MAYO CLINIC

# Clinical Update

Current Trends in the Practice of Medicine

Vol. 25, No. 1, 2009

## Treatment of Glioma and Glioblastoma

INSIDE THIS ISSUE



### The Challenge

The average survival rate for patients with glioblastomas who have aggressive treatment, including surgical resection, radiotherapy, and chemotherapy, is about 14 months. Only 27% survive 2 years. Glioblastomas grow at an extremely rapid rate in a given brain site and are also capable of moving to new sites within the brain. Understanding and disabling the "grow and go" abilities of glioblastoma is one of the key challenges that researchers and neuro-oncologists are currently addressing.

### Multimodal Management

A multidisciplinary team can optimize care for patients with glioma. Mayo Clinic has a team of neurologists, neurosurgeons, medical oncologists, neuroradiologists, radiation oncologists, neuropathologists, and physical medicine and rehabilitation physicians who work closely to coordinate care and fast-track patients with aggressive tumors like glioblastoma.

### Points to Remember

- Glioblastoma multiforme (grade IV astrocytoma) is the most common and most aggressive form of glioma (primary malignant brain tumor).
- Surgical debulking remains the mainstay of treatment, provided unacceptable neurologic injury can be avoided. The extremely infiltrative nature of this tumor makes complete surgical removal impossible.
- The median survival of patients receiving radiotherapy is double that of patients who receive supportive care alone. The addition of chemotherapy to radiotherapy further increases survival.
- Collaboration between brain tumor researchers and clinical staff allows Mayo Clinic to make in-house research advances available more quickly to brain tumor patients.

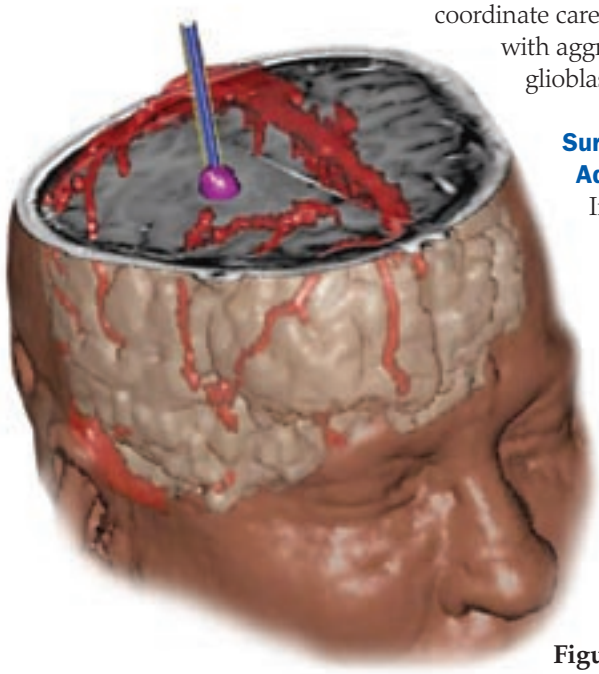

**Figure 1.** *Technologies such as 3-dimensional computer models help Mayo neurosurgeons plan the safest and most effective way to surgically treat a brain tumor.*

### Surgical and Imaging Advances

Imaging technology available at Mayo Clinic helps in surgical planning, makes surgery safer, and improves preservation of function (Figures 1 and 2). Diffusion tensor imaging allows mapping of white matter tracts, image-guidance technology during surgery, and the ability to correlate functional imaging with intraoperative electrophysical mapping. Intraoperative MRI with a high-field-strength magnet allows surgeons to re-register the image-guidance system after the tumor has been removed to account for brain shift during surgery.

### Radiotherapy and Chemotherapy

Although radiotherapy rarely cures glioblastoma, research data show that the median survival of patients receiving radiotherapy is double that of those who receive supportive care alone. Patients treated with radiation have a 2-year survival of 10%; recent clinical trials have shown that the addition of chemotherapy (temozolomide) to radiation almost triples the 2-year survival rate to 27%. Current clinical trials build on this base, as other chemotherapeutic agents

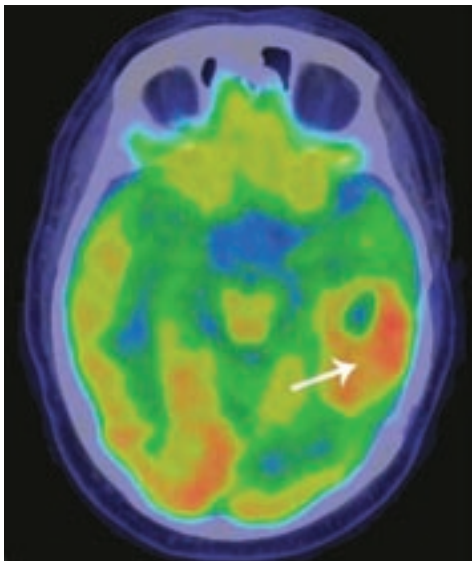

**Figure 2.** *PET scan of glioblastoma multiforme (arrow).*

are evaluated in combination with temozolomide and radiotherapy.

Treatment at tumor recurrence involves the use of other chemotherapy drugs, with recent focus on drugs that inhibit blood vessel formation (angiogenesis inhibitors). Treatment of recurrent tumor must be tailored to the needs of each patient. Because all therapies have limited benefits, symptom control with end-of-life care may also be appropriate.

### Research Advances

Collaboration between brain tumor researchers and clinical staff allows Mayo Clinic to make in-house research advances available more quickly to brain tumor patients. Funded by the National Cancer Institute, Mayo Clinic–led SPORE (Specialized Projects of Research Excellence) focus on clinical trials of new drugs, new diagnostic tests, and molecular prognostic indicators to determine which patients will benefit from a given drug.

#### *Regulating Tumor Invasion*

A protein called Pyk2 plays a key role in enabling glioblastomas to move from site to site in the brain. In conjunction with a pharmaceutical company, Mayo Clinic researchers are in the process of developing a clinical trial for a drug that would target the protein and prevent tumor migration.

#### *Therapeutic Vaccine*

Mayo Clinic researchers are investigating the potential of oncolytic viruses to infect and kill tumor cells while leaving normal cells intact. The goal of this research is to create a dendritic vaccine that stimulates an immune response against glioblastoma tumor cells and disrupts their ability to suppress the immune system itself. Mayo's in-house human cell therapy laboratory is capable of producing clinical-grade cellular treatments.

#### *Prognostic Indicators*

Mayo Clinic researchers are attempting to identify specific genetic markers to help assess a patient's risk for developing gliomas and for predicting response to treatment and survival. Certain tumors express a specific protein that prevents the tumor from responding well to standard chemotherapy treatments. Advances in understanding these differences will help individualize chemotherapy.

#### *Clinical Trials*

The clinical and research efforts and expertise come together in clinical trials offered through the Mayo Clinic Cancer Center and the North Central Cancer Treatment Group (NCCTG). The NCCTG is a Mayo Clinic–led clinical research group that is funded by the National Cancer Institute.

## Minimally Invasive Esophagectomy Reduces Trauma, Speeds Recovery

### The Challenge

Treatment of esophageal cancer is associated with poor survival (Table). According to data from the American Cancer Society and the National Cancer Institute, each year an estimated 16,500 Americans receive a diagnosis of esophageal cancer, and 14,500 die from it.

A major reason for the poor outcomes is that most patients present with late-stage disease that is refractory to treatment. The most common clinical presentation is dysphagia, which typically manifests in advanced stages with nodal metastases. Occasionally, more treatable early-stage lesions are detected during surveillance protocols for gastroesophageal reflux disease or Barrett esophagus.

## Conventional Treatment

Conventional treatment is difficult for patients to tolerate. Invasive tumors with nodal involvement have been traditionally treated by neoadjuvant concomitant chemotherapy and radiotherapy followed by open surgery. The resection typically occurs in 2 or 3 body cavities: in the abdomen to fashion a new tube from the stomach; in the chest to remove the esophagus; and in the chest or neck to reconnect the remaining esophagus to the stomach (Figure 1).

Recovery requires up to 10 or more days in the hospital. It typically is months before the patient is eating well, the incisions are fully healed, and a patient's energy returns. Open esophagectomy is associated with an average mortality of 10% or higher in the United States, particularly when performed by surgeons who do fewer than 10 of the procedures a year. At Mayo Clinic, the mortality rate is less than 3%.

## A New Approach

Mayo Clinic's highly experienced multidisciplinary teams have refined both open procedures and minimally invasive techniques. Encouraging results indicate that minimally invasive esophagectomy is a viable alternative to open surgery. Mayo Clinic is one of a few centers to offer the new approach of combined laparoscopic and thoracoscopic esophagectomy.

## Advantages of Minimally Invasive Esophagectomy

While the procedure still involves resections in 2 or 3 body cavities, the operations are done through smaller incisions using laparoscopic and thoracoscopic visualization and resecting tools. For example, in the abdomen, instead of a full midline resection, the laparoscopic surgeon makes 4 or 5 ports, each 1 cm long, for placement of the laparoscopic instruments (Figure 2). Thoracoscopic ports are placed in the chest in a similar manner. Minimally invasive advantages include achieving oncologic outcomes that are at least equal to Mayo Clinic's open procedures, reducing pain, speeding recovery, and cutting costs by reducing the hospital stay to 5 to 6 days or less vs 7 to 10 days after conventional treatment.

Because the minimally invasive approach is new and performed only at select referral centers, outcome data are just emerging.

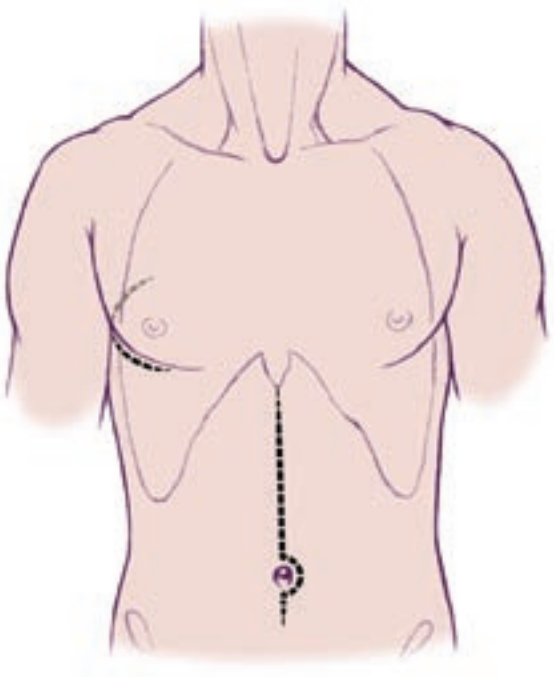

**Figure 1.** *Open esophagectomy incisions.*

### Points to Remember

- According to the American Cancer Society, approximately 16,500 Americans are diagnosed each year with esophageal cancer.
- Most cases are diagnosed in late stages with nodal metastases, often presenting clinically with dysphagia.
- Treatment for stage IIB and above typically involves concomitant neoadjuvant chemotherapy and radiotherapy, followed by open surgery. Nationwide, the mortality rate for this demanding surgery is 10%, while at Mayo Clinic, the mortality rate is less than 3%.
- Minimally invasive esophagectomy at Mayo Clinic has not only reduced surgical morbidity but also decreased hospitalization time from up to 10 days to 5 or 6 days or fewer.

**Table.** *5-Year Esophageal Cancer Survival Rates by Stage*

*(2005 American Cancer Society Data)*

| Stage | 5-Year Relative Survival Rate |
|---|---|
| 0 | 52% |
| I | 41% |
| II | 26% |
| III | 13% |
| IV | 3% |

### Indications

Patients with advanced lesions that cannot be treated by endoscopy or photodynamic therapy (PDT) and who are well enough to withstand surgery are eligible for consideration as candidates for the minimally invasive alternative. Those who have undergone previous surgical procedures and have considerable scar tissue are not typically suitable candidates for minimally invasive treatment approaches.

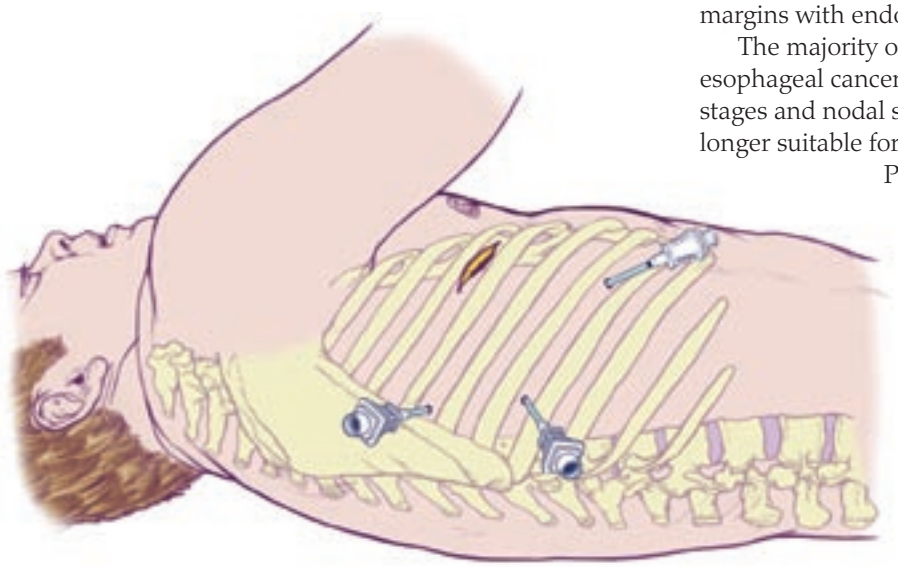

**Figure 2.** *Laparoscopic incisions.*

### Stratifying Patients on the Basis of Mucosal or Submucosal Lesions

Choosing among treatment options can be guided by several pathological presentations. Early, noninvasive mucosal lesions are potentially treatable by endoscopy or PDT. Older patients and those with comorbid conditions who are not candidates for surgery may likewise be suited to treatment by endoscopy or PDT. Submucosal lesions are not treated with these approaches because it is difficult to get good margins with endoscopy in the submucosa.

The majority of patients diagnosed with esophageal cancer present with more invasive stages and nodal spread and are generally no longer suitable for treatment by endoscopy or PDT. Data show that patients with nodal spread and stage II or stage III tumors benefit from neoadjuvant chemoradiation therapy followed by esophagectomy. The majority of patients referred to Mayo Clinic for possible esophagectomy present after chemoradiation therapy.

## Treatment Options for Graves Ophthalmopathy

**Points to Remember**

- The most important factors in prevention of development or progression of Graves ophthalmopathy (GO) appear to be early and accurate control of thyroid dysfunction and counseling patients to quit smoking.
- Determining the appropriate treatment for patients with GO depends on assessing whether the eye disease is active (inflammatory) or inactive (quiescent) and defining the severity of the ocular symptoms.

### The Challenge

Clinically evident Graves ophthalmopathy (GO) occurs in approximately 20% of unselected patients with Graves disease and in approximately 70% of Graves patients if computed tomography (CT) or magnetic resonance imaging (MRI) is used to establish the diagnosis.

Management of GO requires a carefully integrated approach involving the endocrinologist and ophthalmologist, with the goal of preserving the patient's vision and restoring favorable self-perception and quality of life.

### Multimodal Management

Less than 5% of patients with Graves disease have severe GO. Overall, 66% of untreated patients with mild to moderate GO show spontaneous improvement over a 12-month period, while about 10% deteriorate. Several studies have noted a striking association between cigarette smoking and GO. In addition, smoking has been shown to be associated with progression of eye disease after radioiodine therapy and to adversely influence the course of GO during treatment with corticosteroids and orbital radiotherapy.

### Hyperthyroidism Treatment

Early and accurate control of hyperthyroidism

and counseling patients to quit smoking are keys to preventing development or progression of GO. The modality of treatment of hyperthyroidism is less important than effective restoration and maintenance of the euthyroid state.

In patients with moderately severe, active eye disease, especially those who are smokers, antithyroid drugs or the combined use of radioiodine and corticosteroids should be considered. To avoid hypothyroidism, thyroid status should be monitored every 4 to 6 weeks in the initial phases of treatment when changes in thyroid status are expected.

Patients with particularly active and severe GO are best managed initially with antithyroid drugs until their eye disease is inactive and then should be treated with either combined radioiodine and corticosteroids or thyroidectomy.

## Ophthalmopathy Treatment

The majority of patients with GO have mild, self-limited disease course requiring only local measures for symptomatic relief. Instilling artificial tears and taping the eyelids shut at night can prevent nocturnal corneal drying. Worsening of diplopia and soft tissue changes during the night often occur secondary to dependent edema. This edema may respond to nighttime elevation of the head. Sunglasses or tinted lenses may assist in decreasing photophobia. Prisms are occasionally useful for the correction of mild diplopia.

Patients with moderate to severe GO may experience severe periorbital edema, proptosis, eye pain, changes in visual acuity or color vision, or severe restriction of ocular motion. These patients should be assessed by an ophthalmologist to determine whether they require emergent treatment for compressive optic neuropathy or corneal ulceration. If no early surgical intervention is needed, the patient may benefit from a course of immunosuppressive therapy. While approximately 66% of patients with active GO benefit from oral corticosteroids, evidence is mounting that intravenous corticosteroids may be somewhat more effective in providing relief from pain, injection, and conjunctival edema.

Pulse therapy with intravenous methylprednisolone acetate may be considered. However, this therapy should be undertaken only in centers with appropriate GO expertise, given the small risk for fatal hepatotoxicity. In addition, orbital radiotherapy, alone or in combination with corticosteroids, may be beneficial to patients with active GO, especially those with extraocular muscle dysfunction.

**Figure.** *Patients with severe Graves ophthalmopathy (GO). Top, The patient has extreme proptosis, corneal ulceration, and lid retraction, and extraocular muscle dysfunction. She would likely benefit from orbital decompression followed by extraocular muscle and eyelid surgery. Bottom, The patient has active inflammatory GO. He would likely respond to corticosteroid therapy.*

## Surgical Options

Orbital decompression is generally considered for patients with GO who have severe proptosis, orbital congestion, or ocular exposure or for patients who desire an improvement in appearance (Figure). In addition, orbital decompression is effective for treatment of optic neuropathy and as adjunctive therapy for corneal ulceration related to excess proptosis. Patients with active disease who have shown intolerance or insufficient response to immunosuppressive therapy or who have debilitating retrobulbar or periorbital pain may also benefit from decompression surgery. It is important to restore thyroid hormone levels to normal before any type of orbital surgery is performed. An exception to this occurs when severe GO threatens vision and requires urgent orbital decompression.

Eye muscle surgery (strabismus surgery) is typically performed after decompression if the patient has diplopia postoperatively. In patients not requiring decompression, strabismus surgery may be performed after at least 6 months of stable eye deviation measurements without concurrent corticosteroid therapy. The goal of strabismus surgery is single vision in primary gaze and the reading position; diplopia with looking left or right may persist after surgery.

Eyelid surgery for GO usually follows orbital decompression and strabismus procedures. Upper and lower eyelid retraction is relieved by weakening (recessing) the muscles. Blepharoplasty (removal of excess eyelid and orbital tissue that prolapses anteriorly from the increase in orbital volume) may be indicated in selected patients.

# Robotic Mitral Valve Repair Safe, Durable Alternative to Open Surgical Approaches

## The Challenge

Mitral valve regurgitation due to mitral prolapse is common, and many patients will eventually require surgery to repair the faulty valve. Mitral regurgitation is a clinically challenging condition because it can be asymptomatic early on. Most patients at the time of diagnosis are young and otherwise healthy. They tend to have little understanding of the potential for valve leakage leading to irreversible heart failure. Severe regurgitation may lead to severe irreversible heart damage if not treated.

Data show that medical management of severe mitral regurgitation results in excess mortality. The traditional surgical treatment has been valve repair through a median sternotomy, which was pioneered at Mayo Clinic more than 50 years ago. While very effective, median sternotomy may discourage some patients from seeking timely treatment because it is an open-chest procedure, and patients fear a long, painful recovery. An equally effective, minimally invasive alternative that patients find more tolerable has become available to overcome the limitations of traditional treatment, allowing patients to return to normal activity more quickly.

### Points to Remember

- Mitral valve prolapse is a common condition affecting between 3% and 5% of patients. Those with mitral prolapse and greater than moderate to severe mitral regurgitation require valve repair to avert irreversible heart damage.
- More than 99% of Mayo Clinic patients with pure mitral valve regurgitation due to degenerative mitral leaflet prolapse undergo valve repair rather than prosthetic valve replacement.
- The discomfort and recovery time associated with traditional median sternotomy may discourage some patients from seeking needed treatment.
- A minimally invasive robotic repair alternative is now being used to treat patients with mitral valve disease and other heart conditions at Mayo Clinic.

## Robotic Repair

Robotic mitral valve repair is now performed regularly at Mayo Clinic and a few other high-volume advanced cardiovascular surgery centers

**Figure 1.** *Operating room set-up for robotic heart surgery. Surgeon using robotic instruments at lower left. Tableside surgeon at upper right. Two cardiac surgeons participate during robotic procedures at Mayo Clinic.*

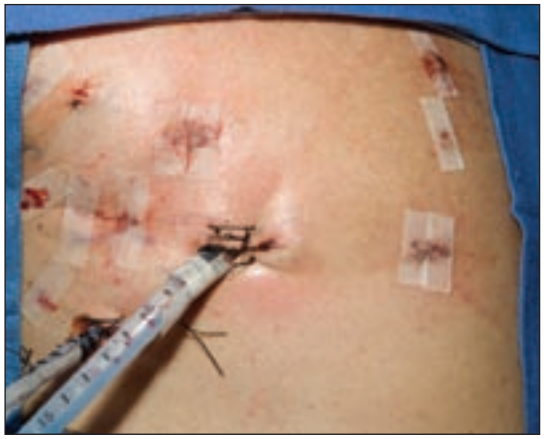

**Figure 2.** *Small incisions speed recovery. The patient typically leaves the operating room with topical skin dressings. No large incisions are required.*

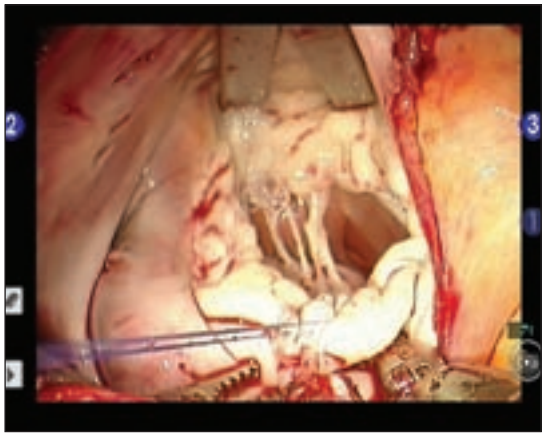

**Figure 3.** *Mitral valve prolapse being repaired with triangle resection and annuloplasty, exactly as would be performed by sternotomy.*

(Figure 1). A minimally invasive robotic repair of the mitral valve relies on 3-dimensional, high-definition video guidance to visualize the intricate heart anatomy and robotic instrumentation to perform precise valve surgery through several very small incisions.

As one of a few centers performing robotic mitral valve repairs, Mayo Clinic in Rochester, Minnesota, evaluates more than 500 patients a year for mitral valve procedures. Traditional prosthetic valve replacement surgery is an option for some patients, but more than 99% of Mayo Clinic patients with pure mitral valve regurgitation due to degenerative disease undergo valve repair to correct leakage. Mayo Clinic investigators have determined that mitral valve repair offers improved survival compared with mitral valve replacement, allowing patients without atrial fibrillation to remain free of long-term warfarin use. Mayo Clinic studies have shown that mitral valve repair is as durable as mechanical valve replacement. Valve repair is also associated with a low likelihood of needing a repeat operation. Robotic mitral valve repair provides patients the same excellent results of open mitral valve repair and is performed through small closed-chest incisions.

## Advantages

For the patient, robotic mitral valve repair offers several advantages over sternotomy. It eliminates the pain and morbidity associated with median sternotomy because the incisions are small—between 1 and 3 cm in length (Figure 2)—and generally do not involve cutting bones or ribs. Hospitalization time is reduced from 7 to 10 days after sternotomy to 3 or 4 days. Patients may return to work within about 2 to 4 weeks after robotic repair compared with 8 weeks of recovery generally needed with an open-chest approach.

Mitral valve repair using robotic techniques is desirable for the surgeon because it offers improved precision using instruments designed to mimic the real-time movements of the surgeon's hands and wrists. Instruments are used in conjunction with a high-definition camera, which provides excellent visualization for these complex procedures (Figure 3).

## Disadvantages

The main disadvantage of robotic repair is the investment required for surgeons to master the high-precision equipment. At Mayo Clinic, multiple robotic systems are used to perform many robotic-assisted procedures each day.

## Indications

At Mayo Clinic, all referred mitral valve patients are considered potential candidates for minimally invasive robotic repair. After a comprehensive evaluation by the medical team, the surgeon decides who is an appropriate candidate on an individual basis.

**Mayo Clinic Clinical Update**

**Medical Editors:**
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



# Contact Us

Referrals and Consultations

**Arizona**
866-629-6362

**Florida**
800-634-1417

**Minnesota**
800-533-1564

**www.mayoclinic.org/medicalprofs**

# CME Opportunities

**Clinical Reviews and Primary Care Update** – June 8 - 11, 2009
Amelia Island Plantation, Amelia Island, FL

Clinical Reviews and Primary Care Update consists of lectures, discussions, and workshops on problems of general interest in various areas of medicine, surgery, and pediatrics. Medical staff from Mayo Clinic and Nemours Children's Clinic, Jacksonville, Florida, provide reviews and updates in the areas of cardiology, dermatology, endocrinology, gastroenterology, infectious diseases, internal medicine, neurology, women's health, pediatrics, pulmonology, and sports medicine. An audience response system will be used. The electronic syllabus will be available to attendees in 2 forms: 1) online before and 6 months after the meeting and 2) onsite on a flash drive. Participants will be notified as soon as syllabus materials are available online, enabling them to print specific presentations before the meeting. Attendees are encouraged to bring their laptops to the meeting to view the syllabus on the flash drive. Upon conclusion of this program, participants should be able to develop strategies for coronary artery disease risk reduction; evaluate and treat dizziness; differentiate between pain pharmacotherapy options; identify abnormal electrocardiograms; recognize skin cancer; diagnose and treat irritable bowel syndrome; evaluate and treat chronic obstructive pulmonary disease; identify and treat mild cognitive impairment; and evaluate thyroid nodules.
Contact: 800-462-9633; e-mail: cme-jax@mayo.edu

**Controversies in Women's Health** – June 18 - 20, 2009
Glacier Canyon Lodge, Wilderness Territory, Wisconsin Dells, WI

This course is designed to assist health care providers improve care of female patients based on emerging scientific and clinical evidence related to medical conditions that are unique to women, occur more frequently in women, or present differently in women. The course will include presentations from key women's health specialty and subspecialty disciplines, including obstetrics and gynecology, reproductive medicine, sexual health, menopausal medicine, cardiology, endocrinology, internal medicine, and preventive medicine. Learners will participate in didactic presentations, panel discussions, and small workshops.
Contact: 800-323-2688; e-mail: cme@mayo.edu

**For a listing of all Mayo Clinic CME opportunities visit www.mayo.edu/cme/**

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

Go to www.mayoclinic.org/medicalprofs/ to sign up for Mayo Clinic's new Physician Update e-mail newsletter.


MAYO CLINIC Physician Update

March 2008

Regional News
- Mayo Clinic in Arizona
- Mayo Clinic in Florida
- Mayo Clinic in Minnesota

Clinical Trials
Clinical Trials Open to Patient Recruitment

Referring a Patient
Arizona Referrals
(866) 629-6362
Florida Referrals
(800) 634-1417
Minnesota Referrals
(800) 533-1564
See Medical Professionals page for more physician resources.

Comments?
We're interested in your

Welcome to the first issue of Physician Update e-mail newsletter. This newsletter will offer access to articles from the Clinical Update print publication, plus other items of general interest to a physician audience.

Patient Care

**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

MAYO CLINIC

4500 San Pablo Road
Jacksonville, FL 32224

200 First Street SW
Rochester, MN 55905

13400 East Shea Boulevard
Scottsdale, AZ 85259

MC2024-0409

**www.mayoclinic.org**