

**THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND
THE AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS
POSITION STATEMENT ON THE DIAGNOSIS AND MANAGEMENT
OF PRIMARY HYPERPARATHYROIDISM**

AACE/AAES Task Force on Primary Hyperparathyroidism

Co-Chairpersons

John S. Kukora, MD, FACS, FACE

Martha A. Zeiger, MD, FACS

Committee Members

Orlo H. Clark, MD, FACS

Clive S. Grant, MD, FACS

Stephen F. Hodgson, MD, MACE

George L. Irvin III, MD, FACS

Michael Kleerekoper, MD, FACE

Janice L. Pasieka, MD, FACS

Ashok R. Shaha, MD, FACS

Geoffrey B. Thompson, MD, FACS, FACE

Jon A. van Heerden, MD, FACS, FRCSC

Collin J. Weber, MD, FACS



THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS POSITION STATEMENT ON THE DIAGNOSIS AND MANAGEMENT OF PRIMARY HYPERPARATHYROIDISM

AAACE/AAES Task Force on Primary Hyperparathyroidism

Abbreviations:

BMD = bone mineral density; **DEXA** = dual-energy x-ray absorptiometry; **FHH** = familial hypercalcemic hypocalciuria; **HPT** = hyperparathyroidism; **NIH** = National Institutes of Health; **PHPT** = primary hyperparathyroidism; **PTH** = parathyroid hormone

DEFINITION, EPIDEMIOLOGY, AND PATHOGENESIS

Primary hyperparathyroidism (PHPT) is a disease characterized by hypercalcemia attributable to autonomous overproduction of parathyroid hormone (PTH). Although some patients with PHPT may have normal serum calcium concentrations, most have hypercalcemia. Therefore, PHPT can often be detected by routine serum calcium measurement. PHPT is present in about 1% of the adult population. The incidence of the disease increases to 2% or higher after age 55 years and is 2 to 3 times more common in women than in men.

PHPT is caused by a single parathyroid adenoma in about 80 to 85% of cases. The rest of the cases of PHPT can be ascribed to multiple gland hyperplasia affecting all parathyroid glands in about 10%, double adenomas in 4%, and parathyroid carcinoma in 1%. The cause of PHPT may be multifactorial and appears to be associated with overexpression of cyclin D1 and a deficiency of the *MEN1* tumor suppressor gene (1). The clinical features of PHPT are mainly due to the direct and indirect effects of excess PTH on the skeleton, kidneys, and intestine and normally include (1) bone resorption of calcium and phosphorus, (2) enhanced intestinal absorption of calcium, (3) renal tubular reabsorption of calcium, and (4) hypercalciuria.

Surgical removal of a solitary parathyroid tumor or subtotal resection of all pathologic parathyroid tissue in patients with hyperparathyroidism (HPT) results in normalization of PTH secretion, normalization of serum calcium levels, and a durable cure. Parathyroidectomy is the only curative therapy for PHPT and is both safe and cost-effective.

DIAGNOSIS

PHPT is the most common cause of hypercalcemia in the outpatient setting and is usually discovered by routine laboratory testing. Most patients with PHPT are asymptomatic. If patients are symptomatic, common related findings may include a history of renal calculi, bone pain, pathologic fractures, bone shaft tumors, proximal muscle weakness (especially of the lower extremities), or nonspecific symptoms such as depression, lethargy, and vague aches and pains.

Occasional patients may have a history of head and neck irradiation, a family history of multiple endocrine neoplasia syndromes (type 1 or 2), familial HPT (non-multiple endocrine neoplasia), or familial HPT and jaw tumor. The last-mentioned finding is associated with parathyroid cancer. Profound mental obtundation or coma is an infrequent but life-threatening complication of severe hypercalcemia (hypercalcemic crisis). All patients with calcium-containing renal stones should be evaluated for PHPT, and in patients with clinical manifestations suggestive of PHPT, a serum calcium measurement should be performed. Patients with recurrent HPT and patients with multiple gland hyperplasia in the absence of renal disease should be screened for the *MEN1* gene mutation.

The diagnosis of PHPT is confirmed by demonstrating persistent hypercalcemia (or high-normal serum calcium levels) in the presence of inappropriately normal or elevated PTH concentrations (Fig. 1). Normally, PTH levels are suppressed in the presence of increasing serum calcium levels. If suppression of PTH does not occur when serum calcium levels are increasing, the presence of PHPT should be considered. Immunoassay of the intact PTH molecule is the preferred method of measurement. The finding of an elevated ionized serum calcium level confirms the diagnosis of normocalcemic or intermittent hypercalcemic PHPT. This diagnosis should be suspected in symptomatic patients (typically with renal calculi, renal dysfunction, osteopenia, or osteoporosis) who have minimally increased PTH levels and high-normal serum calcium levels (normocalcemic PHPT) or intermittently increased serum calcium levels (intermittent PHPT) (2).

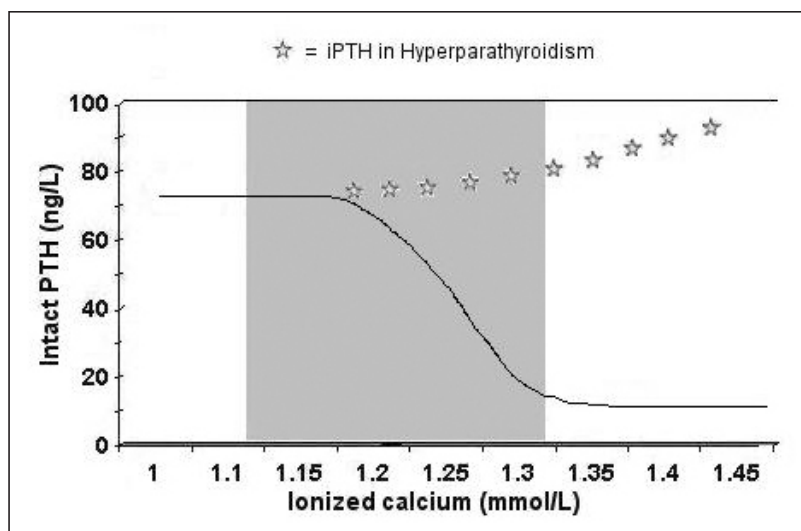


Fig. 1. Relationship between intact parathyroid hormone (*iPTH*) and ionized calcium in normal physiologic state and hyperparathyroidism. Shaded area = normal range for ionized calcium.

Whenever the diagnosis of PHPT is suspected, a 24-hour urinary collection for calcium and creatinine excretion should be obtained to distinguish patients with PHPT from those with the uncommon disorder of benign familial hypercalcemic hypocalciuria (FHH). A calcium-to-creatinine clearance ratio below 0.01 has been suggested as the cutoff for separating patients with FHH from those with PHPT. Characteristically, patients with FHH have mild hypercalcemia in conjunction with high-normal or slightly increased PTH levels. Patients with FHH derive no benefit from parathyroidectomy and can be diagnosed when the calcium-to-creatinine excretion ratio is reduced or when family members younger than 10 years of age have hypercalcemia. FHH is caused by a systemic under-expression of the calcium sensing receptor gene. A family history of hypercalcemia is often present. Urinary calcium excretion is usually increased in patients with PHPT. When present, excessive urinary calcium excretion (>400 mg/24 h) is considered a predictive risk factor for future complications from PHPT and serves as a basis for recommending parathyroidectomy. A concurrent vitamin D deficiency or use of drugs such as thiazides affects renal calcium excretion.

Associated laboratory abnormalities that may be detected in patients with PHPT include decreased serum phosphate levels and high-normal or increased serum chloride levels. Uncommonly, elevated levels of blood urea nitrogen, creatinine, and alkaline phosphatase (bone fraction) are present in patients with PHPT.

Dual-energy x-ray absorptiometry (DEXA) measurement of bone mineral density (BMD) has become widely available for screening and monitoring of osteopenia and osteoporosis. All patients with a diminished BMD (osteopenia or osteoporosis) on the basis of DEXA measurements should be screened for hypercalcemia; if this laboratory abnormality is found, PHPT should be excluded.

Similarly, most patients with PHPT should undergo bone density screening. In patients with evidence of osteoporosis—National Institutes of Health (NIH) criterion, BMD that is more than 2.5 SD below peak bone mass (T -score <2.5)—parathyroidectomy should be considered (3). Losses of BMD from PHPT are more pronounced in the forearm (cortical bone) than in the spine (trabecular bone) and hip (mixed cortical and trabecular bone) but may occur at all skeletal sites. Although forearm losses of BMD may be more commonly associated with PHPT, the benefit from surgical treatment is more notable for the hip and spine because of the morbidity and mortality associated with fracture. Patients with PHPT should undergo DEXA scanning of these 3 sites for reliable documentation of their BMD status as a criterion for recommending parathyroidectomy.

Parathyroid imaging has no role in the diagnosis of PHPT, but ultrasonography or sestamibi scanning (or both) of the parathyroid glands should be used for operative planning. Specifically, if preoperative ultrasonography or sestamibi scanning localizes an adenoma, this information facilitates a focused or minimally invasive surgical approach. Although some surgeons do not obtain preoperative imaging for patients at high risk of hyperplasia, preoperative ultrasonography or sestamibi scanning can be helpful in localizing an ectopic parathyroid gland. Ultrasound-guided fine-needle aspiration of a parathyroid adenoma for PTH analysis may be more specific than sestamibi scanning and less expensive.

NATURAL HISTORY OF UNTREATED PHPT AND BENEFITS OF PARATHYROIDECTOMY

The consequences of untreated PHPT can range in severity from no demonstrable health effects to major life-threatening problems. To date, no reliable laboratory

values have been identified that predict which asymptomatic patients with mild hypercalcemia will experience progression of symptoms. Patients with serum calcium levels in excess of 13 mg/dL are at increased risk for metabolic problems and risk of premature death due to hypercalcemic crisis (4).

Severe classic symptoms and findings of PHPT are uncommon at the time of diagnosis in patients from Western industrialized societies. Milder forms of these classic features will be present in only 30 to 40% of patients diagnosed with PHPT. These features can include renal calculi, nephrocalcinosis, renal dysfunction, osteopenia or osteoporosis, hypertension, osteitis fibrosa cystica, severe muscle weakness, and altered neurologic function with obtundation, delirium, or coma. Severe symptoms, when present, are compelling indications for early operative management. Successful parathyroidectomy reliably reverses accelerated bone mineral loss, diminishes future risk for renal calculi, increases the left ventricular myocardial index, improves muscle strength, and decreases neurologic symptoms.

The future risk of developing symptoms or complications in patients with observed "asymptomatic PHPT" ranges from 23 to 62% at 10 years (5,6). Such patients have a lifelong risk of progression of disease, and the possibility of rapid development of severe complications or symptoms makes regular and careful follow-up imperative. The most likely risks are (1) progressive silent bone loss that increases the future risk of occurrence of fractures and (2) nephrolithiasis or nephrocalcinosis with impairment of renal function.

Numerous investigative assessments of patients with so-called asymptomatic PHPT have documented that many of these patients have easy fatigability, apathy, depression, malaise, mood swings, sleep disorders, irritability, and impaired mental clarity. These symptoms usually diminish after successful parathyroidectomy, even in patients with very mild disease. This finding calls into question whether patients with minimal hypercalcemia are truly asymptomatic and underscores the importance of assessing the neuropsychiatric status and sense of well-being among patients with PHPT as factors in making treatment recommendations (7-9).

Other observations have suggested that patients with untreated PHPT have increased risk of premature death from cardiovascular diseases and malignant lesions. The linkage of PHPT to cardiovascular complications and death is incompletely characterized physiologically but may be a result of decreased glucose tolerance or overt diabetes mellitus, altered lipid metabolism, obesity, hypertension, or altered vasomotor tone (10,11). All these findings have been described in patients with PHPT, along with improvement after successful operative treatment. The risk from premature death is present up to 10 years before parathyroidectomy (12). After parathyroidectomy, the risk decreases to that seen in the general population.

The risk of premature death also seems to correlate with the severity of the hypercalcemia (13). Finally, PTH and 1,25-dihydroxyvitamin D levels correlate with the risk of bone fractures, and bone mineral content improves after parathyroidectomy (14,15).

BENEFITS AND RISKS OF OPERATIVE MANAGEMENT

Operative management is currently the only curative therapy for patients with PHPT. Procedures such as percutaneous ethanol injection, laser therapy, and radio-frequency ablation are considered experimental at this point. Operative cure rates of 95 to 98% with complication rates of 1 to 2% are possible when parathyroidectomy is performed by experienced surgeons. Serious complications consist of recurrent laryngeal nerve injury, persistent or recurrent HPT, permanent hypoparathyroidism, and bleeding. Mortality from operative intervention is extremely low. The main causes of operative failures are multiglandular disease, ectopic or supernumerary parathyroid glands, parathyroid cancer, and surgical inexperience.

Recent surgical advances include the ability to perform focused resection of preoperatively imaged enlarged parathyroid glands by means of a limited neck dissection, with use of small incisions of 2 to 3 cm (minimally invasive parathyroidectomy) (16-18). Such procedures can be facilitated by the use of intraoperative measurement of real-time intact PTH levels. A few surgeons also recommend intraoperative gamma-probe localization of abnormal parathyroid glands with ^{99m}Tc-labeled sestamibi scanning (19). The increased availability of intraoperative PTH assessment to document completeness of operative resection is helpful and enables more patients to undergo focused resection through small incisions with greater certainty of cure and less postoperative pain and discomfort. Unfortunately, the use of intraoperative PTH measurements to predict cure is not as accurate in patients with multiple abnormal parathyroid glands in comparison with single gland involvement (20).

MEDICAL MANAGEMENT

No convincing data support the long-term efficacy of medical therapy or simply observation in the management of PHPT. Patients with mild HPT should be kept well hydrated. They should avoid medications such as thiazide diuretics that increase serum calcium levels. Furosemide is helpful in well-hydrated patients. Estrogen replacement in postmenopausal women decreases bone resorption by decreasing osteoclastic activity. Its role is to stabilize BMD in those patients unable or unwilling to undergo surgical treatment (21). Bisphosphonate therapy has been shown to improve BMD in patients with PHPT without any changes in serum PTH or calcium levels (22). Estrogen receptor agonists have been tried but show limit-

ed overall effectiveness. Although calcimimetic medications are still considered experimental, one agent (cinacalcet) recently appeared effective in lowering PTH concentrations and normalizing serum calcium levels in a randomized double-blind study (23). After several years of follow-up, the costs of monitoring and medical management of patients with PHPT who do not undergo surgical treatment have been shown to surpass the costs for patients who undergo successful surgical treatment (24).

SURGICAL STRATEGIES

The goal of operative treatment of PHPT is normalization of serum PTH and calcium levels with minimal associated morbidity. The basic requirements for successful parathyroid operations are meticulous, bloodless dissection, in combination with an understanding of the embryologic development and migration of parathyroid glands and their resulting anatomic locations. The skills and training of an experienced endocrine surgeon cannot be replaced by imaging technology that facilitates targeted or minimally invasive parathyroidectomy. The traditional 4-gland neck exploration is still necessary for 20 to 40% of patients with negative or equivocal preoperative scans as well as for patients with familial HPT. Importantly, although imaging may suggest a single adenoma, some of these patients may harbor double adenomas or 4-gland hyperplasia.

The traditional cervical procedure includes bilateral neck exploration with identification of all 4 parathyroid glands and removal of the abnormal parathyroid adenoma (or adenomas) or subtotal resection of 3½ glands in patients with parathyroid hyperplasia. Recently, several innovations have emerged that are purported to benefit the patient undergoing parathyroidectomy. These changes include the following: (1) preoperative localization by ^{99m}Tc-sestamibi scanning with use of single-photon emission computed tomography, (2) use of intraoperative measurement of circulating intact PTH, and (3) improved resolution of ultrasound examinations. Some surgeons also recommend the use of handheld gamma detection devices for radio-guided parathyroidectomy (25); others use cervical block or local anesthesia rather than general anesthesia. Most influential in changing the surgical approach are the improved localization procedures and the use of the intraoperative PTH assay. Both factors have made focused parathyroid operations possible (26,27). Currently, minimally invasive parathyroidectomy, performed endoscopically or as an open or radio-guided technique, is possible and can be done as an outpatient procedure (28,29).

The surgical approach to patients with PHPT is likely to remain a surgeon-specific strategy, depending on experience, preferences, and availability of new technologies. At present, no consensus exists about the need for any of these new modalities for optimal initial parathyroid

operative success, and the cost-effectiveness of these technologies, alone or in combination, may vary among differing practice environments. Ultimately, none of these technologies is a substitute for an experienced surgeon.

CONSENSUS GUIDELINES FOR RECOMMENDATION OF SURGICAL TREATMENT

Operative management is clearly indicated for all patients with classic symptoms or complications of PHPT. The recommendation of surgical treatment for seemingly asymptomatic patients with PHPT, however, remains controversial. Although the benefits of successful operative management are recognized in terms of correcting the disordered calcium metabolism in the preponderance of patients undergoing parathyroidectomy, concern remains about exposing such patients to the risks of operation (albeit low) for a disease that may be minimally problematic for at least half of them.

A consensus conference organized by the NIH in 1990 attempted to define a rational basis for recommending parathyroidectomy for asymptomatic patients. A follow-up conference of the NIH and the National Institute of Diabetes and Digestive and Kidney Diseases in 2002 recommended parathyroidectomy for the following patients: (1) those <50 years of age, (2) who cannot participate in appropriate follow-up, (3) with a serum calcium level >1.0 mg/dL above the normal range, (4) with urinary calcium >400 mg/24 h, (5) with a 30% decrease in renal function, or (6) with complications of PHPT, including nephrocalcinosis, osteoporosis (*T*-score <2.5 SD at the lumbar spine, hip, or wrist), or a severe psychoneurologic disorder (30).

Other authorities have recommended more liberal guidelines in managing PHPT based on the inability to determine predictably whether complications or progression of the disorder will develop in a specific patient. Furthermore, long-term follow-up of patients with PHPT not treated surgically is time-consuming, costly, and unacceptable to many patients. Such patients must avoid dehydration and excessive calcium intake. The most common evolving sequelae of PHPT in asymptomatic patients include ongoing bone loss, nephrolithiasis, and renal colic. In addition, patients with PHPT are at risk for indolent cardiovascular complications with left ventricular hypertrophy, neurobehavioral impairment, and associated diminished quality of life. Hypercalcemia also complicates the management of other medical problems, such as congestive heart failure. Living with PHPT as a long-term metabolic disorder with a potential for multiple associated health problems may be unacceptable for many patients when a straightforward durable surgical cure can be readily achieved in most cases. In this context, we believe that operative management should be considered and recommended for all asymptomatic patients with PHPT who have a reasonable life expectancy and suitable operative

and anesthesia risk factors. Consultation with an experienced endocrinologist and surgeon can help clarify the patient's risk-to-benefit ratio in this regard.

CONCLUSIONS AND RECOMMENDATIONS

PHPT remains a relatively common disorder of calcium metabolism that is readily cured by a low-risk operation in 95 to 98% of patients when performed by a qualified surgeon. Operative management is the treatment of choice for all symptomatic patients and all asymptomatic patients younger than age 50 years or for patients who cannot participate in adequate medical follow-up. Operative management should also be considered for all other asymptomatic patients with suitable risk and a reasonable life expectancy (31).

ACKNOWLEDGMENT

We thank Kathleen Cook for secretarial and administrative support, and Shirley Thompson for preparation of the final manuscript.

REFERENCES

1. **Arnold A, Shattuck TM, Mallya SM, et al.** Molecular pathogenesis of primary hyperparathyroidism. *J Bone Miner Res.* 2002;17(Suppl 2):N30-N36.
2. **Monchik JM.** Normocalcemic hyperparathyroidism. *Surgery.* 1995;118:917-923.
3. **Bilezikian JP, Potts JT Jr, Fuleihan G-H, et al.** Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Bone Miner Res.* 2002;17(Suppl 2):N2-N11.
4. **Edelson GW, Kleerekoper M.** Hypercalcemic crisis. *Med Clin North Am.* 1995;79:79-92.
5. **Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP.** A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery [erratum in *N Engl J Med.* 2000;342:144]. *N Engl J Med.* 1999;341:1249-1255.
6. **Silverberg SJ, Brown I, Bilezikian JP.** Age as a criterion for surgery in primary hyperparathyroidism. *Am J Med.* 2002;113:681-684.
7. **Clark OH, Wilkes W, Siperstein AE, Duh QY.** Diagnosis and management of asymptomatic hyperparathyroidism: safety, efficacy, and deficiencies in our knowledge. *J Bone Miner Res.* 1991;6(Suppl 2):S135-S142.
8. **Talpos GB, Bone HG III, Kleerekoper M, et al.** Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey [with discussion]. *Surgery.* 2000;128:1013-1021.
9. **Rao DS.** Parathyroidectomy for asymptomatic primary hyperparathyroidism (PHPT): is it worth the risk? *J Endocrinol Invest.* 2001;24:131-134.
10. **Richards ML, Thompson NW.** Diabetes mellitus with hyperparathyroidism: another indication for parathyroidectomy? *Surgery.* 1999;126:1160-1166.
11. **Procopio M, Borretta G.** Derangement of glucose metabolism in hyperparathyroidism. *J Endocrinol Invest.* 2003;26:1136-1142.
12. **Vestergaard P, Mollerup CL, Frokjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L.** Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg.* 2003;27:216-222.
13. **Leifsson BG, Ahren B.** Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab.* 1996;81:2149-2153.
14. **Nordenstrom E, Westerdahl J, Lindergard B, Lindblom P, Bergenfelz A.** Multifactorial risk profile for bone fractures in primary hyperparathyroidism. *World J Surg.* 2002;26:1463-1467.
15. **Vestergaard P, Mosekilde L.** Fractures in patients with primary hyperparathyroidism: nationwide follow-up study of 1201 patients. *World J Surg.* 2003;27:343-349.
16. **Carty SE, Worsley J, Virji MA, Brown ML, Watson CG.** Concise parathyroidectomy: the impact of preoperative SPECT 99mTc sestamibi scanning and intraoperative quick parathormone assay [with discussion]. *Surgery.* 1997;122:1107-1116.
17. **Monchik JM, Barellini L, Langer P, Kahya A.** Minimally invasive parathyroid surgery in 103 patients with local/regional anesthesia, without exclusion criteria. *Surgery.* 2002;131:502-508.
18. **Udelsman R.** Six hundred fifty-six consecutive explorations for primary hyperparathyroidism [with discussion]. *Ann Surg.* 2002;235:665-672.
19. **Norman JG.** Minimally invasive radioguided parathyroidectomy: an endocrine surgeon's perspective. *J Nucl Med.* 1998;39:15N, 24N.
20. **Gauger PG, Agarwal G, England BG, et al.** Intraoperative parathyroid hormone monitoring fails to detect double parathyroid adenomas: a 2-institution experience. *Surgery.* 2001;130:1005-1010.
21. **Marcus R.** The role of estrogens and related compounds in the management of primary hyperparathyroidism. *J Bone Miner Res.* 2002;17(Suppl 2):N146-N149.
22. **Khan AA, Bilezikian JP, Kung AW, et al.** Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab.* 2004;89:3319-3325.
23. **Shoback DM, Bilezikian JP, Turner SA, McCary LC, Guo MD, Peacock M.** The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2003;88:5644-5649.
24. **Heath DA, Heath EM.** Conservative management of primary hyperparathyroidism. *J Bone Miner Res.* 1991;6:S117-S120.
25. **Burkey SH, van Heerden JA, Farley DR, Thompson GB, Grant CS, Curlee K.** Will directed parathyroidectomy utilizing the gamma probe or intraoperative parathyroid hormone assay replace bilateral cervical exploration as the preferred operation for primary hyperparathyroidism? *World J Surg.* 2002;26:914-920.
26. **Boggs JE, Irvin GL III, Molinari AS, Deriso GT.** Intraoperative parathyroid hormone monitoring as an adjunct to parathyroidectomy. *Surgery.* 1996;120:954-958.
27. **Irvin GL III, Carneiro DM.** Management changes in primary hyperparathyroidism. *JAMA.* 2000;284:934-936.
28. **Costello D, Norman J.** Minimally invasive radioguided parathyroidectomy. *Surg Oncol Clin N Am.* 1999;8:555-564.
29. **Henry JF, Raffaelli M, Iacobone M, Volot F.** Video-assisted parathyroidectomy via the lateral approach vs conventional surgery in the treatment of sporadic primary hyperparathyroidism: results of a case-control study. *Surg Endosc.* 2001;15:1116-1119.
30. **Bilezikian JP, Potts JT Jr.** Asymptomatic primary hyperparathyroidism: new issues and new questions—bridging the past with the future. *J Bone Miner Res.* 2002;17(Suppl 2):N57-N67.
31. **Eigelberger MS, Cheah WK, Ituarte PH, Streja L, Duh QY, Clark OH.** The NIH criteria for parathyroidectomy in asymptomatic primary hyperparathyroidism: are they too limited? *Ann Surg.* 2004;239:528-535.