for radiation therapy,” adds Dr. Wernicke. “One method to improve efficiency is to provide a more automated approach for the patient set-up and treatment. This novel technology provides either 4-D or a full 6-D robotic alignment. Furthermore, it allows us to condense the number of treatments from one to five fractions.” Treatments, delivered on an outpatient basis, range from half an hour to 45 minutes.

In addition to providing the latest in radiosurgical techniques, the Weill Cornell team has developed unique protocols not available elsewhere for the treatment of various tumors that further reduce the overall treatment time. “For instance, we treat meningiomas from the benign to atypical to malignant types with one to five fractions of radiotherapy within a week’s time,” says Dr. Wernicke. “This essentially avoids the previously utilized protocols of five to six weeks of five-day-a-week radiation. Our results are equivalent, if not superior, to the standard fractionation protocol used in other centers.”

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Both Drs. Wernicke and Pannullo cite the importance of the multidisciplinary nature of radiosurgery. “This frameless technology, in particular, allows us to work as a group to deliver the best treatment to patients with a range of conditions of the brain and spine,” says Dr. Pannullo. “It is a team effort by a neurosurgeon and a radiation oncologist along with physicists and radiation therapists. The neurosurgeon’s primary role is to outline the area that is to be treated, and also to define the areas that are to be avoided during the treatment. The primary role of the radiation

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has received a compassionate use exemption to allow DBS as a treatment modality.” In 2009, DBS was granted a limited humanitarian device exemption by the FDA, permitting its use in intractable OCD.

For the past two decades, DBS has been successfully utilized in the neurosurgical treatment of movement disorders such as Parkinson’s disease (PD), essential tremor, and dystonia. More recently, DBS has been used to treat psychiatric diseases, including OCD.

“With its success in treating movement disorders, groups in the late ‘90s started to ask whether DBS could be used to treat psychiatric disorders as well,” says Dr. Sheth. “One of the advantages there, as opposed to a lesion, is that a stimulating electrode is not a permanent change to the brain. You are putting in an electrode that you can turn off or even take out. You can also turn it on and off in a blinded fashion, making DBS amenable to study in randomized clinical trial protocols.”

According to Dr. Sheth, brain imaging of patients with OCD compared to normal subjects shows differences – at an anatomical and likely a neurochemical level – in various regions of the cortex, including prefrontal areas such as the orbitofrontal and cingulate cortex. There are also differences in the basal ganglia structures.

Current research is guided by both understanding brain circuitry as well as deconstruction of the disorder into pathological components. At this point, DBS is intended to be used in conjunction



Dr. Sameer A. Sheth

with other therapies to treat patients with refractory OCD. In addition, DBS may allow us to “gain an understanding of the brain mechanisms underlying obsessions and compulsions to lead us to novel treatments in the future,” says Dr. Simpson.

There remain relatively few publications on the effects of DBS on OCD, and the million-dollar question, as both Dr. Sheth and Dr. Simpson say they seek to understand through their research, is: Who is most likely to benefit? In this nascent area of investigation for neurosurgery, they stress excitedly there is a lot more to be learned.

“The future will show how effective it is and whether we can predict who is most likely to benefit,” says Dr. Sheth. “The

number of indications for DBS seems to be increasing as we learn more about the different parts of the brain, how they function, and how their dysfunction underlies the pathophysiological mechanism of OCD and other disorders.”

“Columbia University has expertise in DBS for movement disorders and could become a leader in applying DBS to select psychiatric disorders,” says Dr. Simpson. “The idea here moving forward is to do this extremely carefully and with the goal that it’s always in the best interest of our patients and advancing the science.”

The Departments of Psychiatry, Neurosurgery, and Neurology at NewYork-Presbyterian/Columbia have launched a new clinical service offering stereotactic lesions and deep brain stimulation for patients with severe, refractory OCD.

For more information or to make a referral, call (646) 317-4638.

Reference Articles

Karas PJ, Mikell CB, Christian E, Liker MA, Sheth SA. Deep brain stimulation: a mechanistic and clinical update. *Neurosurgical Focus*. 2013 Nov;35(5):E1.

Mian MK, Campos M, Sheth SA, Eskandar EN. Deep brain stimulation for obsessive-compulsive disorder: past, present, and future. *Neurosurgical Focus*. 2010 Aug;29(2):E10.

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oncologist is to determine the appropriate dosing and directly oversee the treatment. The physicist helps to construct the safest and most optimal treatment plan, which is then approved by the neurosurgeon and the radiation oncologist.”

“We work together to develop the treatment plan, execute the treatments, follow patients in their after-treatment care, and review their results in our weekly multidisciplinary Brain and Spine Tumor Board,” says Dr. Wernicke.

As radiosurgery becomes more and more a part of brain tumor and spine treatment, Dr. Pannullo notes that she will meet with the neurosurgeon who is performing open surgery preoperatively to develop a combined treatment approach. “The advantage is that the neurosurgeon can then go into the OR with a plan to leave a portion of tumor that would otherwise be very risky to remove with the

knowledge that I can follow up with radiosurgery on that remaining piece of tumor,” says Dr. Pannullo. “An adaptive hybrid surgery analysis is built into the Novalis system, enabling us to bring the benefits of both approaches to maximize the treatment outcome.”

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Stessin AM, Schwartz A, Judanin G, Pannullo SC, Boockvar JA, Schwartz TH, Stieg PE, Wernicke AG. Does adjuvant external-beam radiotherapy improve outcomes for nonbenign meningiomas? A Surveillance, Epidemiology, and End Results (SEER)-based analysis. *Journal of Neurosurgery*. 2012 Oct;117(4):669-75.

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Clinical Trials Update: NewYork-Presbyterian Hospital Participating in NeuroNEXT Clinical Trial for Progressive Multiple Sclerosis (SPRINT-MS)

NeuroNEXT, a National Institute of Neurological Disorders and Stroke initiative to conduct Phase II trials in neurological conditions, has committed funding for a clinical trial for progressive multiple sclerosis (MS).

Patients with multiple sclerosis are characterized into one of three variants: relapsing-remitting, secondary progressive, and primary progressive. Despite recent improvements in pharmacotherapy for relapsing-remitting multiple sclerosis, there are no therapies with demonstrated efficacy in either secondary progressive or primary progressive multiple sclerosis in the absence of relapses.

This research study is being conducted to determine the safety, tolerability, and activity of ibudilast (MN-166) administered orally twice daily over a 96-week period in subjects with primary and secondary progressive multiple sclerosis. A total of 250 male and female subjects from 21 to 65 years old, inclusive, are planned to be enrolled into two treatment arms (ibudilast or matching-placebo).

Subjects may be on injectable immunomodulating therapies (interferon-beta or glatiramer acetate) or on no immunomodulating therapies. The trial will utilize advanced brain imaging to assess disease progression and correlate clinical activity with these imaging measures.

The study is being conducted at NewYork-Presbyterian/Columbia, NewYork-Presbyterian/Weill Cornell, and other NeuroNEXT sites around the country.

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Upcoming NeuroNEXT Studies

NN103 – A Phase II Trial of Rituximab in Myasthenia Gravis
Weill Cornell Medical College
Principal Investigator: Jonathan M. Goldstein, MD
Coordinator: Lauren Langford
Email: langfordl@hss.edu

Columbia University Medical Center
Principal Investigator: Thomas H. Brannagan, MD
Study will start soon.

NN104 – RHAPSODY:
Safety Evaluation of 3K3A-APC in Ischemic Stroke
Columbia University Medical Center
Principal Investigator: Jan Claassen, MD
Study will start soon.