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Parathyroid Carcinoma: Update on Treatment Options

Parathyroid carcinoma is a rare condition, accounting for 0.005% of all cancers in the United States and less than 1% of patients with primary hyperparathyroidism (HPT). However, the incidence of parathyroid carcinoma appears to be increasing. The Surveillance, Epidemiology, and End Results Cancer Registry showed a 60% increase in incidence from 1988 to 2003.

Robert A. Wermers, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Parathyroid carcinoma should be suspected in patients with primary HPT who have severe hypercalcemia (ie, serum calcium concentrations that are 3 to 4 mg/dL above the upper limit of the reference range) and markedly increased blood concentrations of parathyroid hormone (PTH) (ie, concentrations that are 3- to 10-fold greater than the upper limit of the reference range). Complications related to primary HPT (eg, nephrolithiasis, renal insufficiency, metabolic bone manifestations) are more likely to be present in patients with parathyroid carcinoma. Additional clinical clues that a patient with primary HPT may have parathyroid carcinoma include a palpable neck mass,

recurrent laryngeal nerve paralysis, and recurrent primary HPT in a patient with severe primary HPT. Parathyroid carcinoma has been identified in patients with familial primary HPT due to mutations in *HRPT2*—the gene associated with hyperparathyroidism–jaw tumor syndrome (HPT-JT). An estimated 15% to 20% of primary HPT cases in families with HPT-JT are due to parathyroid carcinoma. Some patients

with sporadic parathyroid carcinomas have also been shown to have somatic or germline mutations in *HRPT2*."

The natural history of parathyroid carcinoma can be variable, with some individuals experiencing a long, indolent course. Geoffrey B. Thompson, MD, of the Department of Surgery at Mayo Clinic in Rochester, explains: "Complete surgical resection of the tumor is the mainstay of treatment of parathyroid carcinoma, with *en bloc* tumor resection being the procedure of choice [Figure]. A review from Mayo Clinic Rochester that spanned 70 years showed that disease recurrence is frequent, with 26 of 43 (60%) patients requiring a second operation."

When locally invasive disease or metastases are present, chemotherapy and radiation therapy have been used, with varying degrees of success. Robert L. Foote, MD, of the Department of Radiation Oncology at Mayo Clinic in Rochester, comments: "In general, radiation therapy for inoperable parathyroid carcinoma has been found to be ineffective. However, case reports of adjuvant radiation therapy for parathyroid carcinoma have shown promise. We recently reviewed our experience with 5 patients with parathyroid carcinoma who received adjuvant radiation therapy because of the concern of possible residual microscopic disease after surgery. The median radiation dose was 70 Gy (range, 60-70 Gy), administered in 35 fractions (range, 30-35 fractions) over 50 days (range, 42-63 days). At the time of last follow-up, with a median follow-up period of 101 months (range, 77-115 months), none of the 5 patients who had undergone adjuvant radiotherapy to the operative bed and adjacent lymph nodes had evidence of recurrence. In 22 patients with parathyroid carcinoma who did not receive radiation therapy after surgery, recurrent disease was evident in 9 (41%)

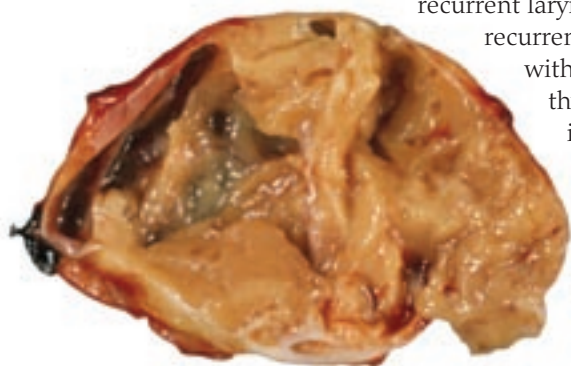


Figure. Cut surface of gross pathology specimen from a large parathyroid carcinoma. The carcinoma measures 5 cm at its largest diameter.

patients. Five patients in this subset died, with 3 deaths occurring directly from the consequences of recurrent parathyroid cancer. Complications from adjuvant radiotherapy included hypothyroidism (n=2), esophageal stricture (n=2), transient mucositis and dermatitis (n=5), and xerostomia (n=1), and possibly Lhermitte sign (n=1), which resolved spontaneously. Although the data are limited by the small number of patients, it appears that parathyroid carcinoma may be a radiosensitive tumor. Furthermore, some patients with parathyroid carcinoma appear to benefit from adjuvant radiation therapy. However, it is unclear which patients may benefit the most from adjuvant radiotherapy, given the often unpredictable nature of this malignancy."

Dr Thompson explains: "Aggressive resection of recurrent disease can offer considerable clinical benefit in patients with metastatic parathyroid carcinoma. The lung is the most common site of distant metastases in patients with parathyroid carcinoma. Long-term remission has been described in patients undergoing removal of lung metastases."

Dr Wermers adds: "When parathyroid carcinoma is widely metastatic and surgical resection is no longer an option, treatment of the hypercalcemia becomes the primary clinical focus since it is the main cause of death. Saline infusions and potent, intravenously adminis-



Robert A. Wermers, MD, Geoffrey B. Thompson, MD, and Robert L. Foote, MD

tered bisphosphonates may control hypercalcemia transiently. Cinacalcet hydrochloride is a calcimimetic agent that is approved by the US Food and Drug Administration for the treatment of refractory hypercalcemia due to parathyroid carcinoma. It directly reduces PTH secretion by binding to the calcium-sensing receptor on parathyroid cells, thereby increasing their sensitivity to extracellular calcium. However, the use of cinacalcet is limited by its high cost and adverse effects, the most severe of which is nausea. Anti-PTH immunotherapy has also shown promise, with biochemical improvement and tumor shrinkage in a small number of patients with refractory parathyroid carcinoma."

Mayo Clinic Hospital Rules–Based System for Nutrition Services: Feeding Effectively Using Electronic Data

Mayo Clinic Hospital Nutrition Support Services (NSS) is staffed by consultants from the divisions of endocrinology, gastroenterology, and preventive medicine. M. Molly McMahon, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Although many hospital nutrition services are not staffed by endocrinologists, we believe that our role is important in this field. Each hospital team also includes dietitians, nurses, pharmacists, and house staff. Nutrition support is a costly form of therapy that provides substantial benefits when



John W. Wilson, MD, and M. Molly McMahon, MD

used appropriately, but it also carries risks. Initially, we advise whether nutrition support is indicated and, if so, which route (gastric or jejunal tube feeding or parenteral nutrition [PN]) is optimal. Subsequently, we recommend the nutrition program tailored to the patient and the patient's clinical condition and provide a metabolic monitoring program. One of our goals is to prevent or minimize the frequency of nutrition-related complications, including overfeeding (with potential for hyperglycemia). We also address nutrition access device concerns, site care issues, and drug-nutrient interactions."

Mayo Clinic has a hospital rules-based system (HRBS), which is a Web-based program developed to rapidly identify and communicate needed information to clinicians to optimize patient care and safety, standardize care, and enhance workload efficiency. John W. Wilson, MD, of the Division of Infectious Diseases at Mayo Clinic in Rochester, chairs the HRBS Oversight Committee and oversees development and resource allocation for each of the HRBS subsystems. Dr Wilson explains: "Compilation and integration of patient information from various sources had been estimated to consume up to one-third of a physician's time. HRBS markedly decreases this onerous task by integrating computerized data from hospital admissions, laboratory, microbiology, PN, and pharmacy databases into 1 place that can be used by a number of subsystems. The Feeding Effectively Using Electronic Data (FEED) program was developed in 1999 for use on our hospital nutri-

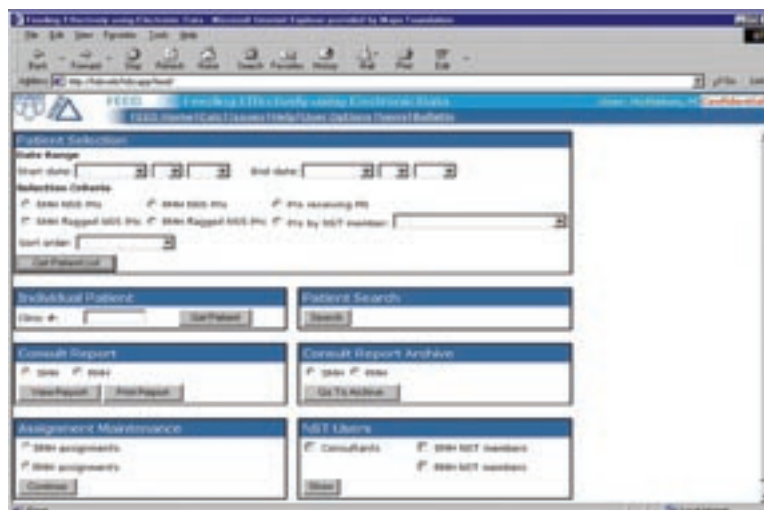


Figure. Computer screen shot showing the initial electronic page in the Feeding Effectively Using Electronic Data program.

tion services [Figure]. Other subsystems are used for computer-based antimicrobial monitoring (the initial program and template), pharmaceutical care, surveillance of infection, and heparin dosing."

FEED uses rules created by nutrition physicians (Box 1) and incorporated into computerized logic algorithms by the information technology programmers. The rules can use information from any of the integrated electronic data systems. Dr McMahon highlights: "Rules tested include PN calories prescribed compared with the Harris-Benedict estimate of daily caloric requirement; PN protein based on body weight and as a percentage of total calories; PN fat as a percentage of total calories; nutrient substrate (levels of glucose, sodium, potassium, triglycerides, international normalized ratio, and minerals); organ function (renal, hepatic, pancreatic, and thyroid laboratory results); and PN or intravenous insulin with no glucose determination in the past 24 hours. A list was created for medications with drug-nutrient or tube-feeding interactions or with metabolic or gastrointestinal effects. FEED tests rules daily at 6:00 AM and flags the name of patients for whom PN formulas or laboratory results are out of range. In the future, tube-feeding formula information will be added to allow testing of rules."

FEED also has a calculator component. Automated calculations are performed and displayed, including body mass index and the Harris-Benedict equation, to estimate basal daily caloric requirements. A specialized calculator can compute a PN formula, including maintenance fluid or fluid-restricted formulas, and osmolality, which is needed for peripheral

Box 1. Rules Tested in the Feeding Effectively Using Electronic Data Program

- Calories prescribed compared with Harris-Benedict estimate
- Protein portion based on body weight and as a percentage of total calories
- Fat portion as a percentage of total calories
- Nutrient substrate: glucose, sodium, potassium, triglycerides, INR, and minerals
- Organ function: renal, hepatic, pancreatic, and thyroid
- PN or intravenous insulin: no glucose check in past 24 h

Abbreviations: INR, international normalized ratio; PN, parenteral nutrition.

PN formula design.

Dr McMahon continues: “The system displays data from multiple electronic sources in a specially formatted report used for daily rounds. The report offers information about nutrition data, PN composition (macronutrient and micronutrient composition and PN insulin), biochemical and microbiology results (eg, blood culture results for patients with PN catheters), radiologic studies (eg, position of central catheter tip), and surgical reports (eg, amount of bowel resected). FEED provides information about the prescribed PN content (compared with estimated needs), metabolic and laboratory test data, and medication profiles [Box 2]. Team members can review biochemical data with knowledge of specific PN formulas and additives. Patients requiring more focused PN analysis are efficiently identified. This Web-based system communicates needed patient information, improves safety,

Box 2. Clinical Uses of Feeding Effectively Using Electronic Data

Glucose management: review for overfeeding; PN dextrose; dextrose from other crystalloid infusion; PN, intravenous, and subcutaneous insulin; PN discontinuation; medications that can affect glucose levels (eg, corticosteroids, propofol, sympathomimetics); and glucose trends

Volume excess: evaluate potential for fluid-restricted PN

Obesity: review PN calories and protein

Propofol use: check triglyceride value and reassess PN fat content

Refeeding risk: review PN content with electrolyte and mineral values

CVVHD or HD: review PN content with electrolyte and mineral values; assess protein content

Highlight vitamin levels

Medications on consult report

- Nutrition supplements: electrolyte, mineral, and vitamin supplements
- Drug-nutrient interactions: amphotericin B and phenytoin
- Endocrine-related medications: insulin, corticosteroids, and thyroid hormones
- Gastrointestinal medications: prokinetics, antidiarrheals, and laxatives

Abbreviations: CVVHD, continuous venovenous hemodialysis; HD, hemodialysis; PN, parenteral nutrition.

standardizes care, enhances efficiency of daily rounds, and improves team satisfaction but does not take away from the value of the clinician’s judgment.”

Evaluation and Management of the Incidentally Found Pituitary Mass

You review the magnetic resonance imaging (MRI) scan of a patient who presented with headaches after head trauma. No brain injury is present, but a mass is visible in the pituitary gland (Figure)—a pituitary incidentaloma, or an asymptomatic mass in the pituitary gland found on imaging done for an unrelated reason. What tests, if any, should you obtain? Does the pituitary mass need treatment, or may it be monitored rather than treated?

Todd B. Nippoldt, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “To answer these questions and to develop rational recommendations for



Todd B. Nippoldt, MD

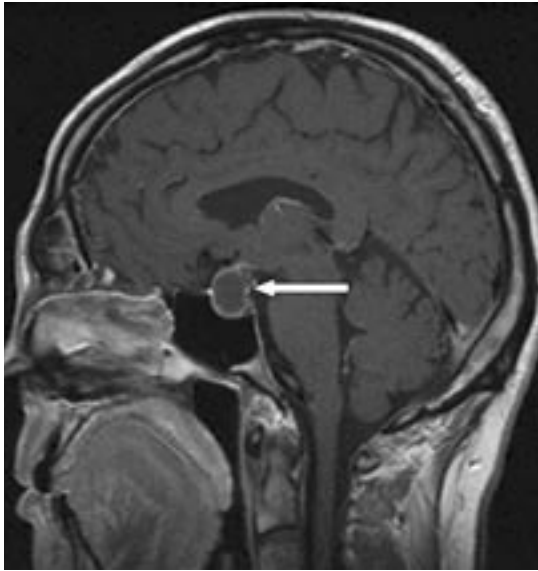


Figure. Magnetic resonance imaging scan (sagittal image) showing an incidentally discovered 2-cm pituitary mass (arrow).

the testing and follow-up of a patient with a pituitary incidentaloma, the physician needs to 1) confirm that the patient is asymptomatic, 2) consider the possible etiologic factors of the mass, and 3) consider the potential for and the clinical impact of hormone deficiency, hormone excess, and mass growth.”

Autopsy and head MRI studies indicate that the prevalence of incidentally discovered pituitary masses is approximately 10%. Most pituitary incidentalomas are less than 1 cm in largest diameter and prove to be pituitary adenomas or Rathke cleft cysts.

Potential for Hormonal Hyperfunction

Dr Nippoldt explains: “Prolactin-producing pituitary adenomas are common (12%-28%) in patients with pituitary incidentalomas. Prolactinomas have potential for morbidity, testing is easy, and treatment is safe and effective. The incidence of growth hormone (GH) production by an incidentally found pituitary mass is between 2% and 8%. Patients whose pituitary incidentaloma is detected early in the course of disease may have GH-related symptoms and physical findings that are subtle. However, there is potential for serious morbidity and increased risk of death when GH excess goes undiagnosed. In addition, the likelihood of surgical cure for a GH-secreting pituitary adenoma is increased when the tumor is small.”

Dr Nippoldt continues: “Although 1% of the pituitary adenomas detected at autopsy are corticotroph adenomas, no instances of

corticotropin excess have been reported in clinical studies of pituitary incidentaloma. Cushing disease is a serious disorder, but testing for corticotropin excess in asymptomatic patients with pituitary incidentaloma is not recommended because of the low prevalence of disease and the high false-positive rates associated with the case detection tests used for this disorder. Gonadotroph cell adenomas represent approximately 4% of pituitary adenomas discovered at autopsy. Most gonadotroph cell adenomas do not hypersecrete luteinizing hormone or follicle-stimulating hormone. Thus, there is no reliable preoperative biochemical test to detect gonadotroph adenomas. Thyrotrophin (TSH)-secreting pituitary adenomas are exceedingly rare, and none have been reported in clinical or autopsy series of incidentally found masses. Patients with TSH-secreting pituitary tumors usually present with signs and symptoms of hyperthyroidism.”

Potential for Hormonal Hypofunction or Growth

Pituitary microadenomas (≤ 10 mm in largest diameter) have a very low probability of being associated with hormonal hypofunction of the neighboring pituitary gland; most studies report an incidence of 0%. However, macroadenomas (>10 mm in largest diameter) (Figure) are frequently (15%-57%) associated with varying degrees of pituitary hypofunction. Both microadenomas and macroadenomas have the potential to increase in size over time. Growth may occur after several years of apparent stability. Growth of a macroadenoma is more likely to be detected (up to 50% enlarge) during imaging follow-up than growth of a microadenoma (up to 22% enlarge). Any increase in the size of a macroadenoma is associated with an increased probability of clinically important mass effects (eg, hypopituitarism, vision loss).

Recommended Management for Pituitary Incidentaloma

Dr Nippoldt advises: “To exclude excess hormone production, measurement of prolactin and insulinlike growth factor 1 (IGF-1) should be obtained in all patients with pituitary incidentalomas (Box). Laboratory testing to exclude pituitary hormone deficiencies is not needed for patients with microadenomas. However, the following blood tests should be obtained for patients with macroadenomas: TSH, free thyroxine, cortisol measured at 8 AM, prolactin, and IGF-1. With regard to gonadal

Box. Recommended Laboratory Studies for Patients With Pituitary Incidentalomas

	To Assess Subclinical Hormone Excess		To Assess Subclinical Hormone Deficiency	
Blood Tests	Microadenoma ^a	Macroadenoma ^b	Microadenoma ^a	Macroadenoma ^b
Prolactin	X	X		
IGF-1 ^c	X	X		X
FT ₄ , TSH				X
Testosterone (men)				X
8 AM cortisol ^c				X

^a Adenoma ≤10 mm in largest diameter.

^b Adenoma >10 mm in largest diameter.

^c IGF-1 and 8 AM cortisol levels may not be sufficient to indicate normalcy or deficiency, and dynamic studies may be necessary.

Abbreviations: FT₄, free thyroxine; IGF-1, insulinlike growth factor 1; TSH, thyrotropin.

function, a menstrual history should be obtained for women and serum testosterone concentration should be measured for men. The physician should keep in mind that baseline blood levels of cortisol and IGF-1 may not be sufficient to indicate normalcy or deficiency and that dynamic studies may be necessary. Quantitative perimetry to assess visual fields should be obtained when a macroadenoma is near or in contact with the optic chiasm.”

Dr Nippoldt continues: “Observation is appropriate when there is no evidence of pituitary hormone hyperfunction or hypofunction and when the pituitary mass is not causing

or threatening vision loss. Reevaluation with pituitary-directed MRI should be completed 6 to 12 months after the initial scan, annually for 2 to 4 years, and periodically thereafter. All follow-up scans should be compared with the baseline scan in addition to the prior scan, since slow changes in size may not be appreciated from one year to the next. The follow-up for pituitary macroadenomas should also include formal visual field assessment, since the decision to remove a nonfunctioning macroadenoma rests primarily on the development or risk of vision loss.”

Treatment of Diabetic Gastroparesis

Gastrointestinal symptoms are commonly reported by people with diabetes mellitus. The evaluation of diabetic gastrointestinal dysmotility was reviewed in Volume 4, Issue 2, of Mayo Clinic *Endocrinology Update*. Herein is a discussion on the treatment of diabetic gastroparesis.

Gianrico Farrugia, MD, of the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota, explains: “The treatment of complications of diabetes

should be directed only toward symptoms and not toward test results. This approach is taken because often a disconnect exists between the severity of symptoms and the severity of the abnormality measured. For example, patients may have markedly delayed gastric emptying yet be asymptomatic, or patients may have severe nausea and vomiting with relatively normal gastric emptying—the latter most likely due to the counteracting effects of decreased contractility and reduced accommodation.”

Adrian Vella, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, advises: “A medication history will pick up drugs that can delay gastric emptying, such as synthetic analogues of amylin and functional analogues of glucagon-like peptide 1. Experimental evidence strongly suggests that the cellular defects in diabetic gastroparesis can be reversed by reducing oxidative stress. From a practical standpoint, a reduction in oxidative stress can be most easily accomplished by optimizing glycemic control. Although there is no well-established link between long-term high glucose levels and damage to interstitial cells of Cajal or enteric nerves, improved glucose control is usually accompanied by decreased oxidative stress. However, the clinical utility of antioxidant use has not been tested in gastroparesis. The next step should be to modify the diet. Small, frequent meals with less fat are easier to empty from the stomach than standard meals. Also, meals should be low in fiber to prevent bezoar formation. If calories are an issue, liquid caloric supplementation (a low-fiber version) is usually well tolerated.”

Nausea and vomiting are often features of diabetic gastroparesis and should be aggressively targeted with such drugs as prochlorperazine. Dr Farrugia comments: “The current promotility armamentarium is limited. Metoclopramide hydrochloride (10 mg administered orally 4 times a day) improves gastric emptying by about 26%. However, its well-known adverse effect profile—including the risk of tardive dyskinesia—limits the use of this drug. Domperidone maleate is an agent that is widely used outside of the United States. Although it is not approved by the US Food and Drug Administration (FDA) for general prescribing, the FDA has set up a program that allows prescription of domperidone with local institutional review board approval. Erythromycin works on motilin receptors found on both enteric nerves and smooth muscle cells. It is a powerful prokinetic; however, after a few days of use, its effect wears off rapidly because of tachyphylaxis. Lower doses of the drug (eg, 125 mg administered orally 3 times a day) work better than higher



Adrian Vella, MD, and Gianrico Farrugia, MD

doses. Erythromycin is best reserved for use in hospital as an intravenous agent during flare-ups of the disease, although some physicians find it beneficial to use on an every-other-week dosing strategy. Initial enthusiasm for the use of botulinum toxin injected into the pylorus has waned after the publication of 2 studies that found no benefit.”

In recent years, gastric pacing has been introduced. Smooth muscle cells have a cyclic oscillation in membrane potential, known as the *slow wave*. Contractions occur only at the most depolarized portion of the slow wave. Dr Farrugia explains: “We now know that the origin of the slow wave is the interstitial cell of Cajal, which functions as a pacemaker cell. Laboratory studies have shown that with enough energy and the right pulse frequency, one can entrain the stomach and deliver a slow wave that will increase gastric emptying. To date, because of energy limitations, these stimulators do not entrain the native slow wave and have a frequency of 12 pulses per minute (unlike the human antral contractions with a frequency of 3 to 4 pulses per minute). However, by activating afferent nerves, these devices do work to decrease nausea and vomiting and sometimes to a dramatic degree. Placement of stimulators has potential complications (eg, infection at the site of the leads or the battery pocket), and effectiveness varies from patient to patient. After stimulators are implanted, close monitoring of the patient is required because adjustments to the electrical parameters may be needed.”

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2009 Graduating Endocrine Surgery Fellow

Kimberly Vanderveen, MD, and her program director, Clive S. Grant, MD. Dr Vanderveen's new appointment is at Presbyterian Hospital in Albuquerque, New Mexico.



CME Opportunities

Mayo Clinic Nutrition and Wellness in Health and Disease

September 24-25, 2009, Graves 601 Hotel, Minneapolis, Minnesota. This course—designed for physicians, nurse practitioners, physician assistants, dietitians, and health and wellness staff—will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory and hospital settings. An additional objective is to discuss wellness programs that include nutrition, activity, and other lifestyle behaviors. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

13th Mayo Clinic Endocrine Course,

July 14-17, 2010, Rochester, Minnesota. This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

Highlights From the 2009 Mayo Clinic Endocrine Course

The 12th Mayo Clinic Endocrine Course—held March 16-20, 2009, in Big Island of Hawaii—included 225 physicians from 19 countries. Simultaneous Japanese translation was provided. Other unique aspects of the course included short lectures, case-based debates, clinical pearls sessions, computer-based clinicopathologic case presentations, and case snappers presented by course attendees.



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