MAYO CLINIC

Neurosciences Update

Neurologic Surgery and Clinical Neurology News

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INSIDE THIS ISSUE

Glioblastoma: Surgical Advances and Immunologic Findings

Glioblastomas, the most common and aggressive primary brain tumors, have been called *grow and go* tumors. They not only grow rapidly at a given site, they also move rapidly to new sites. As a neurosurgeon and immunobiologist, Ian F. Parney, MD, PhD, approaches glioblastoma from both a clinical and a research perspective. In the clinical sphere, he is using novel techniques to reduce functional complications during surgical resection of large tumors. On the research front, he and his coinvestigators at Mayo Clinic in Rochester, Minnesota, have made two recent discoveries that help explain mechanisms of immune suppression and tumor recurrence and that advance understanding of potential targets for immunotherapy.

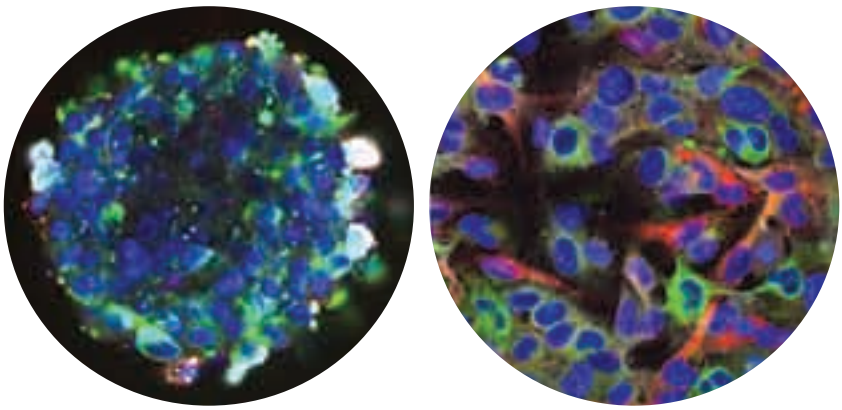


Figure. *Fluorescent micrographs showing glioma stem cells (left; growing as spheres) and differentiated glioma cells (right; growing as a monolayer) in culture. Nuclei are stained dark blue in both cultures. Turquoise, green, and red stains represent markers for oligodendroglial (O4), neuronal (B-tubulin), and astrocytic (GFAP) differentiation. Glioma stem cells express minimal glioneuronal differentiation markers, but these markers are highly expressed by differentiated glioma cells, a finding that demonstrates the ability of differentiated glioma stem cells to have pluripotency.*

Tumor Resection: Improvements in Preserving Function

Dr Parney notes that there is increasing evidence that in low- to intermediate-grade gliomas, the more tumor removed, the better the outcome—a difference that can be measured in years, not just weeks or months. Removing large gliomas while sparing as much function as possible is a difficult challenge. To meet it, Dr Parney and colleagues have been combining intraoperative MRI (iMRI) with functional brain mapping during awake craniotomy. Among the few institutions worldwide that have reported using this technique, Mayo Clinic has the largest series of cases.

Initial reports of combining electrophysiologic brain mapping (EPM) with iMRI used low-field (0.2-0.5 tesla) scanners. Mayo is fortunate to have a high-field (1.5 tesla) scanner that generates high-resolution 3-D images for presurgical planning and image reregistration during surgery. High-field iMRI improves image guidance and accuracy of brain-shift measurements during surgery. It thus facilitates more extensive tumor resection.

Functional imaging, such as fMRI, can be incorporated into image-guidance systems, but brain shift during surgery can make fMRI interpretation problematic. EPM is considered the gold standard for functional brain mapping, offering the most precise localization of

eloquent cortex. However, use of EPM with high-field scanners has been difficult because the patient's head and entire upper body must be cocooned in sterile drapes. Extensive draping can interfere with airway protection in sedated patients and can make alert patients feel claustrophobic during brain monitoring.

To address the problem, Dr Parney and colleagues designed a technique of minimal draping that allows safe and comfortable intraoperative EPM while high-field iMRI is used. The utility of the combined techniques was demonstrated in a patient in whom EPM showed a critical speech area to be approximately 1 cm away from the speech areas identified on fMRI (*World Neurosurgery*, in press). Dr Parney states, "Combining EPM and iMRI is the best of both worlds. We've been very successful in removing more tumor while keeping our complication rates extremely low."

Ian F. Parney, MD, PhD

Treatment Outcomes in Elderly Patients

Aggressive management of glioblastoma in the elderly must be weighed against age-related health risks. However, in a recent five-year retrospective study of 105 patients aged 65 years and older, Dr Parney, Shota Tanaka, MD, and colleagues found that elderly patients who had standard surgery, irradiation, and chemotherapy had more positive outcomes than those who did not have treatment and those who had been treated in a previous 10-year retrospective study. Dr Parney speculates that one reason for this result may be that chemotherapy drugs, such as temozolomide, have improved outcomes in the general population. He cautions that deciding to treat glioblastoma in elderly patients must be done on a case-by-case basis but that "although the risks may be higher for them, the benefits are there."

New Directions in Immunotherapy Research

Dr Parney notes that "even with the most aggressive resection, microscopic tumor cells that the surgeon cannot see will remain." The growth of these cells, combined with their possible immune-suppressing mechanisms, may explain relentless recurrence of glioblastoma and its resistance to chemotherapy. Previous immunotherapies, such as dendritic cell vaccines and immunogene therapy, have not successfully translated from animals to humans. However, two recent discoveries by Mayo researchers under the direction of Dr Parney and Allan B. Dietz, PhD, head of Mayo's Human Cellular Therapy Laboratory, have helped explain why. Their work sheds light on the role of glioma-mediated immunosuppression and points to a new direction in designing immune-mediated treatments.

Tumor-Based Reeducation of Normal Monocytes

As in other cancers with tumor burden, glioblastomas are heavily infiltrated with myeloid-derived suppressor cells (MDSCs), which are white blood cells similar to a normal macrophage but specialized to suppress immune responses within the tumor. Drs Dietz and Parney and their colleagues hypothesized that normal human monocytes exposed to glioblastoma cells assume an immune-suppressing phenotype similar to MDSCs and that the level of MDSCs is increased in the peripheral blood of patients with glioblastoma compared with healthy control subjects. Their findings support these hypotheses and help explain the systemic (vs local) suppression effects of gliomas on the immune system. From their research, it appears that normal monocytes infiltrate the tumor, where they receive an immunosuppressive "education" before returning to the bloodstream. When they are again in the peripheral blood supply, they, like MDSCs, work to suppress the immune system.

A New Vaccine Target: Brainstem Tumor Cells

Until the discovery of neural stem cells that can produce neurons in the adult CNS, glioblastoma was thought to be caused by changes in the astrocyte. That theory has been called into question with the discovery of another type of stem cell called *brainstem tumor cell* (BSTC) (Figure, see page 1). Newer theories suggest that these cells might arise from normal stem cells. BSTCs help drive tumor growth and may be a major factor in tumor recurrence. They also may be the cells that are the most resistant to chemotherapy and irradiation.

For all these reasons, Dr Parney and his team decided to focus on BSTCs as potential targets for immunotherapy. The first step was to investigate ways in which BSTCs differ from normal neural stem cells. Using a neurosphere culture system, Dr Parney and colleagues have been able to reproduce BSTC survival and proliferation independent of exogenous mitogenic stimulation both in vitro and in vivo. Their findings have important implications for identifying the reproductive mechanisms of BSTCs and the pathways that might be used to target them without affecting normal neural stem cells. Together with improved understanding of the mechanism's immunosuppression, this work represents a critical step toward the development of an effective vaccine.

Supporting Neuronal Growth: Regenerative Neuroscience at Mayo Clinic

Mayo Clinic scientists are providing nerves with a platform for neural regeneration, using advanced biomedical technology and novel methods of tissue engineering to manipulate neural growth factors, guidance cues, and the extracellular environment. Three integrated research initiatives are addressing regeneration in the spinal cord, the brain, and the limbs. Two of these projects—one fostering axonal extension across large-gap peripheral nerve injuries and one preventing cell death and promoting neural regeneration in the brain—are about to enter clinical trials. Work on spinal cord regeneration is being tested in animals.

Making a Hostile Environment Permissive

In the developing nervous system, nerve growth cones—the cone-like tips of axons and dendrites—extend and retract, "sniffing out" the molecules needed to help the cones reach and connect with their targets. A complex array of molecular guidance cues tell them whether to continue, to keep on their path, or to turn left or right. The extracellular environment and intrinsic cell signaling are primed to help them in their search and act as a compass on their journey.

Neural growth factors and low levels of neural guidance cues are also available in the fully developed nervous system. However, an array of inhibitory factors create an environment that is hostile to regeneration in the CNS. In the PNS, it is the lack of a permissive pathway that prevents projection of axons across large gaps. Many of these inhibitory factors have been identified, and by eliminating them in the laboratory, researchers have been able to generate nerve cell growth in vitro. Translating this success into the human nervous system has been a major challenge.

Enhancing Neural Growth

Early, but unsuccessful, efforts at human nervous system regeneration in the 1990s focused on creating antibodies to counteract inhibitory factors. Mayo Clinic took a different approach. Led by Anthony J. Windebank, MD, a neurologist and molecular neuroscientist, Mayo researchers pioneered ways of reengineering autologous mesenchymal stem cells to enhance their ability to produce trophic and growth factors. Dr Windebank's theory was that after implantation, the stem cells could serve as delivery vehicles for neural growth factors, promoting nerve regeneration. What was needed was a permissive environment that could sustain growth and, equally important, enable axons to find and connect with appropriate targets.

Michael J. Yaszemski, MD, PhD, and John R. Henley, PhD

Providing a Physical Scaffold

Michael J. Yaszemski, MD, PhD, a Mayo Clinic orthopedic surgeon and biomedical engineer, developed a physical structure that could house such an environment. Made of a copolymer called polycaprolactone fumarate, it joins two compatible polymers never before brought together. The resulting synthetic tubing (Figure 1) provides a biodegradable scaffold between severed axons, within which neural growth factors, signaling molecules, and guidance cues can sustain new growth and axonal projection. It also provides physical channels through which axons can extend more readily (Figure 2, see page 4), helping to prevent undirected peripheral nerves from forming neuromas. The scaffold degrades naturally when axons reconnect, a process that can take weeks to months.

Anthony J. Windebank, MD

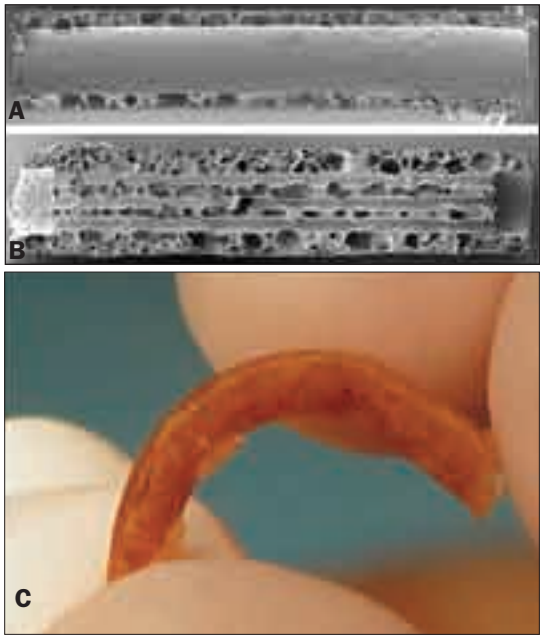


Figure 1. *Single-lumen or tubule (A) and multiple-lumen (B) biodegradable nerve scaffolds. Panel C shows the flexibility of a nerve guidance scaffold, which mimics the properties of a normal peripheral nerve.*

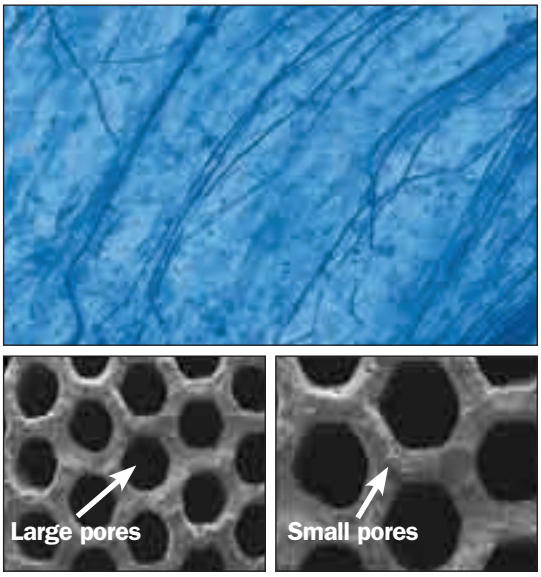


Figure 2. *Close-up views of the synthetic polymer scaffolds, with an image (top) of myelinated nerve fibers that have grown in the scaffolds.*

Redirecting Guidance Cues

Providing a permissive environment within the scaffold depends on overcoming inhibitory factors and directional miscues. For example, after nerve injury, soluble fragments of myelin components, such as myelin-associated glycoprotein, are released that prevent neurons from growing and can cause nerve growth cones to collapse. In addition to such growth-preventing proteins, other factors at the injury site may steer growing nerve tips in the wrong direction. Thus, even if growth is initially supported, neurons must be redirected toward their targets or they will not survive.

John R. Henley, PhD, a Mayo Clinic molecular neuroscientist and director of the Neurodevelopment and Regeneration Laboratory, has devoted his career to identifying and manipulating the second messengers that regulate neurite growth and that transduce extracellular guidance signals through a cascade of intracellular events to mediate directional guidance. These are the cues that facilitate axonal attraction or repulsion and directional turning. Dr Henley and his colleagues have had success in altering certain second messengers to prevent misdirected axonal tip turning. For example, in an assay that elevates the intracellular second messenger cyclic adenosine monophosphate (cAMP), repulsive turning responses can be converted into attractive ones. He says that this work is directed at priming nerves to grow on inhibitory substrates by altering not only the external molecular environment, but also the intrinsic state of a neuron—something previously not thought possible.

Clinical Initiatives

Peripheral Nerve Regeneration

Dr Yaszemski, a brigadier general in the US Air Force Reserves who has served as deputy commander of the hospital at Balad Air Base north of Bagdad, has had direct experience with the extensive limb wounds of soldiers in Iraq and Afghanistan. He and Dr Windebank serve as codirectors for nerve injury research in the Armed Forces Institute of Regenerative Medicine, a Department of Defense–funded consortium of 16 institutions to generate new treatments for war-wounded persons. Work at Mayo Clinic focuses on nerve regeneration. Within one year, in conjunction with Robert J. Spinner, MD, a Mayo Clinic peripheral nerve surgeon, Drs Windebank and Yaszemski will begin the first human clinical trials of the polymer scaffold implants at Mayo Clinic in Rochester, Minnesota.

Spinal Cord Nerve Regeneration

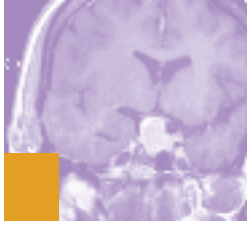
The spinal cord presents a particular set of challenges. As Dr Henley notes, neurons in the CNS face an environment that is more hostile to regeneration than do peripheral nerves. In addition, axonal growth must be bidirectional (both toward the brain and away from it), and scar tissue at the interface of the spinal cord and scaffolding exerts an extra-inhibitory environment. Drs Windebank and Yaszemski and their colleagues have applied the scaffolding technology to the injured spinal cord in animals. Dr Henley's work in elevating the influence of second messengers to reprogram growth cones will help push growing nerves beyond the scaffolding and into the native spinal cord. He envisions a timed release of modulating factors and a second messenger cascade of calcium, cAMP, and other second messengers, to coordinate with the dissolving scaffolding tube as nerve tips reach the native spinal cord. This work may be five to 10 years away from human trials.

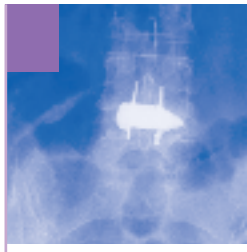
Neuronal Regeneration in ALS

A third regeneration initiative at Mayo Clinic is focused on restoring neural function in progressive CNS disease. Using the same approach in which autologous mesenchymal stem cells supply growth factor to neurons, Dr Windebank and colleagues are ready to conduct human safety trials. They have harvested stem cells from the adipose tissue of a patient with amyotrophic lateral sclerosis (ALS). After they ensured that the cells are normal, the patient has undergone stem cell injection via lumbar puncture without adverse effects. The study will now move forward to a larger safety trial to be conducted on an additional 15 patients. The next step will be to conduct a clinical trial using stem cells that have been reengineered to enhance growth factors, with the goal of generating new neuronal growth.

As Drs Henley, Windebank, Yaszemski, and Spinner point out, regenerative medicine requires extensive collaboration among the departments of neurology, neurosurgery, orthopedic surgery, biomedical engineering, molecular neuroscience, immunology, and physiology. By integrating these areas of expertise, research teams under the investigators' direction have made substantial progress toward regenerating nerves that were once considered impossible to save.

Research Highlights





Microseizures and the Spatiotemporal Scales of Human Partial Epilepsy

Mayo Clinic researchers investigated the spatiotemporal scale of focal epilepsy with wide-bandwidth electrophysiological recordings, using clinical macroelectrodes and research microelectrodes, in patients with epilepsy and control subjects with intractable facial pain. Seizure-like events that were not detectable with clinical macroelectrodes were observed with isolated microelectrodes. These "microseizures" were sparsely distributed, more frequent in brain regions that generated seizures, and sporadically evolved into large-scale clinical seizures. Rare microseizures observed in control subjects suggest that this phenomenon is ubiquitous, but that the density of microseizures distinguishes normal brain activity from epileptic brain activity. Epileptogenesis may involve the creation of these topographically fractured microdomains and ictogenesis (seizure generation), the dynamics of their interaction, and their spread. This study was published in the August 2010 issue of *Brain*. Authors: M. Stead, M. Bower, B. Brinkmann, K. Lee, W. Marsh, F. Meyer, B. Litt, J. Van Gompel, and G. Worrell.

REM Sleep Behavior Disorder Preceding Other Aspects of Synucleinopathies by Up to Half a Century

A Mayo Clinic study evaluated 27 patients with a history of REM sleep behavioral disorder predating the onset of clinical Parkinson's disease (PD), dementia with Lewy bodies, or multiple-system atrophy by more than 15 years. Study results illustrate that the ά-synuclein pathogenic process may start decades before the first symptoms of PD, dementia with Lewy bodies, or multiple-system atrophy. This study was published in the July 2010 issue of *Neurology*. Authors: D. Claassen, K. Josephs, J. Ahlskog, M. Silber, M. Tippmann-Peikert, and B. Boeve.

Apathy and Depression Predict Progression From Mild Cognitive Impairment to Dementia

A Mayo Clinic study found that apathy and depression significantly predict an individual's progression from mild cognitive impairment (MCI) to dementia. After adjusting the data for age, sex, and education, the researchers determined that individuals with MCI and depression had a 66% greater risk of dementia than those individuals with MCI without depression. Similarly, individuals with MCI and apathy had a 99% greater risk of dementia than those individuals with MCI without apathy. The study was presented at the 2010 International Conference on Alzheimer's Disease. Authors: Y. Geda, R. Roberts, D. Knopman, T. Christianson, V. Pankratz, B. Boeve, W. Rocca, R. Ivnik, E. Tangalos, and R. Petersen.

Good Nutritional Control May Prevent Polyneuropathy After Bariatric Surgery

Previous research has shown that peripheral neuropathy occurred after bariatric surgery and was associated with malnutrition. Published in the July 2010 issue of *Muscle Nerve*, a study by Mayo Clinic scientists found that a systematic, multidisciplinary approach of intensive nutritional management before and after bariatric surgery and with frequent follow-up greatly decreased development of peripheral neuropathy (especially sensory polyneuropathy) in patients receiving bariatric surgery. Authors: P. Thaisetthawatkul, M. Collazo-Clavell, M. Sarr, J. Norell, and P.J.B. Dyck.

Differences in Type of Dementia in People With and Without Diabetes

Researchers from Mayo Clinic in Florida say that dementia in some people with diabetes is caused by vascular disease in the brain and that dementia in people without diabetes is most likely associated with the plaque deposition seen in Alzheimer's disease. This research suggests that the vascular dementia associated with diabetes, which appears to be related to small-blood-vessel disease and strokes, can potentially be averted if the development of diabetes is prevented. The findings were presented at the 2010 International Conference on Alzheimer's Disease. Authors: N. Graff-Radford, J. Crook, J. Lucas, L. Younkin, G. Nah, S. Younkin, and M. Haan.

To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org.

Improving the Maintenance of Cervical Kyphotic Deformity Correction

Chronic pain, numbness, weakness, tingling in the extremities, and restricted forward gaze are characteristic symptoms of mild to moderate cervical kyphotic deformity. In advanced cases, pain becomes debilitating, and myelopathy from compression or stretching of the spinal cord can induce bowel and bladder dysfunction, gait instability, and weakness in the upper or lower extremities, or both. Swallowing and breathing difficulties can result from compression of the esophagus and trachea due to the deformity itself.

Stephen Pirris, MD, and Eric W. Nottmeier, MD

The two most common causes of kyphotic sagittal deformity are degenerative conditions, such as arthritis, and iatrogenic processes. For example, kyphosis can occur after initially successful fusion surgery because of stress above or below the fused area. Other causes include trauma, malignancy, infection, inflammatory diseases, and neuromuscular diseases and conditions. The kyphosis resulting from some conditions is not as amenable to surgical correction as it is in others. Stephen Pirris, MD, a neurosurgeon at Mayo Clinic in Florida, notes that, for example, patients with severely compromised bone strength due to osteoporosis or from immune-modulating drug therapy may not be good surgical candidates.

William E. Krauss, MD

William E. Krauss, MD, a neurosurgeon at Mayo Clinic in Rochester, Minnesota, points out that surgical correction in appropriate candidates is more feasible now than it was 10 years ago because of improved instrumentation. Successful surgical correction depends on many factors, including the overall health of the patient, the cause of the kyphosis, the surgical approach taken in reconstruction, and the accurate placement of posterior instrumentation.

360° Reconstruction

The surgical approach taken for correction of kyphotic cervical deformity can be unilateral (anterior or posterior) or circumferential, which is also known as a 360° approach. As Naresh P. Patel, MD, a neurosurgeon at Mayo Clinic in Arizona, explains it, a circumferential approach allows surgeons to correct the deformity by decompressing and freeing the spinal cord and nerve roots and removing discs and bone from the front, replacing them with a bone graft. Then, from the back, the graft and other aspects of the correction are locked into place with rods and screws (Figure 1). Dr Patel notes that reconstruction is more efficient from the front but that securing instrumentation from the back is optimal for maintaining certain types of correction.

Naresh P. Patel, MD

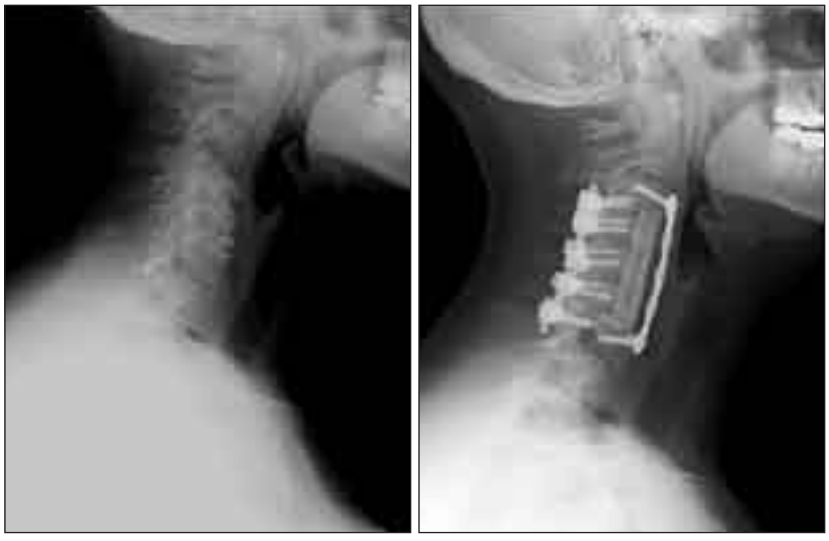


Figure 1. *Preoperative (left) and postoperative (right) radiographs showing correction of a midcervical kyphotic deformity in a 54-year-old woman. A 360° approach was used, in which 3 vertebral bodies were removed and a bone graft was placed, correcting the deformity from the front, and instrumentation was placed from the back to lock the deformity correction in place.*

Although a unilateral approach is a less extensive surgery and thus might have less perioperative risk, the 360° approach was found to be both safe and effective in a recent retrospective study led by Eric W.

Nottmeier, MD, a neurosurgeon at Mayo Clinic in Florida (*Journal of Spinal Disorders Techniques*, 22 [6], 2009). In their review of outcomes for 41 patients with a minimum follow-up period of 1 year, Dr Nottmeier and his Mayo Clinic colleagues found that not only was there was no loss of correction on follow-up, but also the fusion rate was 97.5%.

Not every kyphotic correction requires the 360° approach. In the Mayo practice, common indications for this approach include deformity secondary to postlaminectomy instability, traumatic instability with marked ligamentous injury, multilevel corpectomy (removal of a vertebral body), and substantial risk of pseudoarthrosis. Another, less frequent indication is severe antecollis caused by dystonia (Figure 2, left panel). Mark A. Pichelmann, MD, a neurosurgeon at Mayo Clinic in Minnesota, states that by using the circumferential approach, the surgeon can section dystonic muscles, as well as correct the deformity, from the front and that the optimal way to secure the instrumentation and bone graft in such severe cases is from the back (Figure 2, right panel).

Benefits of Image Guidance

As Figures 1 and 2 illustrate, cervical kyphotic deformity correction may involve the upper thoracic spine, which is known to be a challenging area for screw placement. Visualizing the area with lateral fluoroscopy is difficult, and the pedicles in that region are small. The reported frequency of misplaced screws can be as high as 41%. A 2009 Mayo Clinic study that used independent CT scan review of 34 patients who underwent cervicothoracic fusion found that with use of 3-D image guidance, 93% of the screws in the first three thoracic vertebrae were perfectly placed and that there was only a minimal breach of the bony pedicle in the remaining 7% (Bledsoe et al, *The Spine Journal*, 9 [10], 2009).

In image guidance, the surgeon's instruments are equipped with light-emitting diodes that send signals to a camera connected to a computer. The computer then triangulates the location of the instrument on the patient's anatomy and integrates it into the MRI image on a screen in the operating room. The integrated image may be 2-D or 3-D, depending on the type of image-guidance system used.

It can be challenging to use 3-D image guidance in the upper cervical spine at the C1 and C2 levels because of the physical difficulty of fixing the image-guided reference arc in a way that does not impede screw placement. To overcome this problem, Dr Nottmeier and colleagues modified the technique by attaching the reference arc to the headholder. A study of 18 patients who had screws placed with 3-D image-guidance modification at the occipital, C1, or C2 levels found that 81 of 82 screws were placed accurately (*Operative Neurosurgery,* 66 [1], 2010). Dr Pirris notes that image guidance not only facilitates accurate screw placement but also is helpful in detecting pathologic factors that may have gone unnoticed with standard imaging techniques.

Using 3-D image guidance modified when necessary and a 360° approach when indicated, Mayo Clinic surgeons are improving outcomes for the correction and maintenance of cervical kyphotic deformity reconstruction.

Mark A. Pichelmann, MD

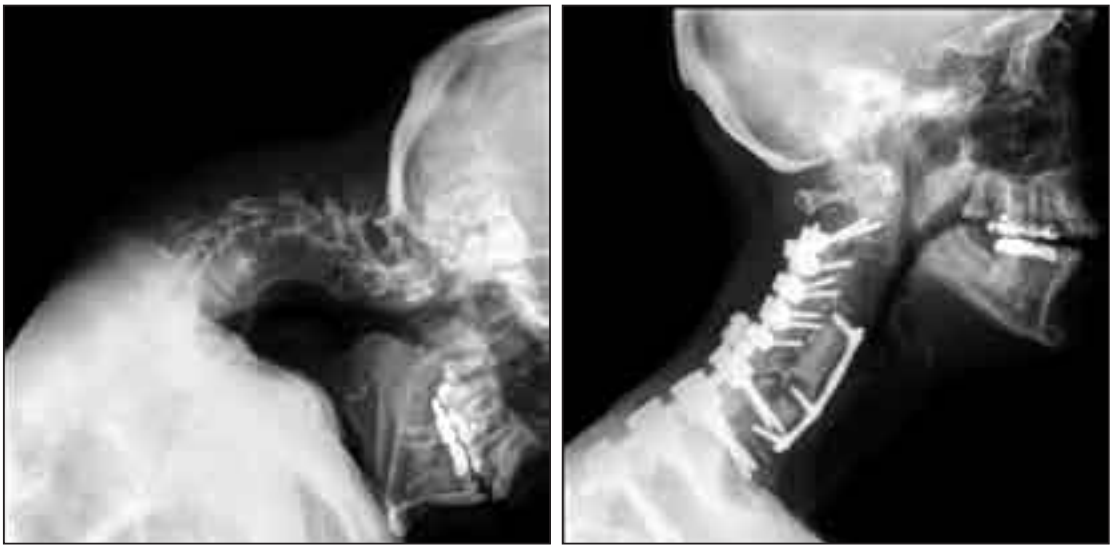


Figure 2. *Preoperative and postoperative radiographs of a patient with cervical dystonia that manifested as antecollis with severe cervical kyphosis (chin-on-chest deformity) (left) and required anterior and posterior reconstruction (right).*

Mayo Clinic Neurosciences Update

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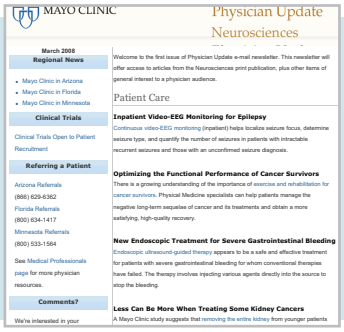
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Inpatient Video-EEG Monitoring for Epilepsy
Continuous video-EEG monitoring (inpatient) helps localize seizure focus, determine seizure type, and quantify the number of seizures in patients with intractable recurrent seizures and those with an unconfirmed seizure diagnosis.

Optimizing the Functional Performance of Cancer Survivors
There is a growing understanding of the importance of exercise and rehabilitation for cancer survivors. Physical Medicine specialists can help patients manage the negative long-term sequelae of cancer and its treatments and obtain a more satisfying, high-quality recovery.

New Endoscopic Treatment for Severe Gastrointestinal Bleeding
Endoscopic ultrasound-guided therapy appears to be a safe and effective treatment for patients with severe gastrointestinal bleeding for whom conventional therapies have failed. The therapy involves injecting various agents directly into the source to stop the bleeding.

Less Can Be More When Treating Some Kidney Cancers
A Mayo Clinic study suggests that removing the entire kidney from younger patients

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