

## Inside This Issue

Endoscopic Mucosal Resection for Barrett Esophagus-Related Dysplasia and Cancer . . . . . 2

Mayo Clinic ALITO Trial for HER2-Positive Breast Cancer Patients Open for Enrollment . . . . . 5

Optimizing the Functional Performance of Cancer Survivors, Stroke Patients . . . . . 7

## Inpatient Video-EEG Monitoring Aids in the Diagnosis and Localization of Difficult Seizure Cases

### The Challenge

Epilepsy occurs in approximately 1% of the US population. For many epilepsy patients, electroencephalography (EEG) successfully localizes and classifies seizure type as a basis for devising optimal treatment. But in some cases, EEG is not sufficiently discriminating to yield a precise diagnosis or a rational basis for initiating treatment.

Some patients present with conditions whose symptoms may be confused with epilepsy. These conditions include conversion-reaction disorders, anxiety disorders, cardiac arrhythmias, drug toxicity, migraine, mood disorders, orthostatic hypotension, panic attacks, transient ischemic attack, tremor, valvular heart disease, and vasovagal syncope. For these patients, a more comprehen-

### Points to Remember

- **A more precise diagnostic tool than electroencephalography (EEG) is often needed to clarify confusing symptoms, to diagnose and localize intractable recurrent seizures, or at times to confirm seizure diagnosis.**
- **Inpatient video-EEG monitoring provides continuous video footage of patient behavior during a seizure with time-matched EEG readings of brain activity.**
- **Research shows that inpatient video-EEG monitoring can detect previously undiagnosed seizures in up to 20% of monitored patients. Data also show that video-EEG monitoring can improve seizure control in as many as 60% to 70% of patients.**



**Figure. Continuous monitoring.** All 3 Mayo Clinic locations offer inpatient video-EEG monitoring units such as this one at Mayo Clinic in Rochester, Minnesota. Continuous monitoring of patient behavior coupled with long-term EEG recordings—in adults and children—helps clinicians determine spell type, localize seizure focus, and quantify the number of seizures or spells.

sive diagnostic tool (inpatient video-EEG monitoring) is needed to establish an accurate diagnosis and precise localization to assure optimal outcomes of treatment, including surgical resection. The potential indications for inpatient video-EEG monitoring include indeterminate spells that suggest possible seizure activity, seizure classification, quantification of seizure activity, and acute management of intractable seizures, ie, those previously refractory to medication.

### An Important Tool

Inpatient video-EEG monitoring is a specialized diagnostic procedure that simultaneously records patient behavior and brain wave activity (Figure). It is a powerful diagnostic aid in a safe environ-

To refer a patient to Mayo Clinic, please call: Rochester, Minnesota, 800-533-1564; Scottsdale/Phoenix, Arizona, 866-629-6362; Jacksonville, Florida, 800-634-1417.

### Conditions With Symptoms That May Be Confused With Epilepsy

- Anxiety disorders
- Behavioral spells
- Autonomic disorders
- Cardiac arrhythmias
- Cerebrovascular disease
- Drug toxicity
- Migraine
- Mood disorders
- Orthostatic hypotension
- Panic attacks
- Transient ischemic attack
- Tremor
- Valvular heart disease
- Vasovagal syncope
- Vestibular disorders

ment. For example, all the rooms on the inpatient video-EEG monitoring units at all 3 Mayo Clinic campuses are hard-wired with ceiling video cameras and monitored 24 hours every day by highly trained observers (see sidebar). Because patients are continually monitored in a fully equipped hospital setting, they can safely be taken off medications that might otherwise mask seizure activity. If emergency medication is needed, it can be admin-

istered quickly. Monitoring may be used anywhere from 24 hours to several days.

From the camera's visual data stream, physicians evaluate the patient's body responses to seizure discharge. They then integrate this information with the brain activity data obtained by continuous EEG recording, through either external or intracranial EEG leads, such as subdural grids or implanted depth electrodes. By correlating the 2 concurrent data streams of visually apparent behavior with internal electrical activity of the brain, video-EEG helps clinicians make more accurate diagnoses. Video-EEG also overcomes a common source of error in seizure classification: the eyewitness reports of friends or family members present during a seizure. Because these accounts are often emotionally charged, they may not be as reliable as continuous video camera documentation of seizure events.

### The Inpatient Advantage

Research shows that inpatient video-EEG monitoring can detect previously unconfirmed seizures in up to 20% of monitored patients. Among its advantages that lead to this improved detection rate are its abilities to localize seizure focus, quantify the number of seizures over time, and differentiate physiologic events that may be confused with epilepsy. Outcome data on inpatient video-EEG monitoring demonstrate that these improvements translate into better patient care: seizure control improves in as many as 60% to 70% of patients.

## Endoscopic Mucosal Resection for Barrett Esophagus–Related Dysplasia and Cancer

### The Challenge

Barrett esophagus (BE) is a premalignant metaplastic condition that has traditionally been challenging to diagnose, stage, and treat prior to the development of adenocarcinoma. An estimated 10% of patients with chronic reflux symptoms present with BE at endoscopy, and BE patients face a 30- to 125-fold increased risk of developing esophageal cancer in a progressive process that can be asymptomatic (Figure 1).

Early detection produces the best outcomes. But optimal diagnosis and management of cancers aris-

ing from BE have been hampered by the small size and unreliability of histologic samples available by traditional means of endoscopic biopsy. Missing an area of cancer or dysplasia is always a risk because the biopsy sample may not come from the most diseased area and most of the involved areas of advanced dysplasia or early cancer cannot be visually identified. Further complicating diagnosis is the distribution pattern of BE. It can occur diffusely over a large area, thus increasing the chances that a cancer may be misdiagnosed as dysplasia because too little cancerous tissue was evident in the limited

traditional biopsy sample. Thus, one of the greatest weaknesses of managing BE by traditional means is the risk that even though the dysplasia is removed, high-grade dysplasia or even cancerous lesions are left behind.

### A New Approach

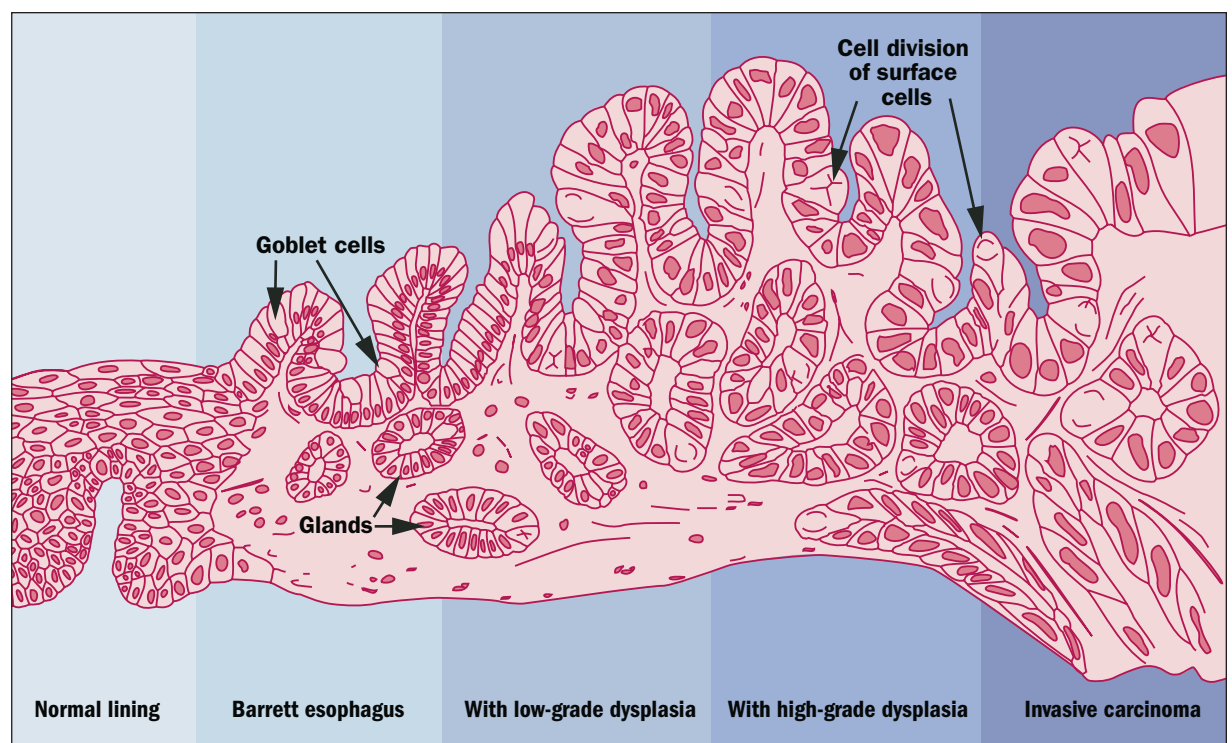
A new outpatient technique called endoscopic mucosal resection (EMR) overcomes the limits of traditional diagnosis and management of BE. Pioneered and used successfully in Japan since 1990, EMR enables physicians to take a much larger biopsy specimen: 3 cm<sup>2</sup> as opposed to the traditional sample size of 6 mm<sup>2</sup> (see the “Bigger Is Better” box and Figure 2, on page 4). In addition, EMR offers outpatient advantages of requiring no hospitalization versus at least 7 days of hospitalization after open surgical treatment, retaining the esophagus, and resuming a fairly normal lifestyle.

In as many as 70% of patients, removal of tissue in the EMR biopsy itself may be a cure. However, while dysplastic changes in the epithelial mucosa tend to occur in discrete locations that can be resected, the predisposing genetic abnormality is usually distributed throughout. This means that vigilant follow-up for recurrence is necessary because tissue that appears noncancerous after resection has a 15% to 30% chance of recurrence. In 2005, research from

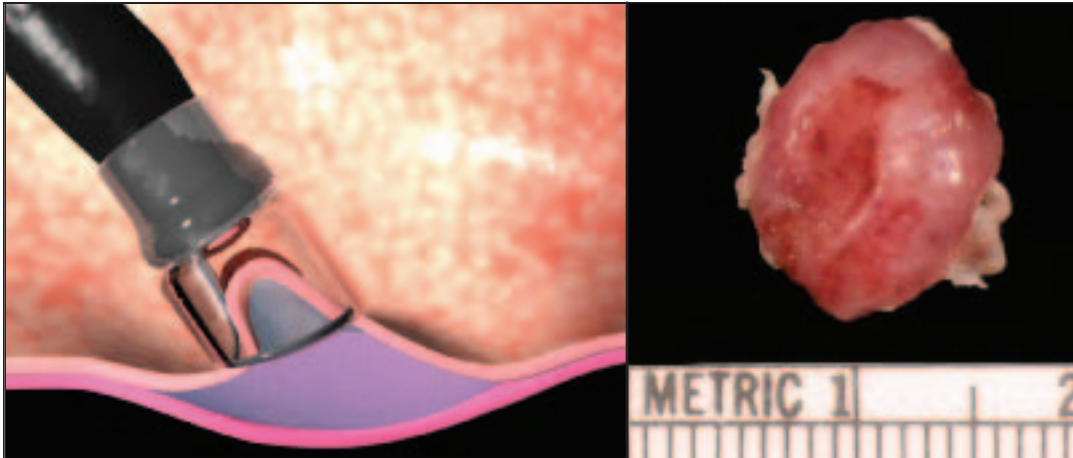
### Points to Remember

- **Endoscopic mucosal resection (EMR) is an outpatient technique for improving both the diagnosis and treatment of high-grade dysplasia and early superficial cancer in patients with Barrett esophagus (BE).**
- **Submucosal cancer diagnosis by EMR may require open surgical treatment.**
- **EMR helps overcome the longstanding problem of sampling error due to the small biopsy specimens provided by traditional means.**
- **The combined EMR experience of Mayo Clinic physicians from all 3 campuses is greater than that of most other US institutions, and Mayo’s complication rates are among the lowest.**

the Mayo Clinic Barrett’s Esophagus Unit demonstrated that for early esophageal cancer, combination treatment with EMR and photodynamic therapy (PDT) to eliminate any residual lesions is feasible.



**Figure 1. Progressive stages of malignant BE. The process is believed to be a progressive change in 1) columnar mucosa without dysplasia to 2) low-grade dysplasia to 3) high-grade dysplasia to 4) adenocarcinoma. EMR is useful for mucosal disease. Submucosal involvement generally requires open surgery.**



**Figure 2.** EMR being performed with the cap technique. Left, A snare is placed over the lesion before removal by the endoscopic device. Right, The resected specimen, with a small cancer localized to the mucosa.

The addition of PDT ablation is a means of completely eliminating metaplastic mucosa.

#### Evidence of EMR Advantages

Mayo Clinic is one of the few US medical centers to offer the evolving technique of EMR. The physicians at all 3 Mayo Clinic sites combined have performed more EMR procedures than most other US institutions, with complication rates among the lowest. The perforation rate has been reported as 1% to 3%, but Mayo physicians have had no perforations in more than 1,000 EMRs. Mayo's gastrointestinal bleeding rate is less than 1% compared with rates of 5% to 10% reported in the literature.

Mayo's results with diagnosis, staging, and treatment support the safety and efficacy of EMR. In 1996, a Mayo Clinic study showed that an estimated 40% of the diagnoses of high-grade dysplasia obtained by surgical means were reclassified to a diagnosis of cancer after EMR biopsy. This is an important finding, given that the literature suggests that up to 50% of high-grade dysplasia patients have cancer. Also, when submucosal cancer is found, open surgical treatment is recommended.

In 2005, Mayo researchers demonstrated that for early esophageal cancer that did not invade the submucosa, combination therapy with EMR and PDT to eliminate any residual lesions is feasible. The addition of PDT ablation is a means of completely eliminating metaplastic mucosa. Five-year follow-up mortality data showed no cancer-related deaths.

In 2007, Mayo Clinic published the first US large-scale study on endoscopic therapy of high-


grade dysplasia arising in patients with BE and demonstrated the ability of endoscopic therapy, including EMR, to treat this condition with mortality rates similar to those after esophagectomy.

#### Indications for Evaluation and Treatment by EMR

In general, any patient with superficial, high-grade dysplasia and early cancer is suitable for EMR evaluation, staging, and treatment. Indications for treatment by mucosal resection include the presence of small, mucosally based cancer, preferably less than 2 cm; no evidence of metastatic disease; and patient


unwillingness or inability to undergo open surgery. EMR is not indicated for patients with submucosal malignant involvement.

**Bigger Is Better**



**2.45 × 2.45 mm**

**Improvement in diagnosis from EMR is facilitated by the much larger biopsy specimen available, ie, a 3-cm<sup>2</sup> biopsy specimen (below) versus the 6-mm<sup>2</sup> specimen (above) taken in traditional biopsies.**



**1.73 cm**

**1.73 cm**

**Although the risk of malignancy within Barrett epithelium has been well established since the naming of the disorder more than 50 years ago, the ability to detect neoplastic tissue within the mucosa has traditionally been a random process. To attempt to capture randomly distributed cancer cells, surgical biopsies have involved taking 4 quadrants every 2 cm throughout the endoscopically visible segment.**

## Mayo Clinic ALTTO Trial for HER2-Positive Breast Cancer Patients Open for Enrollment

### The Challenge

Management of breast cancer patients has been revolutionized in the past 10 years by rapid therapeutic advances and improved understanding of the molecular biology of breast cancer. Because of these changes, many older clinical practice recommendations have become outdated. One of the most important recent findings affects the 15% to 20% of breast cancer patients who have increased amounts of the HER2 protein or gene, which stimulates cell growth leading to more aggressive tumors.

In 2005, HER2-positive patients benefited from a Mayo Clinic collaborative study, the results of which were published in the *New England Journal of Medicine*. The study demonstrated a 52% reduction in tumor recurrence in patients treated with anti-HER2 adjuvant therapy that included trastuzumab (Herceptin) to block HER2 protein activity. The challenge now is to extend the benefits found with the use of trastuzumab by exploring further blockade of the HER2 protein, while minimizing adverse effects seen with trastuzumab such as congestive heart failure.

### The ALTTO Trial

To improve prospects for HER2-positive patients, Mayo Clinic investigators, working with interna-

### Points to Remember

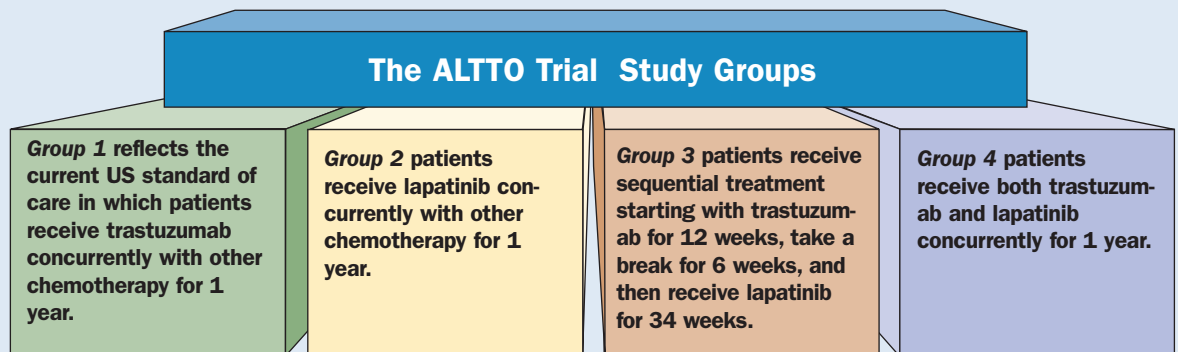
- Improved reclassified understanding of the molecular biology of breast cancer has led to therapeutic advances that have revolutionized the management of breast cancer patients in the past 10 years.
- Mayo Clinic has collaborated in the design of a new international clinical trial for HER2-positive patients, who make up 15% to 20% of all breast cancer patients. Called ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation), the new trial will enroll 8,000 patients worldwide.
- ALTTO builds on Mayo Clinic's 2005 collaborative report that an adjuvant therapy regimen including trastuzumab was associated with a 52% reduction of recurrence in HER2-positive breast cancers.
- Primary care physicians play a critical role in improving breast cancer outcomes by giving patients a positive message about progress in the treatment of breast cancer and by encouraging enrollment in clinical trials.

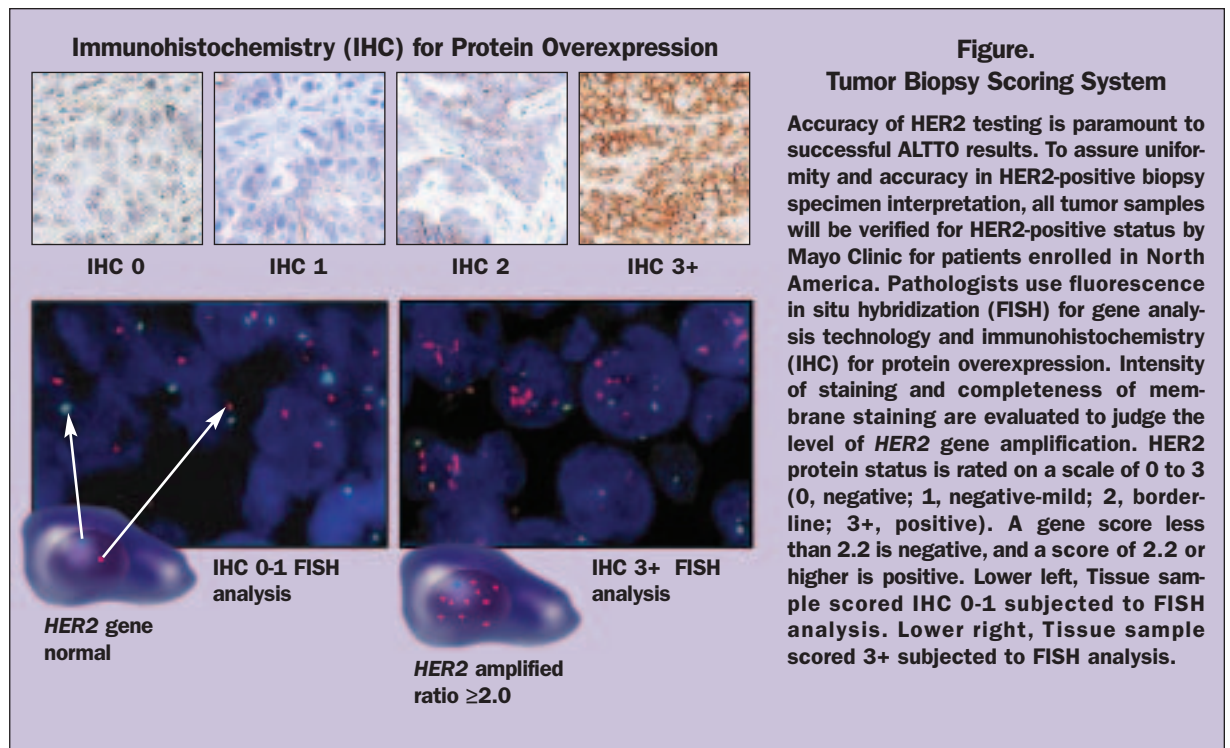
### Organization of the ALTTO Trial

**Accrual** of 8,000 HER2-positive patients for the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial will occur over the next 2½ years, and patients will be randomly assigned to 1 of 4 study groups.

**Chemotherapy** is an important component of treatment of aggressive breast cancer. No single type of chemotherapy is stipulated for inclusion in the trial, but instead several regimens are allowed.

**End Points** consist of 1) generation of evidence that lapatinib treatment is better than or equivalent to the current standard treatment, trastuzumab, and 2) data on efficacy and toxicity of the 2 agents when given in sequence or at the same time. Even if the 2 agents prove to be equally effective, lapatinib may offer a practical treatment advantage because it is given as a tablet and is therefore easier to administer than trastuzumab, which is given intravenously.





tional colleagues, designed a new clinical trial: ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation). The trial opened in North America in February 2008 for enrollment of 8,000 patients, half of whom live outside the United States (see box, on page 5). A major research goal of the study is to analyze tumor specimens from HER2-positive patients to gain understanding of the role of HER2 in tumor biology and of other potential downstream molecules that may be important for predicting resistance to HER2-based treatments. This analysis may lead to the identification of new clinical biomarkers detectable by blood tests and to subsequent improved treatment.

A major clinical goal of the ALTTO trial is to compare the efficacy, sequence, and timing of 2 agents—trastuzumab and lapatinib. Trastuzumab is a monoclonal antibody that binds to part of the HER2 protein on the outside of tumor cells. Binding to this site blocks the protein and prevents it from stimulating cell growth. Lapatinib functions through a different pathway. It is a small molecule that works on the inside of the cell, targeting the intracellular domain of the HER2 receptor. Pre-clinical studies show clinical benefits may accrue from lapatinib even after trastuzumab has been administered. ALTTO will test this.

Another major goal of ALTTO is to investigate the assumption that lapatinib has very little cardiac toxicity. A formal, large-scale toxicity com-

parison of the 2 agents has not been done. By comparing these drugs, ALTTO is expected to answer these questions: Is there a better anti-HER2 approach than trastuzumab that has the potential benefits of both reducing toxicity and predicting which patients will benefit from the treatment? Or is it better to give the 2 drugs (trastuzumab and lapatinib) in sequence or together?

### Inclusion Criteria

Detailed information about ALTTO's inclusion criteria and how to refer patients for enrollment in this study is available online at [http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial\\_id=100564](http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial_id=100564).

To participate in ALTTO, breast cancer patients must have HER2-positive disease (Figure) and be in the care of National Cancer Institute–approved physicians. Patients must also have

- a node-negative tumor larger than 1.0 cm or a node-positive diagnosis, irrespective of tumor size
- a paraffin-embedded tumor specimen (and/or frozen specimen, if available) submitted to Mayo Clinic to corroborate HER2 status
- normal left ventricular ejection fraction
- no prior cancer treatments involving chemotherapy or radiation before the diagnosis of invasive breast cancer

## Optimizing the Functional Performance of Cancer Survivors, Stroke Patients

### The Challenge

The growing involvement of physical medicine and rehabilitation (PM&R) specialists in cancer survivorship and their long-established role in stroke recovery signal an important shift in clinical focus: an expanding understanding of the negative long-term sequelae of the diseases and, in the case of cancer, the treatments.

Negative long-term sequelae need to be managed because they create barriers to obtaining high-quality recoveries. Realizing this, primary care physicians are now keenly interested in the role of exercise and rehabilitation in cancer and stroke recovery. Increasingly they collaborate with PM&R specialists who have the requisite skills to help assess and manage these barriers to recovery.

### Key PM&R Therapies

Figure 1 shows the numerous cancer-related sequelae that PM&R specialists can address. For stroke patients, Mayo Clinic PM&R specialists offer 2 recently devised innovations to manage sequelae: One is constraint-induced movements therapy, as shown in Figure 2, on page 8. It helps stroke patients suffering paralysis of a hand or arm regain function by constraining the unaf-

**HEAD AND NECK** – Some cancer patients lose flexibility during radiation treatments. A radiation therapist can refer a patient to PM&R, knowing the patient is at risk for loss of range and motion.

**GENERAL BODY** – For patients facing end-of-life cancer, the goal is to optimize support through various equipment, medications, and care techniques to keep these patients as active as possible so they have high quality of life in their final days.

**GENERAL BODY** – PM&R specialists can help other health care providers assess patient function, consider barriers affecting optimal patient function, and initiate interventions to minimize those barriers.



**BACK/SPINE** – A long-term barrier to high quality of life for cancer survivors is chronic pain. Gentle exercises, massage, complementary medicine techniques such as acupuncture, and review of medications can all aid in pain control.

**FINGERS** – Some chemotherapeutic agents affect neurologic function, ranging from numbness in fingers and hands to more widespread neuropathies.

**LONG LEG BONES/SPINE** – The tumor itself can affect bony structures, causing weakness in the spine and in the long bones.

### Points to Remember

- **As the population ages and treatments improve, stroke patients and cancer survivors constitute a growing segment of the medical population.**
- **The need to manage negative long-term sequelae of stroke and cancer—and of cancer treatments such as chemotherapy and radiation—is increasing.**
- **Mayo Clinic Physical Medicine and Rehabilitation (PM&R) specialists offer an array of treatments to help manage the negative sequelae of cancer and stroke.**
- **Exercise and rehabilitation therapies can remove barriers to satisfying recoveries, improve quality of life, and optimize functional performance of cancer survivors and stroke patients.**

ected limb in a sling or mitt. The restraint forces the paretic limb to perform repetitive motor tasks guided by a therapist. Partial-weight-bearing gait therapy is another new technique. It is a variant of treadmill training that improves ambulation and mobility by partially supporting the patient in an overhead harness while a therapist guides the patient. The repetitive movements help restore function and endurance in both the upper and lower extremities, as well as improve balance.

### Indications for PM&R Cancer Interventions

For cancer patients, Mayo Clinic's PM&R specialists can intervene at any point on the cancer continuum. The goal of PM&R interventions is to devise individual programs aimed at recovering maximum function to comfortably resume tasks that enrich patients' lives. In addition, evidence from breast and colon cancer patients suggests that those who exercise regularly before treatment have fewer complications during recovery.

PM&R interventions may include

- exercise to loosen soft tissues and strengthen muscles
- massage to loosen tissues and relax muscles
- assessment of and training with adaptive equipment to optimize function
- external bracing to help support underlying structures and improve function

Figure 1. PM&R management of long-term cancer sequelae.

- compression wraps and massage to manage a swollen arm in a patient with breast cancer or massage to maximize mobility in a leg of a patient with prostate or gynecologic cancer

In managing swelling, the emphasis is on the proper use of newer wraps and compression garments, while working with an exercise therapist or physiatrist.

**Indications for PM&R Stroke Interventions**

Both of these new therapies—constraint-induced movements and partial-weight-bearing gait—improve function and coordination through guided repetitive motion training. Functional balance, strength, and dexterity are also developed. Constraint-induced movement therapy can be used once a patient has shown some evidence of movement in the affected hand or arm. Partial-weight-

bearing gait therapy can begin soon after the stroke patient has been medically stabilized.



**Figure 2. Mastering the tasks of daily living through constraint-induced movement therapy. Wearing a mitt on her unaffected limb forces the patient to use her paretic limb to perform motor skills through repetitive, active movements guided by a therapist.**

**Clinical Update**

*Clinical Update*  
Produced by  
Mayo Clinic  
200 1st Street SW  
Rochester, MN 55905

**Medical Editor**  
Scott C. Litin, MD

**Editorial Board**  
Robert P. Shannon, MD  
Douglas M. Peterson, MD  
Carol K. Benson  
Carol F. Lammers  
Megan V. Vandekerckhove

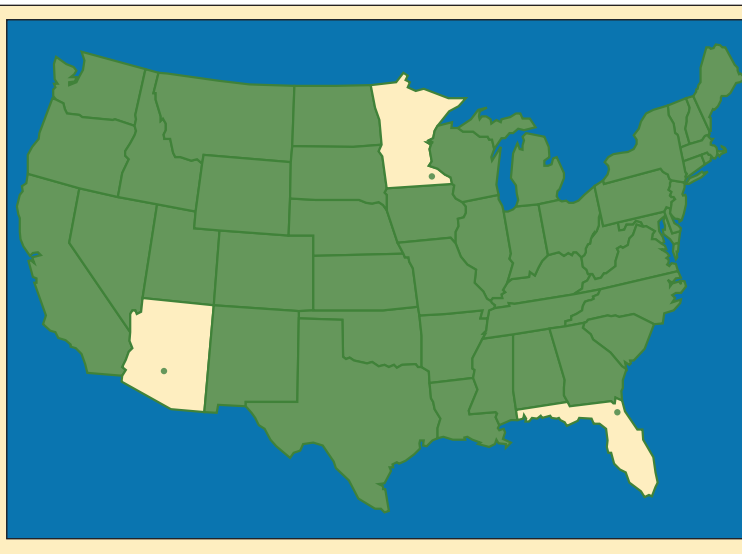
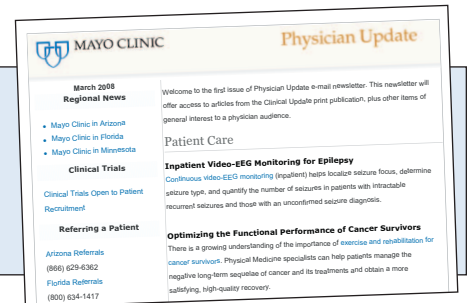
**Science Writer**  
Anne D. Brataas

**Production Designer**  
Connie S. Lindstrom

**Manuscript Editor**  
Jane C. Wiggs

**Interested in receiving Mayo Clinic updates on patient care, research, and education in your inbox?**

Go to [www.mayoclinic.org/medicalprofs/](http://www.mayoclinic.org/medicalprofs/) to sign up for Mayo Clinic's new Physician Update e-mail newsletter.



**To Refer a Patient to Mayo Clinic**

Call the Mayo Clinic Referring Physician Service at one of the following toll-free numbers:

**Rochester, Minnesota**  
**800-533-1564**

**Scottsdale/Phoenix, Arizona**  
**866-629-6362**

**Jacksonville, Florida**  
**800-634-1417**

For more information about Mayo Clinic, visit [www.mayoclinic.org/medicalprofs](http://www.mayoclinic.org/medicalprofs).



4500 San Pablo Road Jacksonville, FL 32224    200 First Street SW Rochester, MN 55905    13400 East Shea Boulevard Scottsdale, AZ 85259

[www.mayoclinic.org](http://www.mayoclinic.org)

© Mayo Foundation for Medical Education and Research (MFMER). All rights reserved. MAYO, MAYO CLINIC and the triple-shield Mayo logo are trademarks and service marks of MFMER.

MC2024-0608