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When is Surgery Indicated for Asymptomatic Primary Hyperparathyroidism?

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BACKGROUND

Over the past 30 years, the industrialized world has observed a shift in the clinical presentation of primary hyperparathyroidism (PHPT). Once a rare symptomatic disorder characterized by kidney stones, bone loss, neuromuscular disorders, and other hypercalcemic signs, PHPT is now appreciated to have a much higher incidence than previously thought, and to usually be only mildly symptomatic or even asymptomatic.¹ In those patients with symptomatic PHPT, there has never been controversy about the need for surgery and its myriad benefits.^{1,2}

However, the indications for surgery in asymptomatic PHPT did not begin to be defined until the first Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism, sponsored by the National Institutes of Health, in 1990. A second international conference in 2002, and a third, in May 2008, have further refined consensus guidelines for surgical indications in asymptomatic PHPT. The current guidelines, summarized in this review, are the consensus recommendations of 10 international endocrine societies, including two endocrine surgical societies. This review will summarize the most recent guidelines from the endocrinology literature for surgeons, a group that includes otolaryngologists–head and neck surgeons, who are participating in an increasing share of patient care and research related to parathyroid disease.³

LITERATURE REVIEW

The endocrinology literature supports surgical treatment for “virtually all” patients with PHPT who have specific end-organ signs or symptoms^{1,2,4}; this is currently a noncontroversial statement. The benefits of surgery in these patients has been well established, including improvements in bone density and fracture rates, cognitive function, kidney stone incidence, quality of life, and even the risk of premature death.^{1,2} For those PHPT patients who do not have any symptoms, guidelines for surgery versus medical management have been refined since 1990. This review will focus on the most recent guidelines, published this year.^{1,2,4,5}

The past and current guidelines are summarized in Table 1. Surgery is recommended for patients who meet any of these guidelines. Parathyroidectomy remains the definitive therapy of asymptomatic PHPT, and is always acknowledged to be an option, even in patients who do not meet surgical criteria, if medical surveillance is not deemed possible or desired.

Several key indications for surgery remained unchanged in the most recent iteration of the consensus guidelines. Age <50 years continues to be a guideline for surgery, as evidence supports greater risk of complications in these patients over time. Silverberg et al.⁵ have demonstrated in longitudinal cohort studies that asymptomatic PHPT patients will exhibit stable serum calcium and parathyroid hormone levels for up to 12 years, and stable bone density for up to 8 years, after which time significant decrement in bone density begins to occur. Over 15 years, 60% of untreated asymptomatic patients will lose >10% of their bone density. Parathyroidectomy definitively corrects biochemical abnormalities and improves bone density.

The threshold value for serum calcium, at which point surgery is recommended, continues to be 1.0 mg/dL above the upper limit of normal of the chemistry laboratory. However, hypercalciuria (without nephrolithiasis) was removed as an indication for surgery. Urine calcium (over 24 hours) should still be initially assessed, to rule out familial hypocalciuric hypercalcemia, but it is no longer considered a risk factor for the ultimate development of kidney stones, or an accurate reflection of “calcium load” on the kidneys.⁵

Renal function remains an important consideration, and has been included in the guidelines since 1990. Rather than adjusting renal function for age and gender, as prior guidelines had, the current guidelines now utilize an absolute threshold, beyond which surgery is supported. Patients with a glomerular filtration rate reduced to <60 mL/min are believed to be at escalated risk of complications. This indication was modified, although certain patients may reach this threshold simply due to age or comorbidity. Certainly clinical judgment is important, and elderly patients with high surgical risk may have competing considerations.

PHPT patients are known to have lower bone density and increased fracture risk; even with normal bone density, fractures over time are more common.² Accordingly, bone densitometry results suggestive of osteoporosis are logical indications for surgery. Surgery decreases the risk of fracture in PHPT patients by 30% over 20 years.⁵

There are two areas not currently included in the formal guidelines: neuropsychiatric and cardiovascular disease. There is emerging evidence that many patients with asymptomatic PHPT have some neurocognitive findings which in some studies, appear to improve modestly after surgery. Randomized prospective trials are still needed.² There is also accepted evidence for escalated cardiovascular risk in patients with marked hypercalcemia, but cardiovascular consequences of mild PHPT are subtle, and have unknown implications.⁵ Further research in these areas may alter surgical recommendations in the future.

Parathyroid surgery is regarded not only as the definitive treatment of PHPT, but also as a cost-effective strategy. Pharmacological therapy is not a cost-effective option unless the annual cost of medication is < \$221 (in 2005 dollars). Parathyroidectomy is cost-effective for patients with life expectancy of 5 years or more. Surgery is less costly than medical treatment when the time interval for medical treatment exceeds 5.5 years.²

Implicit in these guidelines is the understanding that parathyroidectomy is generally safe and effective. The endocrinology and endocrine surgery communities consider surgeon experience to be an important variable, with impact on cure and complication rates in parathyroid surgery. This contention has not been tested in comparison studies, but has been extrapolated from the thyroidectomy literature, and from data demonstrating an association between surgeon volume and outcomes. Large retrospective series of minimally invasive parathyroidectomy have reported long-term cure rates of 95% to 98%, with complication rates ranging from 1% to 3%, results comparable to traditional bilateral exploration.²

For those patients who do not undergo parathyroidectomy, consensus guidelines have also been developed on appropriate medical surveillance. These are summarized in Table 2.

BEST PRACTICE

Patients with primary hyperparathyroidism, whether they are symptomatic or asymptomatic, benefit from consultation with a parathyroid surgeon, since there are risks and benefits to both operative and nonoperative management. The ecumenical consensus guidelines published this year in the endocrinology literature continue to strongly support a role for surgery in most patients with asymptomatic PHPT, in whom end-organ complications of PHPT can be avoided or ameliorated, with an operation that is safe, cost-effective, and highly curative in experienced hands.

LEVEL OF EVIDENCE

The consensus guidelines on indications for surgery have been derived from level I evidence (randomized controlled trials and prospective cohort studies). Data on surgeon experience and cost-effectiveness are largely level II (retrospective cohort studies and economic analyses based on clinically sensible costs and alternatives). Surgical outcomes data are level IV (retrospective case series).

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TABLE 1

Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism.⁴ Patients Who Meet One or More Guidelines Should Be Referred for Surgery.

Criterion	1990 Guidelines	2002 Guidelines	2008 Guidelines
Serum calcium (above upper limit of normal)	1.0–1.6 mg/dL	1.0 mg/dL	1.0 mg/dL
24-hour urine calcium	>400 mg/d	>400 mg/d	Not an indication
Renal function	Creatinine clearance decreased by 30%	Creatinine clearance decreased by 30%	GFR <60 mL/min
Bone density	Z score < –2.0 in forearm	T score < –2.5 at any site	T score < –2.5 at any site, and/or previous fracture fragility [*]
Age	<50 years old	<50 years old	<50 years old

* For premenopausal women or men <40 years old, Z scores rather than T scores are used.

GFR = glomerular filtration rate.

TABLE 2Surveillance Guidelines for Patients Not Undergoing Surgery.⁴

Criterion	1990 Guidelines	2002 Guidelines	2008 Guidelines
Serum calcium	Biannually	Biannually	Annually
24-hour urine calcium	Annually	Not recommended	Not recommended
Creatinine clearance	Annually	Not recommended	Not recommended
Serum creatinine	Annually	Annually	Annually
Bone density	Annually	Annually (3 sites)	Every 1–2 years (3 sites)
Abdominal x-ray	Annually	Not recommended	Not recommended