Proton Beam Therapy in Minnesota and Arizona

For selected patients with neurological tumors, proton beam therapy can be an excellent alternative to conventional photon radiation. Proton beam therapy targets tumors more precisely, limiting damage to surrounding healthy organs and tissue and offering the possibility of using higher doses of radiation for more-beneficial outcomes.

Proton beam therapy is now available at Mayo Clinic’s campuses in Minnesota and Arizona (Figure 1). Both facilities use pencil beam scanning exclusively and are the first centers in the Midwest and Southwest to offer this advanced proton beam therapy technique. The program’s funding mechanism allows Mayo Clinic to offer proton beam therapy to patients at costs similar to intensity-modulated radiation therapy (IMRT).

“Mayo Clinic is providing a very unique approach,” says Bernard R. Bendok, M.D., chair of Neurosurgery at Mayo Clinic’s campus in Arizona. “With minimally invasive endoscopic and microsurgical skull base approaches, we can reduce tumor volume, and then treat the areas we can’t reach safely with proton beam therapy. Our multidisciplinary focus is creating novel treatment pathways that are safer for patients and offer better outcomes.”

Enhanced tumor targeting

Conventional photons are high-energy X-rays that completely penetrate tissue and lose some of their energy along their route — resulting in a relatively high entrance dose and some level of exit dose. In contrast, protons penetrate to a limited depth, based on the energy of the beam, and deposit most of their energy at the end of the beam.

“We’re able essentially to program the protons to stop at a specific point, so radiation delivery can conform to the tumor,” says Elizabeth Yan, M.D., a radiation oncologist at Mayo Clinic’s campus in Minnesota.

The pencil beam technology used at Mayo Clinic offers added precision. “The pencil beam delivers protons in a raster pattern at different specified depths, to better conform to the volume of tumor,” Dr. Yan says. “With a traditional scattered proton beam, physical shapers are placed in the pathway of the beam before it reaches the patient. This results in slightly more entrance dose before the beam reaches its target depth.”

Proton beam therapy can be particularly beneficial for patients with clival chordoma and chondrosarcoma (Figure 2). “In the past, those pathologies have been pretty resistant to conventional radiation treatment. Proton beam therapy allows us to deliver a higher radiation dose to the tumor without toxicity to the brainstem, optic nerve, pituitary gland and other surrounding structures,” notes Jamie J. Van Gompel, M.D., a
Interbody fusion is a common treatment for correcting spinal deformity or treating spinal instability. However, traditional interbody fusion involves dissection of the paraspinal muscles, which may result in significant blood loss or pain.

Mayo Clinic neurosurgeons have extensive experience with minimally invasive procedures for interbody fusion, including lateral interbody fusion and percutaneous interbody fusion. Both procedures can offer patients minimal blood loss, less pain, shorter hospitalization and quicker recovery.

“The mainstay of spinal surgery has been removal of bone,” says Mohamad Bydon, M.D., a consultant in Neurosurgery at Mayo Clinic in Rochester, Minnesota, who frequently performs lateral and percutaneous interbody fusions.

Avoiding muscle disruption
Anterolateral and percutaneous interbody fusions require minimal dissection of muscle. In anterolateral interbody fusion, the spine is approached from the left side anterior to the psoas major, thereby avoiding that muscle and its many nerves (Figure 1). “The advantage is avoiding disruption of the posterior muscles. Dissecting the paraspinal muscles can be a major source of pain and
instability down the road,” Dr. Bydon notes.

The procedure can be especially helpful for a patient who has had prior fusion surgery but now needs spinal surgery above the previous surgical site. “Rather than a large dissection with possible removal of instrumentation from the prior surgery, select patients with adjacent segment disease may be approached laterally in a minimally invasive fashion,” Dr. Bydon says. Blood loss is minimized — usually less than 100 cubic centimeters (cc), compared with 300 to 500 cc with an open procedure — and patients frequently return home one day after surgery.

In cases where anterolateral interbody fusion is not recommended, percutaneous interbody fusion (Figure 2) may be performed posteriorly through small incisions. At Mayo Clinic, intra-operative imaging is an essential component of these specialized minimally invasive spinal surgeries. Advanced neuronavigation technology minimizes patients’ exposure to radiation.

“These minimally invasive techniques enable us to do spinal surgeries less disruptively, allowing for quicker recovery with lower blood loss, smaller incisions, reduced risk of infection and diminished reliance on pain medicine,” Dr. Bydon says.

**Figure 1.** Lateral (left) and anteroposterior (right) X-rays show L4-5 percutaneous screws and interbody spacer placed through an antero-psoas anterolateral approach.

**Figure 2.** Anteroposterior (left) and lateral (right) X-rays show percutaneous screws and percutaneous interbody fusion at L4-5.

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**NMO: Defining the Spectrum, Discovering New Treatments**

Neuromyelitis optica (NMO) is a relapsing inflammatory demyelinating disease distinct from multiple sclerosis (MS) that most commonly affects optic nerves and the spinal cord. Historically misdiagnosed as MS, NMO is characterized by more-severe attacks and less complete recovery. A single NMO attack can leave a patient blind or paraplegic.

Accurate and timely diagnosis is critical, as treatments that are effective for MS or other demyelinating disorders might be ineffective or even harmful for patients with NMO. Once considered an orphan disease, NMO might affect as many as half a million people worldwide, according to a recent Mayo Clinic study that also found the disease is 2.5 times more common in people of African descent than in Caucasians.

Mayo Clinic is a recognized center of excellence for the diagnosis and treatment of NMO. In 2004, Mayo Clinic researchers led by Vanda A. Lennon, M.D., Ph.D., reported the discovery of the first biomarker for the condition — serum aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies. In 2015, an international consensus panel chaired by Mayo Clinic neurologists introduced new diagnostic criteria and defined the unifying term *neuromyelitis optica spectrum disorders* (NMOSD) to acknowledge that some patients with AQP4-IgG antibodies have recurrent transverse myelitis without optic neuritis and vice versa.

“The unified term is meant to capture a series of clinical and MRI patterns associated with AQP4-IgG,” says Dean M. Wingerchuk, M.D., a consultant in Neurology at Mayo Clinic in Phoenix/Scottsdale, Arizona, and co-chair of the consensus panel.

“The new consensus criteria are meant to guide clinicians toward recognition of these key clinical and MRI patterns, so they can establish a confident diagnosis and initiate treatment.”
“Mayo Clinic has led the way in advancing therapeutic approaches for the treatment of both the acute attack — myelitis or optic neuritis — with plasmapheresis and prevention of attacks with immunosuppressant medications,” adds Sean J. Pittock, M.D., director of the Center for Multiple Sclerosis and Autoimmune Neurology at Mayo Clinic in Rochester, Minnesota.

**New diagnostic criteria**

Prior diagnostic criteria for NMO required optic nerve and spinal cord involvement, although more-restrictive or more-extensive central nervous system involvement was known to occur. Under the new criteria, as outlined in the July 14, 2015, issue of *Neurology*, a diagnosis of optic neuritis and myelitis is no longer required to identify NMOSD if serum tests are positive for AQP4-IgG antibodies. More-stringent clinical criteria, with additional neuroimaging findings, are required for NMOSD without AQP4-IgG or when serologic testing is unavailable. Early-stage diagnostic specificity is critical because some established MS therapies — such as interferon-beta, natalizumab, fingolimod and alemtuzumab — appear to aggravate NMOSD.

“We expect the new criteria to increase the number of both seropositive and seronegative cases, and shorten the time from symptom onset to diagnosis and appropriate treatment,” Dr. Wingerchuk says.

About 15 to 20 percent of patients with NMOSD test negative for AQP4-IgG. “These cases present a diagnostic conundrum,” says Eoin P. Flanagan, M.B., B.Ch., a consultant in Neurology at Mayo Clinic’s campus in Minnesota. To capture more of these cases, Mayo Clinic researchers are investigating additional biomarkers of inflammatory demyelinating diseases — some of which have similar phenotypes to NMOSD, including anti-myelin oligodendrocyte glycoprotein (MOG) antibodies.

“Mayo Clinic’s neuroimmunology laboratory has developed a live cell flow cytometry assay to detect MOG antibodies, and this will be available as an orderable test soon,” Dr. Pittock says. “We have found that up to one-third of AQP4 IgG-negative NMO cases and a similar proportion of pediatric acute disseminated encephalomyelitis cases test positive. Interestingly, patients with AQP4-IgG — where the target cell is the astrocyte — may have a very similar phenotype to patients with MOG IgG, where the target cell is the oligodendrocyte.”

The results of several recent Mayo Clinic studies are helping to further refine diagnosis of NMOSD:

- In a study published in the January 2015 issue of *JAMA Neurology*, Dr. Flanagan and colleagues found that short transverse myelitis — historically considered uncharacteristic of NMOSD — is not uncommon in the disorders and can delay diagnosis and treatment. “About 14 percent of NMOSD cases can have short lesions. Their presence doesn’t exclude a diagnosis of NMOSD,” Dr. Flanagan says. Other attributes associated with these short-lesion NMOSD cases included nonwhite race, tonic spasms, coexisting autoimmunity and lack of oligoclonal bands in cerebral spinal fluid.

- In a population-based comparative study published in the May 2016 issue of *Annals of Neurology*, Mayo Clinic researchers found that the incidence of NMOSD is about 2.5 times greater among people of African descent than among Caucasians. The researchers analyzed blood from individuals with inflammatory demyelinating diseases in Martinique (90 percent Afro-Caribbean) and Olmsted County, Minnesota (82 percent Caucasian). Results showed that NMOSD affects 10 out of 100,000 people in Martinique and 3.9 out of 100,000 people in Olmsted County. The age at onset (median 35 to 37 years) was similar in both populations. The researchers estimate that NMOSD affects 16,000 to 17,000 people in the United States.
In a study published in the March 2016 issue of *Annals of Neurology*, Mayo Clinic researchers compared long myelitis of spinal cord sarcoidosis with that of NMOSD and found the MRI results to be particularly helpful in distinguishing these disorders. A long, linear enhancement pattern in the posterior of the spinal cord was characteristic of spinal cord sarcoidosis (Figure 1). “We found a ringlike enhancement in the spinal cord favored NMOSD,” Dr. Flanagan says. NMOSD patients in the study also were more commonly women and were likelier to have systemic autoimmunity, concurrent or prior optic neuritis, and intractable vomiting episodes.

Nausea and vomiting associated with NMOSD are due to the occurrence of lesions in the AQP4-enriched area postrema (Figure 2). “The first symptom for about 12 percent of people with NMOSD is intractable nausea or vomiting,” Dr. Pittock notes. “These patients have multiple gastrointestinal investigations that don’t find anything.”

**Clinical trials**

The Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology is home to a large group of collaborative multidisciplinary physicians and basic scientists who are recognized leaders in understanding the immunopathogenic mechanisms of the disease and identification of novel therapeutic targets. Phase 3 clinical trials of a new immunosuppressant, the complement inhibitor eculizumab, are underway at Mayo Clinic’s campuses in Minnesota and Arizona.

“Activation of complement is probably one of the very early immunological events that cause NMOSD attacks,” Dr. Wingerchuk says. “In a phase 2 study of patients with highly active NMOSD with AQP4-IgG, we found that almost all subjects remained attack-free during one year of eculizumab therapy and that several of them relapsed once the drug was stopped. If the data from the phase 3 trial show that eculizumab is safe and effective, it will be an important targeted immunotherapy option for NMOSD patients.”

**For more information**


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**Heart Brain Clinic: Team Approach to Stroke**

Each year in the United States, more than 800,000 people experience a stroke. It is the fourth-leading cause of death and the leading cause of serious, long-term disability in adults. Preventing stroke or transient ischemic attack is complicated by the fact that patients often have coexisting neurological and cardiovascular conditions.

Mayo Clinic in Rochester, Minnesota, has created a Heart Brain Clinic to provide multidisciplinary evaluations for patients with neurological symptoms that may be due to a cardiac etiology, such as atrial fibrillation (AF) or patent foramen ovale (PFO) (Figure). Specialists from Cerebrovascular Diseases in Mayo Clinic Neurology and specialists in Cardiovascular Diseases collaboratively evaluate patients, meet to discuss cases, make joint recommendations for management, and educate patients and their families.

“One can get a very different perspective on a patient’s cardiac and neurological evaluations when they are discussed directly between a neurologist and a cardiologist, rather than being considered in isolation,” says Robert D. Brown Jr., M.D., a consultant in Neurology at Mayo Clinic’s campus in Minnesota and co-director of the Heart Brain Clinic. “That’s the beauty of both groups coming together to evaluate the patient at the same time, in the same setting.”

**Expertise in AF and PFO**

About 25 percent of cerebral infarctions are caused by a cardiac disorder. In addition to its top ranking in neurology, Mayo Clinic is highly ranked in cardiology and cardiac surgery. Specialists in the Mayo Clinic Cardiac Catheterization Laboratory pioneered catheterization-based techniques for diagnosis and treatment of cardiac conditions.

AF is associated with up to 20 percent of strokes, and is particularly common in older patients. Based on autopsy and echocardiographic studies, the vast majority of strokes in individuals with nonvalvular AF are believed to
be embolic in nature. Although anticoagulation has been found to be effective for stroke prevention, standard anticoagulation regimens may be problematic for individuals who have had prior brain or systemic hemorrhage, or those who are otherwise at high risk of having a bleeding complication.

“With both cardiologists and neurologists discussing the best management approach, we can collaboratively assess the risks compared with the benefits of putting patients on an anticoagulant medication, or considering their suitability for treatment with what is called a closure device,” Dr. Brown says.

Similar balancing of risks and benefits is applied to patients with PFO, which are present in as many as 25 percent of adults. Although these interatrial shunts often are asymptomatic and of no hemodynamic importance, there are some patients in whom the PFO will allow a venous clot to pass into the arterial system, leading to a potential ischemic event. Sluggish blood flow and the funnel-shaped interatrial connection created by some PFOs may facilitate the in situ formation of thrombi. However, PFO can be an incidental finding in a patient who has had a stroke or transient ischemic attack, posing limited, if any, risk of future stroke occurrence.

“When the neurologist sits down with cardiologists to discuss stroke patients who have been found to have a PFO, we can determine whether every other cause of stroke has been ruled out and, if so, whether the PFO may have been related to the stroke. We can then decide whether the PFO should be treated medically or with PFO closure,” Dr. Brown says. “By having this conversation, we can talk through the complexities of the individual patient’s history and exam and evaluation results, and then arrive at the best treatment recommendation.”

Figure. A 63-year-old woman with a remote history of migraine headache awakened with a headache with visual aura, as well as nausea, vomiting and incoordination. She was a former smoker but had no history of hypertension or estrogen replacement, and no family history of stroke. A and B. MRI demonstrated a left cerebellar infarct. C and D. Transesophageal echocardiography demonstrated a large patent foramen ovale (arrow) with an atrial septal aneurysm. E. Contrast injection demonstrated generous flow across the patent foramen ovale (arrow) with Valsalva maneuver. Percutaneous closure was performed.
Research Highlights in Neurology and Neurosurgery

Predicting the End of Symptomatic Relapses in MS
In 14 percent of patients with multiple sclerosis (MS), relapses may continue after the onset of the progressive phase of disease. Even in patients with primary progressive MS, post-progression relapses can occur. In a global study, researchers at Mayo Clinic in Rochester, Minnesota, and colleagues set out to define the overlapping period in late relapsing-remitting MS and the early progressive phase of MS. The researchers studied age at first relapse, age at onset of progressive MS, and age at last relapse before or after progressive MS onset in 964 patients from clinic- and population-based MS cohorts. The overlapping age range for relapsing-remitting and progressive phases of MS as well as absolute lifetime risk of relapse after onset of progressive MS were calculated. The median age at first relapse was 32.6 years. The median age at progressive MS onset was 45.9 years, and the median age at last relapse was 42.0 years. Overall, the researchers found a notable chance that relapses will occur the first time or continue in patients between the ages of 27 and 47, regardless of whether the patients are in the progressive phase of MS. The absolute lifelong risk of further relapses was 18 percent before age 35, but dropped to 5 percent after age 55. The researchers suggest that these age limits can be used to guide decisions about initiating or continuing disease-modifying treatments after the onset of progressive MS. (Novotna M, et al. Predicting the end of symptomatic relapses and disease modifying treatment use decisions in progressive multiple sclerosis. Presentation at: American Academy of Neurology Annual Meeting; 2016; Vancouver, British Columbia, Canada.)

Hand Postures in Generalized Tonic-Clonic Seizures
Epilepsy classification is largely based on patient history, MRI and interictal electroencephalogram (EEG). However, even video-EEG occasionally fails to provide a definitive diagnosis. Researchers at Mayo Clinic in Jacksonville, Florida, have found that distinct ictal hand and finger posturing is present in patients with generalized epilepsy (GE), localization-related epilepsy (LRE) and nonepileptic attacks (NEA). The researchers retrospectively analyzed 98 consecutive videos of generalized convulsions in 64 patients admitted to the epilepsy monitoring unit at Mayo Clinic’s campus in Florida. Hand postures were divided into fanning, fisting, index-finger pointing, clawing and flaccid hand. The postures were compared among patients with LRE, GE and NEA for each stage of the seizure. Index-finger pointing was the most common posture in LRE — present in 96 percent of LRE seizures studied. In GE the most common posture was fanning, occurring in 91.3 percent of seizures and only during seizure onset. The most common hand posture in NEA was the flaccid hand posture. The clawing posture occurred exclusively in NEA. The results suggest that hand posturing during seizures provides unique information and can aid in differential diagnosis and classification of epilepsy. (Siegel J, et al. Hand postures in primary and secondary generalized tonic-clonic seizures: A new semiological feature. Presentation at: American Academy of Neurology Annual Meeting; 2016; Vancouver, British Columbia, Canada.)

AAN Honors Mayo Clinic Researchers
Two Mayo Clinic researchers were awarded top prizes at the annual meeting of the American Academy of Neurology in Vancouver, British Columbia, Canada. Claudia F. Luchinetti, M.D., chair of Neurology at Mayo Clinic in Rochester, Minnesota, received the 2016 John Dystel Prize for Multiple Sclerosis Research. Rosa Rademakers, Ph.D., who directs the Frontotemporal Dementia and Related Disorders Laboratory at Mayo Clinic in Jacksonville, Florida, received the 2016 Potamkin Prize for Research in Pick’s, Alzheimer’s and Related Diseases. Dr. Luchinetti’s research focuses on the immunopathology and pathogenesis of demyelinating diseases. Her seminal observations of brain-tissue patterns in patients with multiple sclerosis (MS) suggested that the disease targets individual patients differently and that personalized-medicine approaches might be needed. Her landmark study, published in 2000, led her to launch the international MS Lesion Project, a collaborative study of the clinical, serologic, genetic and radiologic aspects of the MS lesion. Dr. Luchinetti’s research has also characterized the presence of early inflammatory cortical demyelination in MS, revolutionizing thinking about the mechanisms responsible for lesion formation and disease progression, and paving the way for new treatment strategies. Dr. Rademakers’ laboratory has made several significant discoveries in the molecular genetics of Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and Parkinson’s disease-related syndromes. In 2011, her laboratory identified an unusual mutation of the C9orf72 gene as the most common cause of ALS and FTD. The researchers have since discovered several genetic factors that help explain why some people with the C9orf72 mutation develop ALS while others develop FTD.

To read more about Mayo Clinic neurosciences research and patient care, visit http://www.mayoclinic.org /medical-professionals.
Expedited Patient Referrals to Mayo Clinic Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease