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ENDOCRINOLOGY UPDATE

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Inside This Issue

Surgical Management of Recurrent Papillary Thyroid Cancer

Papillary thyroid cancer (PTC) recurs after apparently successful thyroidectomy in 15% to 30% of patients. Most of these patients have PTC recurrence despite postoperative remnant ablative therapy with radioiodine (RAI). Almost 90% of these recurrences are in the cervical lymph nodes—surgical excision of the recurrence provides the best opportunity for cure. Ian D. Hay, MD, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: "The decision to proceed with surgical intervention is made by the endocrinologist, surgeon, and patient. The factors to consider when making a recommendation for surgery include the extent of disease, risk versus benefit, and the willingness of the patient to undergo a reoperation."

Ian D. Hay, MD, PhD, Melanie L. Richards, MD, and Carl C. Reading, MD

Detection of Recurrent PTC

Dr Hay adds: "Postoperative high-resolution ultrasound (US) surveillance has become a routine component in the care of patients with PTC—a key advantage is that it can detect locoregional recurrences that may not be evident on RAI, computed tomographic (CT), or even positron emission tomographic/CT fusion scans. Neck US has allowed us to detect even tiny (2-5 mm) recurrences early and very accurately."

Melanie L. Richards, MD, of the Department of Surgery at Mayo Clinic in Rochester, says: "In patients undergoing a reoperation, US has a sensitivity of 90% and an accuracy of 88% for detecting locoregional recurrences. Even when a patient has palpable lymphadenopathy, a US study detects additional disease that alters the operation in 40% of patients."

Carl C. Reading, MD, of the Department of Radiology at Mayo Clinic in Rochester, explains: "Ultrasonography is an ideal method to detect PTC-related cervical metastases, not only because of its high sensitivity, but it is noninvasive, accessible, and less expensive than other imaging modalities. In addition, US-guided fine-needle aspiration (FNA) biopsy can be efficiently obtained at the time of the surveillance study. A patient with FNA-confirmed locoregional recurrence of PTC should be considered for surgical excision. A few patients with suspicious findings on imaging but without FNA confirmation may also be considered for surgery."

Operative Strategy

Dr Richards continues: "Reoperation in the neck

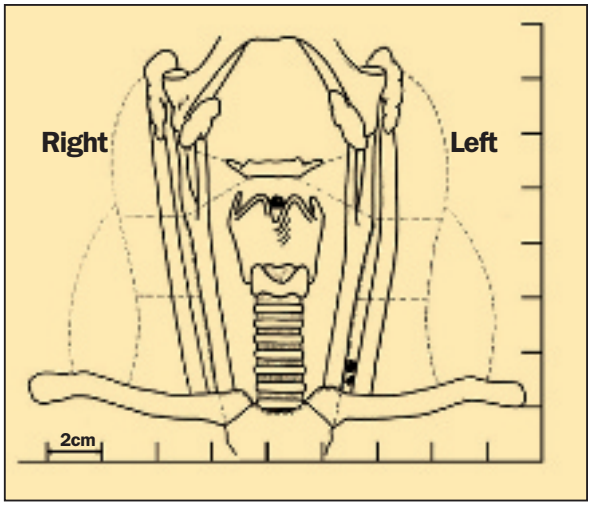


Figure 1. Ultrasound lymph node map in a patient with recurrent papillary thyroid carcinoma. The map shows lymph node metastases in the central compartment (level VI) and in the left lateral neck (level IV).

Figure 2. Neck ultrasound showing an 8-mm lymph node metastasis posterior to the carotid artery and internal jugular vein (arrow).

has traditionally been associated with increased rates of hypoparathyroidism and recurrent laryngeal nerve injury. These risks can be minimal with the technology available today. In the past, we were operating on disease that may have been found on RAI or CT scans. The exact location of the disease was difficult to identify, either secondary to the imaging or when dense scar tissue was encountered intraoperatively. High-resolution US has become a key component of successful operative management of patients with recurrent disease. The preoperative US is a 'road map' that is brought to the operating room. A US lymph node map of a patient with recurrent PTC to the central and lateral neck is shown in Figure 1, and the corresponding US is shown in Figure 2. The lymph node map includes the neck compartments. The recurrent disease is often not palpable, and lymph node mapping provides anatomic guidance for both the surgeon and the intraoperative ultrasonographer. After positioning the patient in the operating room, a US study is performed to identify the exact location of the disease. This allows the surgeon to perform a therapeutic compartment-oriented resection without having to do an extensive blind dissection—thus minimizing the opportunity for recurrent laryngeal nerve and parathyroid gland damage."

Extent of Operation

Dr Richards explains: "In the past, a 'node-picking' procedure was performed. In recent years, we have transitioned to a compartment-oriented approach to lymphadenectomy because there are often more positive nodes than those found on US. The central compartment is bounded by the hyoid bone superiorly, the innominate vessels inferiorly, and the carotid sheaths laterally. A central compartment lymphadenectomy is also referred to as a 'level VI' dissection. This is the site of primary drainage and the site of potential morbidity at reoperation. The best chance for adequate lymph node clearance of the central compartment is at the primary operation. We have found that nearly 40% of patients will have metastasis to the central compartment lymph nodes. Many of these lymph nodes harbor microscopic disease that evades clinical detection with US or palpation. The removal of these lymph nodes can decrease recurrence rates. However, it is unknown whether there is a survival advantage. At a reoperation for central compartment recurrences, the ideal procedure is a complete level VI dissection. However, this may not be possible when there is extensive scarring."

Many patients undergoing a reoperation also will have recurrence in the lateral neck. The lateral compartments or levels are shown in Figure 3. PTC that has spread to the lateral neck will usually be located in levels III, IV, and anterior V lymph nodes. A standard lateral neck dissection for PTC will include removal of these lymph nodes. A patient who has node-positive disease in the high jugular chain (level II) will have a standard lateral neck dissection in addition to removal of the level II nodes. A patient who has had prior central or lateral neck dissection may still develop recurrences in these regions. When this occurs, the patient will generally be treated with excision of the metastatic lymph nodes alone.

Dr Richards concludes: "The management of patients with locoregional recurrences of PTC is not limited to treatment with RAI. Advances in imaging technology have allowed these patients to undergo curative surgical resection with minimal morbidity."

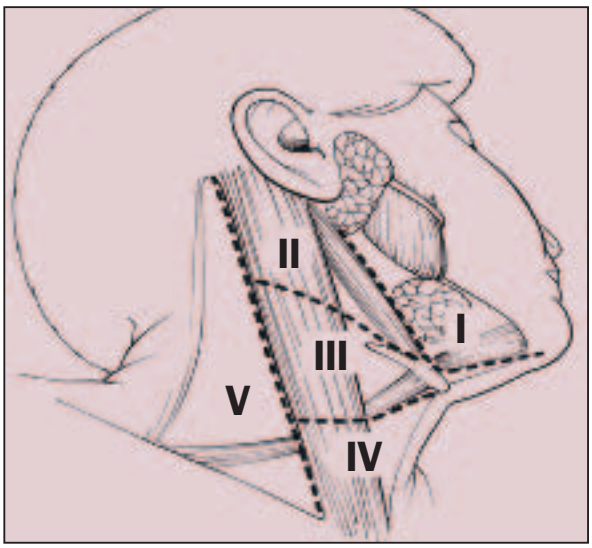


Figure 3. The lateral neck compartment levels.

The Laparoscopic Adjustable Gastric Band: A Recent Addition to the Surgical Options for Treatment of Obesity

The laparoscopic adjustable gastric band (LAGB) is one of the more recent additions to the surgical options for the treatment of obesity. Like other surgical approaches for weight loss, it is approved for use in patients with severe obesity (body mass index [BMI] ≥40 kg/m^2) or for patients with weight-related comorbid conditions and moderate obesity (BMI = 35 to 39.9 kg/m^2).

Florencia G. Que, MD, of the Department of Surgery at Mayo Clinic in Rochester, explains: "The LAGB system consists of a silicone ring with an inner inflatable cuff that is positioned laparoscopically around the upper part of the stomach—creating a small stomach pouch that leads to early satiety with smaller amounts of food (Figure 1). The silicone band is connected to a port in the abdominal wall, and the band can be adjusted by percutaneous addition of or removal of saline. The LAGB can be tightened every 4 to 6 weeks, or as needed. Because the procedure is laparoscopic and does not include bowel incisions, the perioperative risk is typically lower (1/2,500 vs 1/250 mortality rate) and the hospital stay shorter (outpatient or overnight vs 3 days) compared with the risk for Roux-en-Y gastric bypass (RYGB)."

Helen Karakelides, MD, and Florencia G. Que, MD

The rate of weight loss with LAGB is slower (5 to 10 pounds per month) than with RYGB (20 to 40 pounds per month for the first 3 months). However, the monthly weight loss with LAGB continues through the second year, whereas the weight loss with RYGB plateaus at 1 year—thus, after 2 to 3 years, patients treated with LAGB can have a total weight loss that approaches that achieved with RYGB (Figure 2). Three years postoperatively, the excess body weight loss is 39% to 55% with LAGB and 58% to 69% with RYGB. The resolution of weight-related comorbid conditions (eg, type 2 diabetes mellitus) is also more gradual with LAGB than with RYGB. RYGB causes weight loss by both restrictive and malabsorptive mechanisms. However, the mechanism of action of LAGB is restrictive only, and the risk of vitamin and mineral deficiencies is lower than with RYGB. The main risks of LAGB are nausea, vomiting, and aggravation of gastroesophageal reflux disease. The reoperation rate for patients who have had LAGB is equivalent to that of RYGB. Dr Que summarizes: "LAGB offers a safer operation for weight loss with results at 3 and 5 years approaching, but not meeting, those observed with RYGB."

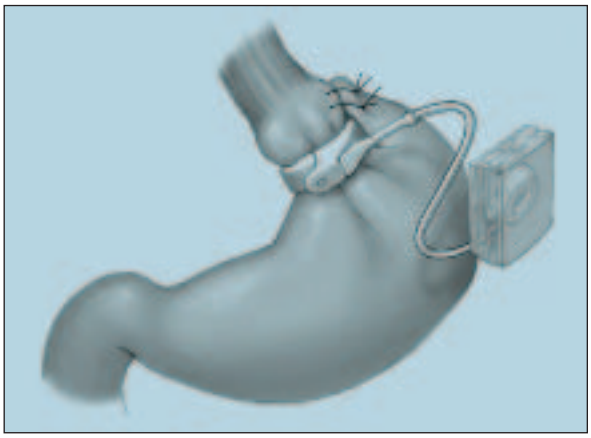


Figure 1. The LAGB bariatric operation consists of a silicone band with an inner inflatable cuff and a reservoir connected by tubing.

Helen Karakelides, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: "As with any bariatric procedure, the risks and benefits of LAGB need to be carefully considered. LAGB should be viewed as a tool to help with weight loss and it is not a solution in and of itself. Lifestyle modification—including healthier eating habits and increased physical activity—is key to successful short-term weight loss and long-term weight loss maintenance. A multidisciplinary approach to help with lifestyle modification before bariatric surgery is an integral part of success. Our team consists of physician nutrition specialists, nurse practitioners, bariatric surgeons, dietitians, psychologists, and physical therapists. Before determining which, if any, surgical procedure to aid with weight loss is most appropriate for a patient, the patient meets with several members of our team. Medical comorbid conditions and possible factors and conditions that may be contributing to obesity are assessed. Healthy eating habits that patients need to integrate into their lifestyle before surgery are reviewed. Behavioral modification—providing the tools necessary to overcome weight loss obstacles patients may have had in the past—aids in making and continuing the kinds of lifestyle modifications that will lead to successful weight loss and weight loss maintenance long term. Physical therapists may

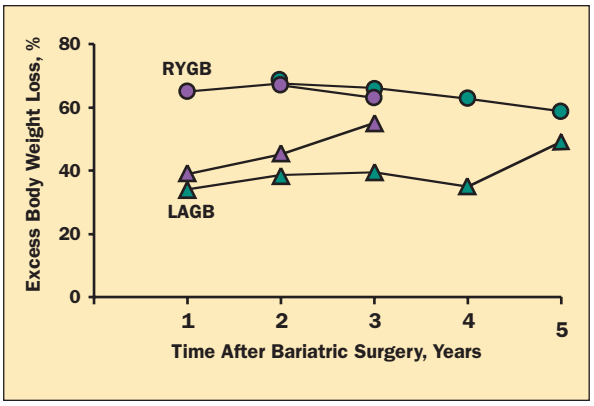


Figure 2. Rate of excess body weight loss over time after laparoscopic adjustable gastric band (LAGB) (triangles) and Roux-en-Y gastric bypass (RYGB) (circles) procedures. Data are from a 5-year follow-up study[a] (green symbols) and a 3-year follow-up study[b] (purple symbols).

[a]Jan JC, Hong D, Bardaro SJ, July LV, Patterson EJ. Comparative study between laparoscopic adjustable gastric banding and laparoscopic gastric bypass: single-institution, 5-year experience in bariatric surgery. Surg Obes Relat Dis. 2007;3:42-50; discussion 50-1. Erratum in: Surg Obes Relat Dis. 2007;3:203.

[b]Galvani C, Gorodner M, Moser F, Baptista M, Chretien C, Berger R, Horgan S. Laparoscopic adjustable gastric band versus laparoscopic Roux-en-Y gastric bypass: ends justify the means? Surg Endosc. 2006;20:934-41.

help develop a physical activity program that is suited for an individual's lifestyle and possible physical limitations."

After surgery, the multidisciplinary team continues to follow the patient at regular intervals for

- LAGB adjustment with the surgeon.
- Dietary guidance with dietitians to ensure the diet is being advanced appropriately. For example, after having the LAGB placed, patients are advised to be on a pureed diet for at least 4 weeks followed by slow progression to more solid food. Patients have to go back to a pureed diet, albeit for a shorter period, after the band has been adjusted.
- Assessment of medical comorbid conditions.
- Reassessment of compliance with ongoing lifestyle modification.

Dr Karakelides concludes: "At Mayo Clinic in Rochester, the LAGB is one of the newer surgical approaches being used to aid with weight loss as part of a multidisciplinary structured program to promote long-term weight loss success and improved health."

Treatment of Graves' Ophthalmopathy

Clinically evident Graves' ophthalmopathy (GO) occurs in approximately 20% of unselected patients with Graves' disease and in approximately 70% of patients if computed tomography (CT) or magnetic resonance imaging (MRI) is used to establish the diagnosis. Rebecca S. Bahn, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: "Fortunately, less than 5% of patients with Graves' disease have severe GO. The natural history of GO is characterized by a period of progression over a span of 3 to 6 months, a plateau phase lasting months to years, and then gradual, but incomplete improvement. Overall, 66% of untreated patients with mild to moderate GO show spontaneous improvement over a 12-month period, while about 10% deteriorate. A striking association between cigarette smoking and GO has been noted in several studies. 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."

James A. Garrity, MD, and Rebecca S. Bahn, MD

Hyperthyroidism Treatment

The most important factors in prevention of development or progression GO appear to be early and accurate control of thyroid dysfunction and counseling patients to quit smoking. The modality of treatment of hyperthyroidism is less important than restoring euthyroidism quickly and effectively and maintaining the euthyroid state. Dr Bahn advises: "In patients with moderately severe, active eye disease, especially

smokers, antithyroid drugs or the combined use of radioiodine and corticosteroids should be considered. The equivalent of 30 to 40 mg of prednisone daily, beginning the day after radioiodine is given with taper over 4 to 6 weeks, is generally used for prophylaxis. Hypothyroidism in these patients is to be avoided and frequent monitoring of thyroid status (every 4 to 6 weeks) is important 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 treated with either combined radioiodine and corticosteroids or thyroidectomy. Thyroidectomy in combination with total thyroid ablation using radioiodine holds the theoretical advantage of removing thyroid antigen, which could potentially serve to bolster the autoimmune response directed against this antigen. However, there is not enough evidence at present to support this as routine treatment."

Ophthalmopathy Treatment

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. Determining the appropriate treatment for patients with GO rests on assessing whether the eye disease is active (inflammatory) or inactive (quiescent) and defining the severity of the ocular symptoms. James A. Garrity, MD, of the Department of Ophthalmology, Orbital Surgery, and Neuro-ophthalmology, explains: "The vast majority of patients with GO have a self-limited and mild disease course requiring only local measures for symptomatic relief. These patients experience modest periorbital and eyelid edema, intermittent diplopia, photophobia, and a sensation of mild ocular irritation or dryness. Symptoms resulting from corneal drying are effectively treated with instillation of artificial tear eye drops and taping the eyelids shut at night to prevent nocturnal corneal drying. Worsening of diplopia and soft tissue changes during the night result from dependent edema, which may respond to elevation of the head. The use of sunglasses or tinted lenses may assist in decreasing photophobia. Prisms are occasionally useful for the correction of mild diplopia."

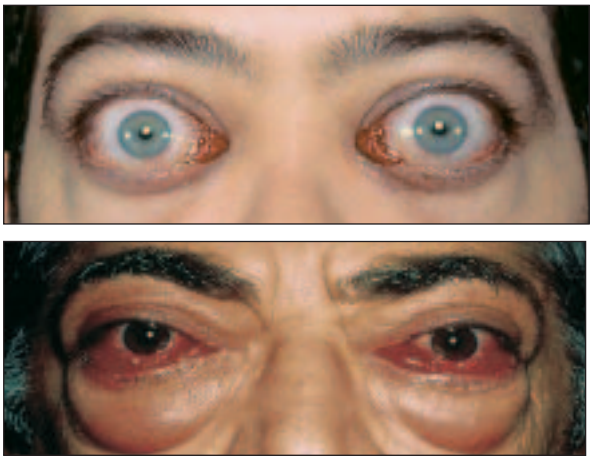


Figure 1. Patients with severe Graves' ophthalmopathy (GO). The patient on the top, with extreme proptosis, corneal ulceration and lid retraction, and extraocular muscle dysfunction, would likely benefit from orbital decompression surgery followed by extraocular muscle and eyelid surgery. The patient on the bottom, with very active inflammatory GO, would likely respond to corticosteroid therapy.

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 (Figure 1). Dr Bahn advises: "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 (Figure 2). While oral corticosteroids have been shown to be effective in approximately 66% of patients with active GO, evidence is mounting that intravenous corticosteroids may be somewhat more effective in providing relief from pain, injection, and conjunctival edema. High-dose intravenous corticosteroids may be effective as a first-line therapy for compressive optic neuropathy; if ineffective after 2 weeks, orbital decompression is recommended. Oral corticosteroid therapy is generally initiated with a relatively high dose, such as 60 to 80 mg of prednisone per day. After 2 weeks, the dose is tapered by 5 to 10 mg every 2 to 3 weeks, with slower taper as doses approach 7.5 mg per day. In many instances, drug withdrawal results in exacerbation, which requires small increases in dosage and a slowing of the rate of subsequent taper. Improvement in soft tissue inflammation begins within 1 to 2 days, and typical courses range from 3 to 6 months. Pulse therapy with intravenous methylprednisolone acetate may be considered—this therapy should be undertaken only in centers with appropriate expertise, given the small risk for fatal hepatotoxicity. In

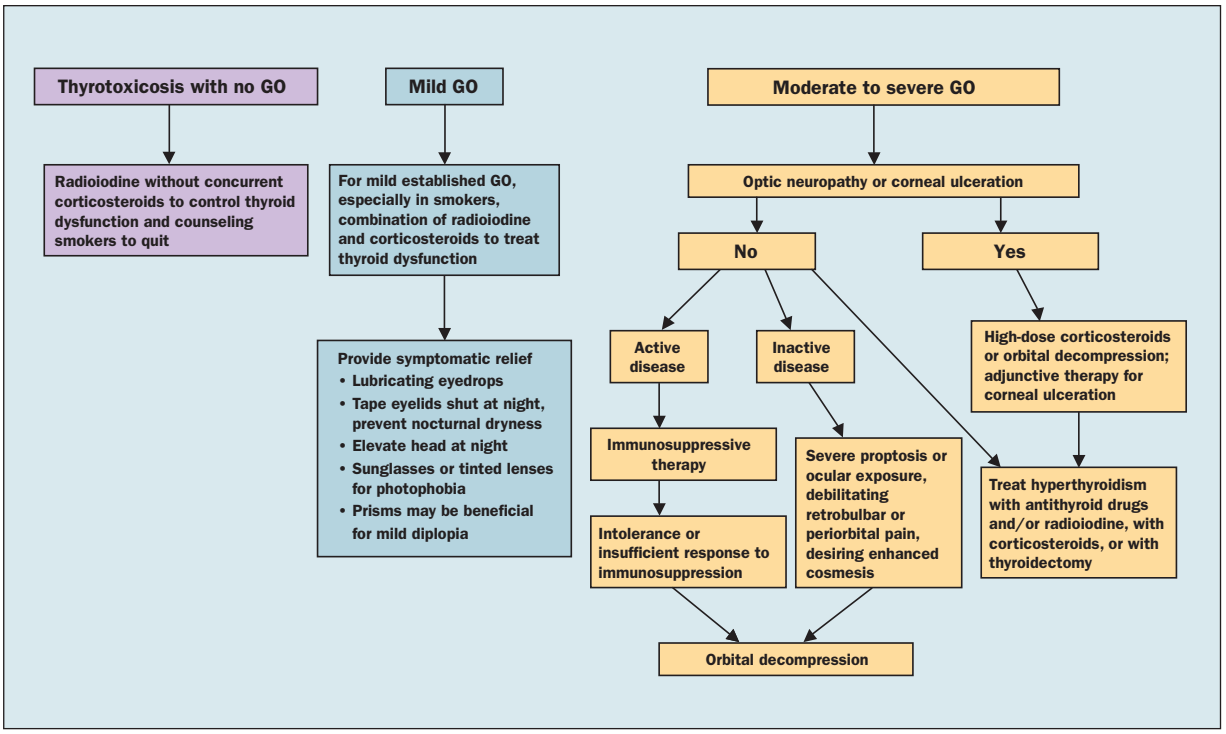


Figure 2. Approach to the treatment of patients with Graves' ophthalmopathy (GO) and associated thyrotoxicosis.

addition, orbital radiotherapy, by itself or in combination with corticosteroids, may be of benefit to patients with active GO, especially those with extraocular muscle dysfunction. We are currently recruiting patients with active, moderate to severe GO for a randomized clinical trial to determine the effectiveness in these patients of rituximab, an immunosuppressive anti-CD20 monoclonal antibody used in the treatment of rheumatoid arthritis."

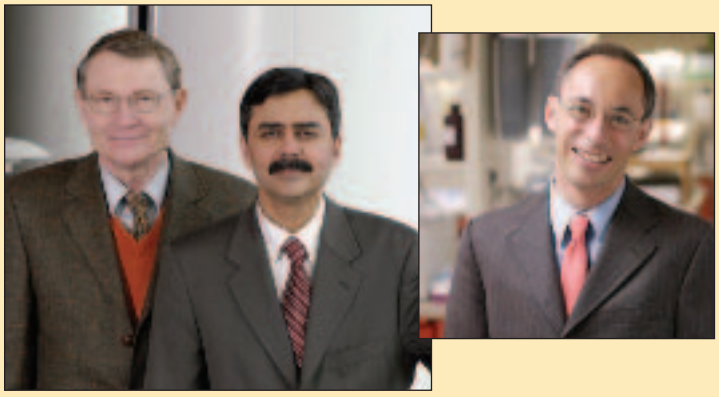
Orbital decompression surgery is generally considered in patients with GO who have severe proptosis, orbital congestion, or ocular exposure or who desire enhanced cosmesis. Dr Garrity adds: "In addition, orbital decompression is effective for treatment of optic neuropathy and as adjunctive therapy for 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. Optic neuropathy is our most common indication for orbital decompression. It is important to recognize that patients with optic neuropathy often have less exophthalmos than do patients without optic nerve compromise because proptosis may 'autodecompress' the orbit. The orbit is decompressed surgically by removing one or more of its bony walls, which expands the eye socket and increases the potential space for the orbital contents. It is important to restore thyroid hormone levels to normal before any type of orbital surgery is performed, with the single exception to this rule being when very severe GO threatens vision and requires urgent orbital decompression.

"Eye muscle surgery (strabismus surgery) is typically performed after decompression surgery if the patient has diplopia postoperatively. In patients not requiring decompression, strabismus surgery may be performed following 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 deviant gaze may persist after surgery. Eyelid surgery for GO usually follows orbital decompression and strabismus procedures, if either or both are needed. The retractors of the upper eyelid, the levator palpebrae superioris and Müller's muscle, undergo pathologic changes similar to those seen in the extraocular muscles. Upper lid retraction is relieved by weakening (recessing) the muscles; lower lid retraction is treated with analogous procedures. Blepharoplasty (removal of excess eyelid and orbital tissue that prolapses anteriorly from the increase in orbital volume) may be indicated in selected patients."

Recognition

Ian D. Hay, MD, PhD, was elected for a second term to the Executive Council of the American Thyroid Association (2007-2011). F. John Service, MD, PhD, will be given the 2008 Endocrine Society Distinguished Clinician Award.

Diana S. Dean, MD, received the 2007 Mayo Clinic Fellows Association Teacher of the Year Award in Endocrinology. Bart L. Clarke, MD, received the 2007 Mayo Clinic Department of Medicine Laureate Award.



Johannes D. Veldhuis, MD, was appointed to the Scientific Board of Councilors of the National Institute on Aging. Sundeep Khosla, MD, was appointed to the National Institute on Aging Council, was elected to the Association of American Physicians, and received the 2007 National Osteoporosis Foundation Award for Innovation in Osteoporosis Research. James A. Levine, MD, PhD, won the 2007 Minnesota Cup for Minnesota's most innovative new business through the State of Minnesota.

Hossein Gharib, MD, is President-Elect of the American College of Endocrinology. Daniel L. Hurley, MD, was elected to Board of Directors of the American Association of Clinical Endocrinologists in 2007.

Roger L. Nelson, MD, received the 2007 Mayo Clinic Rochester Distinguished Educator Award. M. Molly McMahon, MD, was elected to the American Board of Physician Nutrition Specialists' Board of Directors in 2007.

Education Opportunities

11th Mayo Clinic Endocrine Course, April 16-19, 2008, Palma de Mallorca, Spain. This course, created for endocrinologists and interested internists and surgeons, will cover selected topics in endocrinology through short lectures, case-based debates, clinicopathologic sessions, and clinical pearls sessions. For more information about this course, please visit http://endocourse.mayo.edu.

Mayo Clinic Nutrition in Health and Disease, October 9-10, 2008, Chicago, Illinois. This course, designed for physicians, dietitians, nurses, and pharmacists, will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory and hospital settings. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html

Mark Your Calendars! 12th Mayo Clinic Endocrine Course, March 16-20, 2009, on the Big Island of Hawaii. This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. This 5-day course (7:30 AM to 12:30 PM daily) will span the full spectrum of endocrinology.

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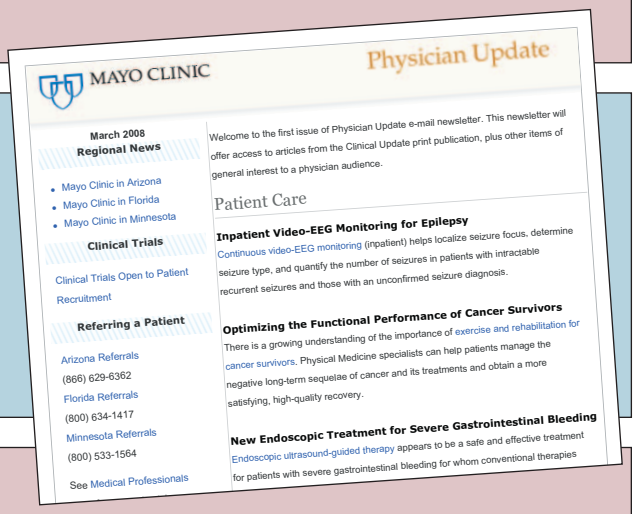
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March 2008
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Welcome to the first issue of Physician Update e-mail newsletter. This newsletter will offer access to articles from the Clinical Update print publication, plus other items of general 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

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