Context: An international workshop on primary hyperparathyroidism (PHPT) was convened on May 13, 2008, to review and update the previous summary statement on the management of asymptomatic PHPT published in 2002.

Evidence Acquisition: Electronic literature sources were systematically reviewed, addressing critical aspects of the surgical issues pertaining to the indications, imaging, surgical treatment, and cost-effective management of patients with PHPT.

Evidence Synthesis: The surgical group concluded that many patients with “asymptomatic” PHPT have neurocognitive symptoms that may be unmasked after successful parathyroidectomy. Furthermore, reduced bone density and increased fracture risk can be improved with parathyroidectomy. When PHPT is symptomatic, it may be associated with nephrolithiasis, increased cardiovascular disease, and decreased survival. Preoperative imaging studies should only be performed to help plan the operation, and negative imaging should never preclude surgical referral. Non-invasive localization studies including ultrasound and sestamibi scans are often employed, especially in anticipation of focused explorations. Invasive localization studies should be reserved for remedial explorations where noninvasive imaging has been unsuccessful.

Conclusions: When performed by expert parathyroid surgeons, parathyroid surgery is safe, cost-effective, and associated with very low perioperative morbidity. Minimally invasive approaches to parathyroid surgery appear to be as effective as the classic bilateral cervical exploration approach.

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An international workshop on primary hyperparathyroidism (PHPT) was convened on May 13, 2008, in Orlando, Florida. The workshop was supported by 10 national and international scientific societies including the American Association of Endocrine Surgeons (AAES) and the International Association of Endocrine Surgeons (IAES). The focus of the workshop was to review and update the recommendations of the summary statement published after the 2002 workshop on asymptomatic PHPT (1). The current overall findings and updated summary statement are also published in this issue of the Journal of Clinical Endocrinology & Metabolism. This manuscript is focused on issues that pertain to the surgical management of patients with “asymptomatic” PHPT. Levels of evidence for references cited in this manuscript are tabulated in Table 1.

Question 1. What are the indications for surgery in patients with PHPT?

There is no controversy that virtually all patients with symptomatic biochemically confirmed PHPT should be referred for
surgical treatment. In these symptomatic patients, cohort studies have demonstrated that after parathyroidectomy, bone density improves and fracture rate declines. Cognitive function appears to improve. In patients who had kidney stones before surgery, the incidence declines after surgery. Cardiovascular disease and premature death also appear to decrease after surgery in symptomatic subjects (2–5). The major focus of the workshop, however, was not on symptomatic patients, but rather on those with asymptomatic PHPT: which patients should be referred for surgery and which ones can be safely monitored (1). In the earlier National Institutes of Health Consensus Conference in 1990 and the subsequent workshop in 2002, asymptomatic patients who were not deemed candidates for surgery had the following features: a serum calcium level less than 1.0 mg/dl (0.25 mmol/liter) above the upper limits of normal, no history of kidney stones or fractures, a creatinine clearance that was within 30% of age- and sex-matched controls, 24-h urine calcium level less than 400 mg/24 h (0.1 mmol/kg · d), and the absence of osteoporosis by T-score.

Neuropsychiatric symptoms and quality of life (QOL)

In this issue of the Journal, Silverberg et al. reviewed the literature with regard to neurocognitive function in PHPT. They confirmed that patients with PHPT often complain of vague, nonspecific symptoms (6–14). These symptoms include fatigue, lassitude, mood swings, irritability, anxiety, depression, difficulty concentrating, memory loss, and increased sleep requirements (5–9, 12, 14–20).

In a population-based Swedish study, patients with PHPT had more complaints of lassitude, fatigue, irritability, and lack of sexual interest than aged-matched controls (18). In a cohort study using the Comprehensive Psychological Rating Scale, Joborn et al. (17) found that the majority of patients with PHPT had considerably more psychiatric symptoms compared with healthy controls and showed improvement of these symptoms after parathyroidectomy. Similarly, Chan et al. (7) observed that the majority of PHPT patients had subjective improvement after parathyroidectomy as determined by questionnaire. In a recent systematic review of all prospective studies in which cognitive function was measured with formal neuropsychological tests, Coker et al. (19) found six small studies characterized by inconsistent findings illustrating the need for prospective investigations with long-term follow-up.

The review of Coker points out the inherent weaknesses in neurocognitive instruments such as the SF-36 QOL scale. A patient-based outcome tool, which quantifies 13 disease-specific symptoms of PHPT has been developed and validated at the University of Calgary (11, 14, 16–21). Using this tool, patients with PHPT were found to have more symptoms relative to a comparison group of nontoxic thyroidectomy patients and to show improvement within 7–10 d after parathyroidectomy.

There are two randomized controlled trials assessing QOL after parathyroidectomy vs. medical management in patients with mild PHPT. A randomized controlled study of 53 patients by Talpos et al. (22) demonstrated improved QOL in two of nine domains of the SF-36 in patients undergoing operation compared with ongoing medical surveillance. In contrast, Bollerslev et al. (23) found no significant difference after surgical treatment vs. medical observation in regard to their overall QOL at 2 yr. These investigators did, however, find that the overall QOL in the PHPT was significantly lower than normal population-based controls. They also found that the medically observed group had a significant decrease in physical domains over 2 yr, whereas no change was seen in the surgical group.

In summary, there is now a considerable body of literature that supports the possibility that many patients with PHPT have neurocognitive features that, in some cases, show improvement after successful parathyroid surgery. However, to resolve this ongoing debate, well-controlled randomized prospective trials are clearly indicated.

Bone density and fracture risk

The majority of studies document that both men and women with PHPT are more likely to have low bone density and increased fracture risk in comparison to controls (24, 25). Patients with PHPT and normal bone density also experience more fractures (24–26). In cohort studies, fracture risk declines after parathyroidectomy. This effect is independent of age, gender, and the initial serum calcium or PTH levels. It is also independent of the weight of the removed parathyroid tissue and the underlying histopathological diagnosis. Although these data are suggestive, we still do not have randomized controlled trial data evaluating the effects of parathyroidectomy on fracture risk in PHPT.

Nephrolithiasis

The frequency of developing new kidney stones among those with a history of nephrolithiasis declines after surgery. Renal concentrating capacity may show improvement after successful parathyroidectomy (27, 28). Mitlak et al. (29) reported that about one third of the 85 patients they followed with minimal or mild PHPT developed impaired renal function or premature osteopenia when followed for 10 yr. The prospective study by

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Silverberg et al. (30) also documented that about 25% of their asymptomatic patients developed problems within 10 yr, included among which was nephrolithiasis.

**Cardiovascular disease**

The subject of cardiovascular disease in PHPT has been reviewed by Silverberg et al., in this issue of the Journal. Other investigators have demonstrated an increased incidence of hypertension (31–34), left ventricular hypertrophy (35), vascular calcification and stiffness (36), and myocardial events (37, 38). Although more studies are required, prevention of these cardiovascular events, when possible, by earlier parathyroidectomy rather than treatment of cardiac complications might be prudent in patients who can be defined to be at risk (37, 38).

**Survival**

Large population-based cohort studies demonstrate that patients with PHPT appear to be at risk for premature death (39–42). Although these data were not specifically derived from asymptomatic patients, those described by Palmer et al. (39) had a median blood calcium level of 10.4 mg/dl (2.6 mmol/liter) and would not have qualified for surgical intervention based on previous consensus guidelines. Most of the deaths were due to cardiovascular disease or cancer (39). Data from Wermers et al. (42) suggest that overall survival was not affected in their cohort with mild PHPT. Increasing serum calcium levels were associated with poorer survival in multivariate analysis. A potential increase in mortality, however, was not seen with conservative treatment of mild PHPT (42).

**Question 2. Who should perform parathyroid surgery?**

Surgeon experience is considered by virtually all experts to be the single most important variable that has a direct effect upon cure and complication rates for parathyroidectomy. Despite this well-accepted tenet, there are few published data that directly test this hypothesis. Due to ethical and selective bias in reporting, a true comparison study is highly unlikely to be performed. Indirect data can be extrapolated from the thyroid literature in which a large retrospective administrative database demonstrated that surgical experience as measured by volume of cases per year was the single most important predictor of clinical and economic outcomes (43). Recent data confirm a linear relationship between surgical volume and optimization of outcomes in endocrine surgery (44). It is also clear that the vast majority of surgical residents completing training programs have insufficient experience in endocrine surgery to be considered experts (45). In recognition of this issue, the AAES has endorsed endocrine surgery fellowship programs throughout the United States and Canada.

Patients and their referring endocrinologists should seek out surgeons and institutions that have devoted the time and resources required to optimize operative outcomes. Due to electronic media sources, there is an overwhelming amount of information available to patients, and unfortunately the quality and accuracy of the data are at times compromised. Although there are no clear minimal standards that can be recommended, it is important that patients and their referring physicians seek information from reliable sources.

**Question 3. What is the role of preoperative imaging?**

Preoperative imaging in the setting of PHPT is designed to assist the surgeon in identifying the anatomic localization of abnormally functioning or enlarged parathyroid glands. Positive imaging studies are not useful for the confirmation of a diagnosis of PHPT. Moreover, negative imaging studies do not exclude the diagnosis of PHPT. Furthermore, all imaging studies demonstrate both false-positive and false-negative findings that can be misleading. Therefore, all patients subjected to preoperative parathyroid imaging studies should have a confirmed biochemical diagnosis of PHPT.

The selection of one or more imaging studies is affected by the anticipated approach (focused vs. bilateral exploration) and whether or not the operation will be a remedial procedure in a scarred operative field. The most commonly employed imaging studies are sestamibi scans and cervical ultrasound. The quality of sestamibi scans, however, varies widely between institutions, and sonography is highly dependent on the skill and interest level of the individual performing the study (46, 47). Computed tomography (CT) and magnetic resonance imaging (MRI) scans are also sometimes used, especially in patients with persistent or recurrent hyperparathyroidism. In patients requiring remedial cervical exploration, PTH assay of the aspirate from an ultrasound-guided fine-needle aspiration (FNA) of a perceived adenoma can confirm the location of parathyroid tissue. Angiography and selective venous sampling for PTH are occasionally employed for remedial cases when noninvasive studies are negative or conflicting.

**Noninvasive imaging**

**Sestamibi scan**

Sestamibi scanning is the most popular and sensitive noninvasive parathyroid localization procedure. It can localize abnormal parathyroid glands in both eutopic and ectopic locations. The quality of sestamibi scanning varies widely among institutions (46). Some series report an accuracy rate of over 90%, but most centers achieve only 50 to 70% accuracy. In a prospective study of 387 patients by Civelek et al. (48), the sensitivity for single adenomas was 90%, but 27% of double adenomas and 55% of hyperplastic glands were missed. The major factors contributing to a nonlocalizing sestamibi study are multigland disease, small parathyroid glands, or coexistent thyroid disease. The main advantage of sestamibi scans is the ability to localize parathyroid glands in ectopic sites including the mediastinum.

**Ultrasound**

In many centers all patients having parathyroid surgery undergo routine preoperative ultrasound, and some endocrinolo-
gists and surgeons believe that this is the most cost-effective procedure. Ultrasonography is painless, noninvasive, and inexpensive; does not expose the patient to radiation; and can be duplicated in the operative theater. Ultrasound can identify coexistent thyroid pathology and be used to locate intrathyroidal parathyroid adenomas. The accuracy of ultrasound is highly operator dependent. Abnormalities identified as possible parathyroid tissue not infrequently prove to be a thyroid nodule or lymph node. One recent study showed that surgeon-performed ultrasound had a sensitivity of 82% with a specificity of 90%, compared with radiology-performed ultrasound, which had a sensitivity of 42% and a specificity of 92% (47). Despite these possible advantages, ultrasonography neither evaluates the mediastinum nor offers functional information.

CT scan
Rapid spiral thin-slice CT scanning of the neck and mediastinum, with evaluation of axial, coronal, and sagittal views, provides impressive delineation of anatomy and vascular flow. The sensitivity is improving and ranges from 50–75%. Recent data suggest that four-dimensional CT scans employing multiple sequences with iv contrast and fine-cut imaging have improved sensitivity and may be particularly helpful in anticipation of remedial cervical exploration (49).

MRI scan
Contrast-enhanced MRI can identify abnormal parathyroid tissue. In comparison to other modalities, it is time-consuming, expensive, less sensitive, and more difficult to interpret. It can be useful for mediastinal lesions but it is not superior to CT, and a significant number of patients are excluded because of indwelling pacemakers and other metallic implants (50). It can nonetheless be useful when performing localization in anticipation of remedial exploration.

Positron emission tomography (PET) scan
PET with or without simultaneous CT scan (PET/CT) can occasionally identify parathyroid adenomas in patients with persistent or recurrent PHPT when other localization studies are negative or equivocal. But because (F-18) fluorodeoxyglucose also concentrates in the thyroid, this technique is somewhat limited.

Invasive imaging
Parathyroid FNA
FNA of a presumed parathyroid gland can be performed and the aspirate can be analyzed for PTH. This technique is safe and relatively inexpensive, but is not recommended for routine de novo cases (51).

Arteriography and selective venous sampling for PTH
These techniques are costly and invasive and require an experienced and committed interventional radiologist. Highly selective venous localization is positive in up to 80% of patients with persistent or recurrent PHPT when other studies are negative or discordant. They should only be used for patients who have failed previous explorations and for whom other localization techniques are noninformative (52).

Question 4. What is the appropriate operation, and what are the cure and completion rates?
The surgical treatment of PHPT has undergone substantive changes since the first successful parathyroidectomy was performed by Felix Mandl in 1925 (53). It is now the expectation that the vast majority of patients will be cured during initial surgical exploration with a low probability of morbidity. A variety of operative techniques can be employed. The conventional time-honored operation employing general endotracheal anesthesia and bilateral cervical exploration is safe and effective when performed by experienced surgeons. Recent technical innovations including improved preoperative localization, availability of rapid intraoperative PTH assays, endoscopic refinements, and intraoperative gamma detection probes have resulted in the broad application of focused or minimally invasive approaches with excellent outcomes.

Sporadic primary hyperparathyroidism is caused by a single enlarged parathyroid gland (parathyroid adenoma) in approximately 85% of cases, whereas multigland hyperplasia occurs in 15% and parathyroid carcinoma is found in less than 1% of patients. Unlike previous dogma that mandated surgical identification of both enlarged and normal parathyroid glands, the current paradigm in many centers is to identify and excise the incident enlarged gland and to confirm operative cure employing a rapid intraoperative PTH assay. Due to the relatively short half-life of PTH (4–5 min), a dramatic drop in circulating hormone can be detected once the abnormally secreting gland or glands have been removed. A curative drop in PTH allows the surgeon to terminate the operation and obviate additional exploration, whereas failure of the PTH levels to demonstrate an adequate decrement mandates additional exploration due to the presence of presumed additional hypersecreting gland(s). Because the majority of patients can be cured by removing a single enlarged gland, many surgeons perform this procedure employing local or regional anesthesia through small incisions on an outpatient basis (54, 55).

Minimally invasive parathyroidectomy procedures can be grouped into three major categories. The most commonly performed technique employs local or cervical block anesthesia, a 1- to 2-in. (2.5- to 5.0-cm) incision, focused exploration to remove the incident gland seen on preoperative imaging, and a rapid intraoperative PTH assay to confirm the adequacy of resection (54, 55). In Europe, two groups perform a similar operation employing an endoscopic camera. These groups suggest that the cosmetic results are superior because the port incisions are smaller than the minimally invasive open techniques (56, 57). The endoscopic technique often requires general anesthesia and, for the most part, has not been adopted in North America because it requires additional personnel and costs and do not improve outcomes or speed of recovery. Another technique employs preoperative administration of radioactive sestamibi and subsequent exploration with an intraoperative gamma probe to
help locate enlarged parathyroid glands. Although the gamma probe concept is theoretically attractive, most groups have abandoned this technique because the incremental gamma probe-derived information adds little to the data obtained from pre-operative localization.

There are few well-designed prospective studies comparing conventional parathyroid exploration with minimally invasive techniques. These studies demonstrate no differences in cure or complication rates when performed by experienced endocrine surgeons (58, 59). Two large retrospective studies of minimally invasive parathyroidectomy demonstrate cure rates of 95–98% and complication rates ranging from 1–3% in previously unexplored patients (54, 55). It is important to distinguish initial operative exploration from remedial cases where the failure and complication rates in the latter are higher. Nonetheless, even in challenging remedial exploration cases, experienced surgeons obtain cure and complication rates that approach those of the unexplored patient (52).

**Question 5. What operative adjuncts are available to assist the surgeon?**

A variety of operative adjuncts are available in specialized centers, including rapid intraoperative PTH assays, employment of a gamma probe in conjunction with a preoperative sestamibi injection, intraoperative ultrasound, and the ability to perform intraoperative internal jugular vein sampling to measure PTH and determine the presence of an ipsilateral venous gradient. All of these techniques are highly institution specific. Most experts agree that the intraoperative PTH assay is the most useful of these techniques (60). Intraoperative venous sampling is reserved for cases where the surgeon is unable to locate the abnormal parathyroid gland and has immediate availability of an intraoperative PTH assay.

**Question 6. Is parathyroid surgery cost effective?**

Cost analyses performed before the introduction of focused or outpatient parathyroidectomy probably do not reflect the current cost-effectiveness of surgical treatment. Before the last decade, parathyroidectomy commonly required a longer operation and an inpatient stay of several days. Despite this, surgery was found to be less costly than the medical treatment of PHPT when the time interval required for medical treatment exceeded 5.5 yr (61).

Guidelines for formal cost-effectiveness analysis (CEA) were outlined by the Panel on Cost-Effectiveness in Health and Medicine in 1996 (62). Many studies claiming to evaluate cost-effectiveness do not conform to these guidelines and are not considered formal CEA. Consequently, there are few formal CEAs on asymptomatic PHPT published in the English language literature. To our knowledge, only three formal studies are available to date that meet the methodological standards to be considered formal analyses (63–65).

Sejean et al. (63) compared bilateral neck exploration, unilateral neck exploration, video-assisted parathyroidectomy, and medical monitoring. The base case scenario was a 55-yr-old woman with asymptomatic sporadic PHPT, and the time horizon was the remaining life expectancy. The authors found that monitoring was less costly but less effective than surgery. Both minimally invasive strategies were more effective than bilateral neck exploration or monitoring, although slightly more costly due to the cost of localization studies. Sensitivity analysis found that surgery remained more effective than monitoring when the age used in the base-case scenario varied between 40 and 80 yr.

Zanocco et al. (64) compared monitoring, pharmacological therapy (i.e. calcimimetics, bisphosphonates, calcitonin, etc.), and parathyroidectomy for sporadic asymptomatic PHPT. The model’s reference case scenario was a 60-yr-old patient who did not meet the 2002 NIH criteria for parathyroidectomy, and the time horizon for the analysis was the patient’s remaining life expectancy. The authors found that monitoring was the least expensive but least effective option. Both inpatient and outpatient parathyroidectomy were cost-effective. Pharmacological therapy was not cost-effective unless the annual cost was less than $221 (2005 U.S. dollars). The incremental cost-effectiveness ratio for cinacalcet was greater than $20 million per quality adjusted life year.

Zanocco et al. (65) examined how age at diagnosis impacts treatment decisions in sporadic asymptomatic PHPT. They compared monitoring, pharmacological therapy, and parathyroidectomy for sporadic asymptomatic PHPT. In the base case scenario, the age at diagnosis was varied. Threshold analysis identified the optimal treatment strategy of life expectancies ranging from 6 months to 75 yr. The authors found that parathyroidectomy was cost effective for patients with a predicted life expectancy of 5 yr (outpatient parathyroidectomy) or 6.5 yr (inpatient parathyroidectomy). For patients with a shorter life expectancy, observation was the most cost-effective strategy. Pharmacological therapy was not found to be cost effective at any age modeled.

The competing strategies evaluated in these three studies were observation, parathyroidectomy, and pharmacological therapy for hypercalcemia. In each study, the strategy of medical monitoring was found to be less effective than surgery. Surgery was found to be less costly and more effective than pharmacological therapy. The conclusion from these formal studies is that parathyroidectomy is a cost-effective treatment strategy for asymptomatic PHPT.

**Summary and Conclusions**

Patients who have overt signs and symptoms of PHPT are symptomatic and in almost all cases benefit from parathyroidectomy. Patients who appear to have asymptomatic PHPT frequently have significant neurocognitive compromise that is only appreciated after a successful parathyroidectomy has unmasked their symptoms. In addition, cohort studies suggest that patients with asymptomatic PHPT often have diminution in bone den-
sity and perhaps an increase in fracture rates that improve with parathyroidectomy.

Patients with biochemically confirmed PHPT should be referred to an experienced parathyroid surgeon for consultation. If surgery is to be performed, the surgeon should organize the imaging studies that are obtained to localize abnormal parathyroid glands. Imaging studies are not appropriate for confirming the diagnosis of PHPT or for screening patients for surgical referral. Negative imaging should not preclude surgical referral or intervention. The success rate of an experienced endocrine surgeon is consistently superior to the true positive rate of imaging.

The type of operative procedure and the employment of operative adjuncts is highly institution specific and should be based on the expertise and resource availability of the surgeon and institution. Parathyroid surgery when performed by an experienced surgeon is safe, cost-effective, and associated with a very high rate of cure and very low rate of perioperative morbidity. Although some patients may elect nonoperative management, they should do so only after being informed of the apparent risks of nonoperative treatment. The authors believe the surgeon is the ideal individual to explain the risks, benefits, and alternatives to operative intervention.

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References

4. Clark OH 2003 How should patients with primary hyperparathyroidism be treated? J Clin Endocrinol Metab 88:3011–3014


44. Stavarakis AI, Ituarte PH, Ko CY, Yeh MW 2007 Surgeon volume as a predictor of outcomes in inpatient and outpatient endocrine surgery. Surgery 142:887–899


