Surgery for Primary Hyperparathyroidism

Are the Consensus Guidelines Being Followed?

Michael W. Yeh, MD, James E. Wiseman, MD,* Philip H. G. Ituarte, PhD,* Jesse D. Pasternak, MD,† Roy S. Hwang, MS,‡ Bian Wu, BS,* In-Lu Amy Liu, MS,§ and Philip I. Haigh, MD‖*

Objective: To determine parathyroidectomy (PTx) rates in patients who satisfy the consensus guidelines for surgical treatment of primary hyperparathyroidism (PHPT).

Background: Surgery for PHPT is recommended for all symptomatic patients and select asymptomatic patients meeting established consensus criteria. Adherence to the consensus guidelines has not been examined systematically, because of inadequate information regarding patients managed nonoperatively.

Methods: All nonuremic patients with PHPT during the period 1995–2008 were identified using the Kaiser Permanente-Southern California laboratory database, encompassing 3.5 million individuals annually. Multivariate logistic regression was used to examine predictors of PTx.

Results: We found 3388 patients with PHPT, of whom 265 (8%) were symptomatic (nephrolithiasis). Nephrolithiasis was predictive of PTx (OR 2.94 vs asymptomatic), with 51% of symptomatic patients undergoing surgery. Among asymptomatic patients, the proportion meeting consensus criteria was 39% during the early period (1995–2002) and 51% during the late period (2003–2008). The PTx rate for these patients exceeded that for asymptomatic patients not meeting consensus criteria but remained low (early 44% vs 19%, $P < 0.0001$; late 39% vs 16%, $P < 0.0001$). The following individual criteria were predictive of PTx: calcium >11.5 mg/dL (OR 2.27), hypercalciuria (OR 3.28, $P < 0.0001$), and age < 50 years (OR 1.54, $P < 0.0001$). However, the absolute PTx rates associated with satisfaction of these criteria were in the 50% range. Bone density scores did not influence likelihood of PTx and renal impairment predicted against PTx (OR 0.35, $P < 0.0001$).

Conclusions: The consensus guidelines regarding PHPT have not been followed in our study population. PTx appears to be underutilized in both asymptomatic and symptomatic patients.

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Primary hyperparathyroidism (PHPT) affects approximately 1% of the adult population, with a higher prevalence among women and the elderly individuals.[1,2] Historically, the diagnosis was made on the basis of the presence of objective clinical findings, such as nephrolithiasis or skeletal abnormalities.[3] With the advent of routine multichannel biochemical testing in the 1970s, however, identification of PHPT in asymptomatic patients became commonplace.[4] There has been general agreement that parathyroidectomy (PTx) is indicated for symptomatic disease, and that surgery remains the only definitive therapy for PHPT. Appropriate management of asymptomatic patients has been a matter of considerable debate, leading to the convention of multidisciplinary conferences in 1990, 2002, and 2008 for the purpose of establishing criteria for surgery in this group, which now represents the great majority of patients with PHPT.[5–7] The initial guidelines published in 1990 defined the following indications for PTx in asymptomatic PHPT: (1) serum calcium level more than 1.0 to 1.6 mg/dL, greater than the upper limit of normal, (2) 24-hour urine calcium excretion more than 400 mg/d, (3) creatinine clearance reduced by 30%, (4) bone density z score less than −2.0 at the distal radius, (5) age less than 50 years, and (6) patients for whom medical surveillance is either not desirable or not possible.

The 2002 International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism produced modifications in 2 guidelines: decreasing the threshold serum calcium level to 1.0 mg/dL greater than the upper limit of normal and changing the bone densitometry criterion to a *T*-score of <-2.5 at any site.[6] The level of compliance with the consensus guidelines is unknown and is the subject of the present work. Systematic study of practice patterns in the management of PHPT has been limited by the unavailability of clinical data on patients who are not referred for surgery. We sought to determine the influence of the consensus guidelines on PTx rates in community practice by examining a large population of patients with an established biochemical diagnosis of PHPT.

METHODS

Subjects

Cases were identified through the Southern California Kaiser Permanente Laboratory Management System patient database system from 1995–2008 under institutional review board approval. Patients possessing all of the following laboratory values were defined as having PHPT: serum intact parathyroid hormone (PTH) more than 65 pg/mL (normal range 15–65), serum calcium more than 10.5 mg/dL (2.6 mmol/L, normal range 8.5–10.5), and serum creatinine less than 2.5 mg/dL (221.0 mmol/L). To avoid contamination of the sample with tertiary hyperparathyroidism patients, any patient who had at least 2 separate blood samples drawn for the measurement of cyclosporine, tacrolimus, or sirolimus was considered a likely kidney transplant recipient and was excluded from the study. A second database, the Southern California Kaiser Permanente Discharge Abstract Database, was cross-referenced to exclude patients with dialysis-dependent chronic kidney disease.

Kaiser Permanente-Southern California (KP-SCAL) is an integrated health care delivery system that serves more than 3 million subscribers annually, representing approximately 20% of the insured population of the region. The KP-SCAL membership closely approximates the population of the greater Los Angeles metropolitan area demographically and socioeconomically, except for the extremes of the income distribution.[8,9]

From the *Division of General Surgery, UCLA David Geffen School of Medicine, Los Angeles, CA; †Department of Surgery, McMaster University, Hamilton, Ontario, Canada; ‡Cleveland Clinic Lerner College of Medicine, Cleveland Clinic Foundation, Cleveland, OH; §Center for Research and Evaluation, Kaiser Permanente Regional Offices, Pasadena, CA; and ‖Department of Surgery, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA.

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Reprints: Michael W. Yeh, MD, FACS, UCLA Endocrine Surgical Unit, Division of General Surgery, 10833 Le Conte Avenue, 72–228 CHS, Los Angeles, CA 90095. E-mail: myeh@mednet.ucla.edu.

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Study Protocol

The main outcome variable was PTx following the biochemical diagnosis of PHPT. To control for other potential predictors of PTx, the following additional data were abstracted: patient sex, race, ethnicity, Charlson comorbidity index (CCI),[10] and 24-hour urinary calcium. Specific *International Classification of Diseases, Ninth Edition* codes were used to identify patients with a history of kidney stones or fracture. To account for the 2002 modification of the consensus criteria, the study population was divided into 2 subgroups on the basis of the year of biochemical diagnosis: the early period (1995–2002) and the late period (2003–2008). Because the calcium threshold was represented by a range during the early period, separate analyses were performed using cutoff values of 11.5 and 12.1 mg/dL to account for the range in clinicians' interpretation of this criterion. We were unable to assess the predictive value of the creatinine clearance criterion for 2 reasons: (1) serum creatinine was used as an initial screen to exclude patients with renal hyperparathyroidism from the study cohort and (2) creatinine clearance was not automatically calculated using the modification of diet in renal disease study equation until 2007. However, despite these limitations, we did model serum creatinine as a continuous variable in our study population of patients with serum creatinine values less than 2.5 mg/dL. Electronic chart review was performed to obtain dual energy x-ray absorptiometry scores, which were available in 827 patients.

Statistical Methods

Student *t* test or contingency table analyses were applied for univariate data analyses. The multivariable logistic regression model included predictors created to test specific consensus criteria. Age (<50 vs ≥ 50 years), serum calcium, and nephrolithiasis were coded as dichotomous variables representing presence or absence of the criterion condition. Model covariates included gender, race, and CCI. An automated procedure created all possible 2-way and 3-way interaction terms among the predictors in the model. Because of this potentially great number of predictors, a forward selection strategy was applied in which each predictor, including interaction terms, was required to meet a significance level of $P = 0.10$ or less to enter the final model. An alpha value of 0.05 was considered statistically significance for predictors in the final models. All analyses were conducted using SAS 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 3388 patients with a biochemical diagnosis of PHPT were identified, 964 (28%) of whom underwent PTx (Table 1). Seventy-nine percent of patients were female. Patients receiving PTx tended to be younger than those who did not. PTx was associated with male gender, nonblack race, and lower comorbidity score. Eighty-seven percent of patients in the study cohort had no significant comorbidities (CCI ≤ 1). These figures were generally consistent during both the early and late periods (Tables 2 and 3).

The proportion of patients meeting criteria for surgery was greater during the late period, during which 51% of patients satisfied one or more criteria, compared to 29% to 39% depending on the serum calcium threshold during the early period ($P < 0.0001$, Tables 4 and 5). The prevalence of nephrolithiasis was greater during the late period (10% vs 6%, $P < 0.01$). The fraction of patients meeting the age less than 50 years and hypercalciuria criteria were similar between periods (16%–17%, nonsignificant [NS]; and 16–18%, NS), as was the fraction with serum calcium >11.5 mg/dL (17%–20%, NS). Only 6% of patients in the early period had serum calcium levels exceeding 12.1 mg/dL.

When the consensus criteria were considered individually, nephrolithiasis was associated with surgical treatment, with approximately half of symptomatic patients undergoing PTx during both periods compared to a 25% to 27% PTx rate for asymptomatic patients (early period OR 3.18, $P < 0.0001$; late period OR 2.94, $P < 0.0001$, Tables 6 and 7). Serum calcium more than 11.5 mg/dL, hypercalciuria, and age less than 50 years were each associated with PTx throughout both periods (early period OR 2.35, 3.68, and 1.48; late period OR 2.06, 2.95, and 1.43; all $P < 0.0001$). Low bone density (forearm Z score < 2.0 SD during early period, or T score < 2.5 SD at any site during late period) did not influence the likelihood of PTx.

When the consensus criteria were considered together as a single body of guidelines, satisfaction of one or more criteria was associated with surgical treatment. During the early period, 44% to 45% of patients satisfying 1 or more criteria were treated surgically, compared to a 19% to 22% PTx rate among those not satisfying any criteria (OR 2.32–2.62 depending on the serum calcium threshold, $P < 0.0001$). During the late period, 39% of patients satisfying 1 or more criteria were treated surgically, compared to a 16% PTx rate among those not satisfying any criteria (OR 2.40, $P < 0.0001$). The earlier mentioned PTx rates (44%–45% compared to 39%, 19%–22% compared to 16%) did not differ significantly between time periods.

Satisfying multiple criteria was associated with an additive effect on the likelihood of PTx. During the early period, the odds ratio was 5.24 (CI [confidence interval] 3.63–7.58, $P < 0.0001$) for patients satisfying 2 criteria and 9.80 (CI 4.15–21.29, $P < 0.0001$) for patients satisfying 3 or more criteria. During the late period, the odds ratio was 5.81 (CI 3.94–8.57, $P < 0.0001$) for patients satisfying 2 criteria and 8.11 (CI 3.84–17.14, $P < 0.0001$) for patients satisfying

TABLE 1. Demographic Characteristics, Entire Cohort (1995–2008) by Parathyroidectomy Status

Characteristic	Sample	No PTx (%)	+PTx (%)	Significance
Mean age	3388	64 yrs	57 yrs	$P < 0.001$
Race				
Black	523 (16%)	394 (75%)	129 (25%)	$P < 0.05$
Nonblack	2862 (84%)	2027 (71%)	835 (29%)	
Gender				
Female	2682 (79%)	1944 (73%)	738 (27%)	$P < 0.05$
Male	706 (21%)	480 (68%)	226 (32%)	
CCI				
0	2411 (71%)	1604 (66%)	807 (84%)	$P < 0.001$
1	549 (16%)	444 (18%)	105 (11%)	
≥ 2	428 (13%)	376 (16%)	52 (5%)	
All patients	3388	2424 (72%)	964 (28%)	

TABLE 2. Demographic Characteristics, Early Period (1995–2002) by Parathyroidectomy Status

Characteristic	Sample	No PTx (%)	+PTx (%)	Significance
Mean age	2048	65 yrs	57 yrs	$P < 0.0001$
Race				
Black	329 (16%)	245 (74%)	84 (26%)	$P = 0.14$
Nonblack	1718 (84%)	1211 (70%)	507 (30%)	
Gender				
Female	1601 (79%)	1151 (72%)	450 (28%)	$P = 0.16$
Male	447 (21%)	306 (68%)	141 (32%)	
CCI				
0	1545 (75%)	1027 (70%)	518 (88%)	$P < 0.0001$
1	264 (13%)	214 (15%)	50 (8%)	
≥ 2	239 (12%)	216 (15%)	23 (4%)	
All patients	2048	1457 (71%)	591 (29%)	

TABLE 3. Demographic Characteristics, Late Period (2003–2008) by Parathyroidectomy Status

Characteristic	Sample	No PTx (%)	+PTx (%)	Significance
Mean age	1340	64 yrs	57 yrs	$P < 0.0001$
Race				
Black	194 (14%)	149 (77%)	45 (23%)	$P = 0.12$
Nonblack	1144 (86%)	816 (71%)	328 (29%)	
Gender				
Female	1082 (81%)	793 (73%)	288 (27%)	$P < 0.05$
Male	359 (19%)	174 (67%)	85 (33%)	
CCI				
0	866 (65%)	577 (60%)	289 (77%)	$P < 0.0001$
1	285 (22%)	230 (24%)	55 (15%)	
≥ 2	189 (14%)	160 (16%)	29 (8%)	
All patients	1340	967 (72%)	373 (28%)	

TABLE 4. Proportion of Patients Satisfying Consensus Criteria, Early Period (1995–2002), n = 2048

Guideline Criterion	Data Available	Criterion Satisfied	Criterion Not Satisfied
Nephrolithiasis	2048	127 (6%)	1921 (94%)
Asymptomatic Criteria			
Ca >11.5 mg/dL	2048	404 (20%)	1644 (80%)
Ca > 12.1 mg/dL		124 (6%)	1924 (94%)
24-hr Ur Ca > 400 mg/d	775	124 (16%)	651 (84%)
Forearm Z score < −2.0 SD	188	11 (6%)	177 (94%)
Age < 50 yrs	2048	340 (17%)	1708 (83%)
Overall 1+ Criteria (Ca > 11.5)	2048	790 (39%)	1258 (61%)
Overall 1+ Criteria (Ca > 12.1)		591 (29%)	1457 (71%)

TABLE 5. Proportion of Patients Satisfying Consensus Criteria, Late Period (2002–2008), n = 1340

Guideline Criterion	Data Available	Criterion Satisfied	Criterion Not Satisfied
Nephrolithiasis	1340	138 (10%)	1202 (90%)
Asymptomatic Criteria			
Ca >11.5 mg/dL	1340	233 (17%)	1107 (83%)
24-hr Ur Ca > 400 mg/d	761	138 (18%)	623 (82%)
T score < −2.5 SD(any site)	446	191 (43%)	255 (57%)
Age < 50 yrs	1340	208 (16%)	1132 (84%)
Overall 1+ Criteria	1340	683 (51%)	657 (49%)

TABLE 6. Proportion of Patients Treated Surgically When Consensus Criteria Satisfied Versus Not Satisfied, Early Period (1995–2002), n = 2048

Guideline Criterion	+PTx if Criterion Satisfied (%)	+ PTx if Criterion Not Satisfied (%)	Not Assessed	OR	CI	Significance
Nephrolithiasis	66/127 (52%)	525/1921 (27%)	0	3.18	2.14–4.73	$P < 0.0001$
Asymptomatic Criteria						
Ca >11.5 mg/dL	181/404 (45%)	410/1644 (25%)	0	2.35	1.81–3.05	$P < 0.0001$
Ca > 12.1 mg/dL	49/124 (40%)	542/1924 (28%)		1.48	0.94–2.33	$P = 0.09$
24-hour Ur Ca ≥ 400 mg/d	85/124 (68%)	204/651 (31%)	1273	3.68	2.38–5.70	$P < 0.0001$
Forearm Z score < −2.0 SD	3/11 (27%)	56/177 (32%)	1860	1.04	0.59–1.86	$P = 0.88$
Age < 50 yrs	144/340 (42%)	447/1780 (25%)	0	1.46	1.12–1.90	$P < 0.0001$
Overall	1+ criteria satisfied	No criteria satisfied				
Ca > 11.5	346/790 (44%)	245/1258 (19%)	—	2.62	2.10–3.27	$P < 0.0001$
Ca > 12.1	266/591 (45%)	325/1457 (22%)	—	2.32	1.85–2.91	$P < 0.0001$

TABLE 7. Proportion of Patients Treated Surgically When Consensus Criteria Satisfied Versus Not Satisfied, Late Period (2002–2008), n = 1340

Guideline Criterion	+PTx if Criterion Satisfied (%)	+PTx if Criterion Not Satisfied (%)	Not Assessed	OR	CI	Significance
Nephrolithiasis	68/138 (49%)	305/1202 (25%)	0	2.94	1.98–4.36	$P < 0.0001$
Asymptomatic Criteria						
Ca >11.5 mg/dL	107/233 (46%)	266/1107 (24%)	0	2.06	1.45–2.93	$P < 0.0001$
24-hr Ur Ca ≥ 400 mg/d	80/138 (58%)	177/623 (28%)	579	2.95	1.97–4.42	$P < 0.0001$
T score < −2.5 SD (any site)	54/191 (28%)	86/255 (34%)	894	1.44	0.57–3.64	$P = 0.44$
Age < 50 yrs	84/208 (40%)	289/1132 (26%)	0	1.43	1.01–2.02	$P < 0.0001$
Overall	1+ criteria satisfied	No criteria satisfied				
	265/683 (39%)	108/657 (16%)	—	2.40	1.80–3.19	$P < 0.0001$

3 or more criteria. The above patterns held true in a subgroup analysis of patients with a comorbidity score of zero.

Several other factors external to the consensus criteria also influenced the likelihood of surgical treatment (Table 8). Each unit increase (pg/mL) in the PTH level was associated with an odds ratio of 1.004 ($P < 0.0001$). The following factors were associated with a lower PTx rate: unit increase (mg/dL) in serum creatinine, 24-hour urinary calcium not measured, and comorbidity score = 1 or ≥ 2 when compared to zero (OR 0.35, 0.67, 0.53, and 0.32, respectively; all $P < 0.0001$).

We modeled probability of PTx as a continuous function of serum calcium, PTH, and creatinine. Controlling for all other variables, the inflection point above which 50% of patients underwent PTx was 11.46 mg/dL. The threshold value for PTH level was 147.4 pg/mL, and the serum creatinine value below which the probability of PTx exceeded 50% was 1.2 mg/dL.

DISCUSSION

To our knowledge, this is the first systematic examination of the degree of adherence to the consensus guidelines regarding surgical management of primary hyperparathyroidism. Our data demonstrate that less than half of asymptomatic patients who satisfy one or more consensus criteria ultimately undergo surgery. The rate of PTx among symptomatic patients with documented nephrolithiasis was similarly low at 51%. Perioperative risk factors do not explain these figures, as the great majority of patients studied were free of significant comorbid disease.

We previously found that PTx is underutilized in the geriatric population, even among healthy individuals who meet objective criteria for surgery.[11] This stimulated us to broaden our analysis to the entire age spectrum and examine the influence of the consensus guidelines on practice patterns in the management of PHPT. It does appear that the consensus guidelines are having some effect on clinical decision making. In most instances, satisfaction of individual consensus criteria did increase the likelihood of PTx, from roughly 25% to 30% in the absence of a given criterion to 40% to 68% when one was met. Patients meeting at least one consensus criterion had more than double the odds of receiving PTx compared to those who did not satisfy any of the criteria.

Several consensus criteria had a neutral or even counterintuitive effect. We were somewhat surprised to find that low bone density scores had no effect on the likelihood of PTx. In addition, an elevated creatinine, which we treated as a surrogate for renal dysfunction in the absence of creatinine clearance values, was highly predictive of nonoperative management. This runs contrary to the intent of the guidelines, which consider worsening renal function an indication for operation.

Our findings related to hypercalciuria suggest that the decision for surgery may largely be a function of physician attentiveness to the diagnosis of PHPT. First, during both periods, hypercalciuria was the single most powerful predictor of PTx, with an odds ratio exceeding even that of nephrolithiasis. Second, patients who did not undergo measurement of the 24-hour urine calcium excretion were very unlikely to be treated surgically. Interestingly, patients in whom the 24-hour calcium excretion was measured and found to be normal were more likely to undergo PTx than those who did not have the test performed. These findings may indicate that physicians who follow through with a complete evaluation of the patient with PHPT are more likely to consider the option of surgery than others who may not be cognizant of the diagnosis and its appropriate management.

KP-SCAL is the largest private medical insurer in Southern California, representing 20% of the insurance market and 36% of the Health Maintenance Organization market in the region. Utilization

TABLE 8. Non–Guideline Predictors of Parathyroidectomy

Factor	Odds Ratio	95% CI	Significance
PTH, per unit increase (pg/mL)	1.004	1.003–1.005	$P < 0.0001$
Serum creatinine, per unit increase (mg/dL)	0.35	0.24–0.49	$P < 0.0001$
Urinary calcium not measured	0.67	0.56–0.79	$P < 0.0001$
Comorbidity score = 1 (vs 0)	0.53	0.42–0.68	$P < 0.0001$
Comorbidity score ≥ 2 (vs 0)	0.32	0.23–0.44	$P < 0.0001$

of this sample is advantageous because of several characteristics inherent to the enrollee population. First, all patients within this cohort possess health care insurance and therefore uniformly have access to care, a factor that has consistently been shown to influence a multitude of outcome measures. Second, the insurance is predominantly employer-based, resulting in a low rate of outmigration and allowing for more consistent long-term follow-up. We previously validated our findings regarding the management of PHPT within KP-SCAL using state-level benchmarks and concluded that practice patterns within KP-SCAL accurately reflect general community practice.[11] In another smaller population-based study, Wermers et al[12] showed that of patients diagnosed with PHPT from 1993 to 2001, 25% were referred for surgical intervention, and 19.8% of the study sample ultimately underwent PTx. These data suggest that, in fact, the rate of PTx at KP-SCAL (28%) is somewhat higher than in the general community.

The reasons for the low level of adherence to the consensus guidelines are likely multifactorial. One possible explanation is the lack of widespread knowledge of their existence among practitioners. In a survey of practicing endocrinologists in the United States, 25% of physicians treating more than 12 patients with asymptomatic PHPT per year (high volume) and 50% of those treating 12 or less patients per year (low volume) were unaware of the 2002 consensus guidelines.[13] Furthermore, only 7% of respondents referred more than 90% of their asymptomatic patients for surgical evaluation, as compared to 31% who referred less than 10%. In a survey-based study performed in Switzerland and published in 2007, 86% of practicing endocrinologists in that country reported reliance upon the 2002 consensus guidelines for their referral practices, although the question of physician awareness was not specifically addressed.[14]

The practice patterns of surgeons are also divergent from the consensus guidelines. A national survey of endocrine surgeons in the United States published in 1998 demonstrated highly variable thresholds for operative intervention in PHPT, with high-volume surgeons having lower thresholds for surgery.[15] These papers suggest, on the basis of subjective data, that while lack of awareness may be partially explanatory of the low compliance rates, perhaps a more important factor is physician preference. Put another way, the consensus guidelines likely represent one of a multitude of factors that are considered in the course of exercising clinical judgment. Our data show that physicians are sensitive to the PTH level and, quite understandably, patient comorbidities, neither of which are represented in the consensus guidelines. We would also like to point out that 16% to 22% of patients who met no criteria underwent surgery, indicating some motivation for surgery in that population. It is also possible that patient preference may play a role.

The Third International Workshop for the Management of Asymptomatic Primary Hyperparathyroidism was convened in 2008.[7] This panel excluded hypercalciuria as an indication and substituted an absolute glomerular filtration rate less than 60 mL/min × 1.73 m^2 for reduction in creatinine clearance. A recent long-term follow-up study of patients with PHPT managed nonoperatively showed a 37% rate of disease progression. The use of antiresorptive medications did not prevent declines in bone density in the patients studied. Importantly, meeting consensus criteria for surgery at the time of diagnosis did not predict who would have progressive disease; 35% of patients exhibited disease progression irrespective of meeting surgical criteria.[16] These findings have called into question whether patients with asymptomatic PHPT should be followed long-term without intervention.

In conclusion, we have demonstrated that the consensus guidelines regarding PHPT have not been followed in our study population. PTx appears to be underutilized in both asymptomatic and symptomatic patients. The magnitude of the discrepancy between recommended practice and actual clinical practice is striking and may warrant greater education of community physicians regarding the appropriate management of this important disease.

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