TABLE 424-2 GUIDELINES FOR SURGERY IN ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM[a]

Parameter	Guideline
Serum calcium (above normal)	>1 mg/dL
24-h urinary calcium	No indication
Creatinine clearance (calculated)[b]	If <60 mL/min
Bone density	T score <−2.5 at any of 3 sites[c]
Age	<50

[a]JP Bilezikian et al: Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary statement from the third international workshop. J Clin Endocrinol Metab 94:335, 2009. [b]Creatinine clearance calculated by Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) equation. [c]Spine, distal radius, hip.

of relative stability. There is concern that this late-onset deterioration in bone density in nonoperated patients could contribute significantly to the well-known age-dependent fracture risk (osteoporosis). One study reported significant and sustained improvements in bone mineral density after successful parathyroidectomy, again raising the issue regarding benefits of surgery. Other randomized studies, however, did not report major gains after surgery.

Cardiovascular disease including left ventricular hypertrophy, cardiac functional defects, and endothelial dysfunction have been reported as reversible in European patients with more severe symptomatic disease after surgery, leading to numerous studies of these cardiovascular features in those with milder disease. There are reports of endothelial dysfunction in patients with mild asymptomatic hyperparathyroidism, but the expert panels concluded that more observation is needed, especially regarding whether there is reversibility with surgery.

A topic of considerable interest and some debate is assessment of neuropsychiatric status and health-related quality of life (QOL) status in hyperparathyroid patients both before surgery and in response to parathyroidectomy. Several observational studies suggest considerable improvements in symptom score after surgery. Randomized studies of surgery versus observation, however, have yielded inconclusive results, especially regarding benefits of surgery. Most studies report that hyperparathyroidism is associated with increased neuropsychiatric symptoms, so the issue remains a significant factor in decisions regarding the impact of surgery in this disease.

DIAGNOSIS

The diagnosis is typically made by detecting an elevated immunoreactive PTH level in a patient with asymptomatic hypercalcemia (see "Differential Diagnosis: Special Tests," below). Serum phosphate is usually low but may be normal, especially if renal failure has developed.

Several modifications in PTH assays have been introduced in efforts to improve their utility in light of information about metabolism of PTH (as discussed above). First-generation assays were based on displacement of radiolabeled PTH from antibodies that reacted with PTH (often also PTH fragments). Double-antibody or immunometric assays (one antibody that is usually directed against the carboxyl-terminal portion of intact PTH to capture the hormone and a second radio- or enzyme-labeled antibody that is usually directed against the amino-terminal portion of intact PTH) greatly improved the diagnostic discrimination of the tests by eliminating interference from circulating biologically inactive fragments, detected by the original first-generation assays. Double-antibody assays are now referred to as second-generation. Such PTH assays have in some centers and testing laboratories been replaced by third-generation assays after it was discovered that large PTH fragments, devoid of only the extreme amino-terminal portion of the PTH molecule, are also present in blood and are detected, incorrectly, as intact PTH. These amino-terminally truncated PTH fragments were prevented from registering in the newer third-generation assays by use of a detection antibody directed against the extreme amino-terminal epitope. These assays may be useful for clinical research studies as in management of chronic renal disease, but the consensus is that either second- or third-generation assays are useful in the diagnosis of primary hyperparathyroidism and for the diagnosis of high-turnover bone disease in chronic kidney disease.

Many tests based on renal responses to excess PTH (renal calcium and phosphate clearance; blood phosphate, chloride, magnesium; urinary or nephrogenous cyclic AMP [cAMP]) were used in earlier decades. These tests have low specificity for hyperparathyroidism and are therefore not cost-effective; they have been replaced by PTH immunometric assays combined with simultaneous blood calcium measurements (Fig. 424-4).

TABLE 424-3 GUIDELINES FOR MONITORING IN ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM[a]

Parameter	Guideline
Serum calcium	Annually
24-h urinary calcium	Recommended
Creatinine clearance	Recommended
Serum creatinine[b]	Annually
Bone density	Annually (3 sites)[a]

[a]Updates guidelines (JP Bilezikian et al: J Clin Endocrinol Metab 2014; epub ahead of print). [b]Creatinine clearance calculated by Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) equation.

TREATMENT HYPERPARATHYROIDISM

Surgical excision of the abnormal parathyroid tissue is the definitive therapy for this disease. As noted above, medical surveillance without operation for patients with mild, asymptomatic disease is, however, still preferred by some physicians and patients, particularly when the patients are more elderly. Evidence favoring surgery, if medically feasible, is growing because of concerns about skeletal,

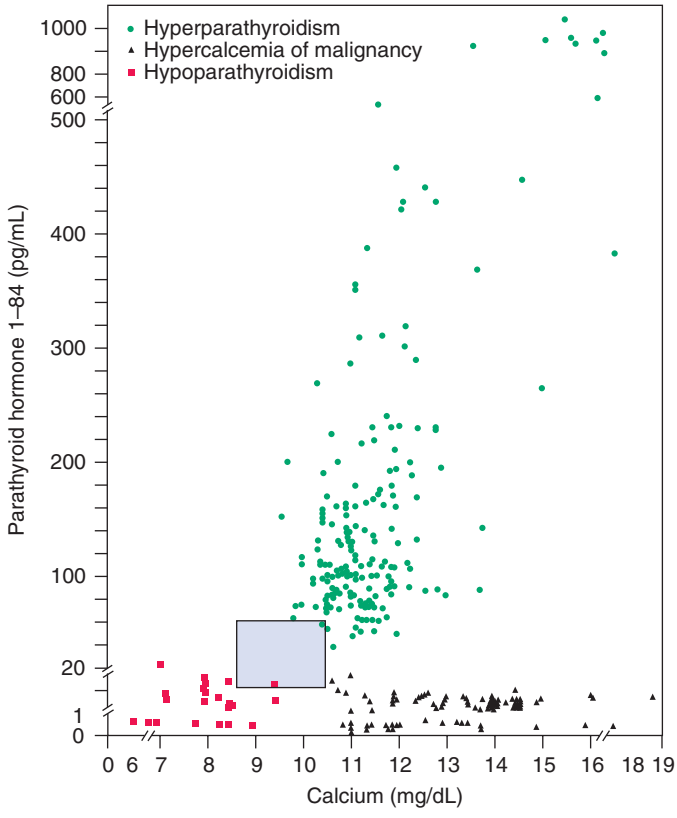

FIGURE 424-4 Levels of immunoreactive parathyroid hormone (PTH) detected in patients with primary hyperparathyroidism, hypercalcemia of malignancy, and hypoparathyroidism. *Boxed area* represents the upper and normal limits of blood calcium and/or immunoreactive PTH. *(From SR Nussbaum, JT Potts, Jr, in L DeGroot, JL Jameson [eds]: Endocrinology, 4th ed. Philadelphia, Saunders, 2001; with permission.)*