

Older Patients With Asymptomatic Primary Hyperparathyroidism: Should Criteria for Surgery Be Expanded?

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Abstract

Context: Patients with primary hyperparathyroidism (PHPT) can present with variable signs, symptoms, and end-organ effects. Clinical practice guidelines influence referral for consideration of parathyroidectomy.

Objective: This study compared the demographic, biochemical, and symptom profile and examine indications for surgery in patients older than 50 years who underwent parathyroidectomy to determine how changes to current guidelines may affect recommendations for parathyroidectomy.

Methods: A retrospective review was conducted of patients age 50 years or older who underwent initial parathyroidectomy for sporadic PHPT from 2012 to 2020. Patients were classified by indications for surgery per guideline criteria (classic, asymptomatic, and no criteria met) and age group (AG): 50 to 59 years; 60 to 69 years; 70 years or older. Patients were treated at a high-volume tertiary medical center by endocrine surgeons.

Results: Of 1182 patients, 367 (31%) classic and 660 (56%) asymptomatic patients met the criteria for surgery. The most common indications for surgery were extent of hypercalcemia (51%), osteoporosis (28%), and nephrolithiasis (27%). Of the 155 (13%) patients who did not meet the criteria, neurocognitive symptoms (AG1: 88% vs AG2: 81% vs AG3: 70%; $P = .14$) and osteopenia (AG1: 53% vs AG2: 68% vs AG3: 68%; $P = .43$) were frequently observed regardless of patient age. If the age threshold of younger than 50 years was expanded to 60, 65, or 70 years, an additional 61 (5%), 99 (8%), and 124 (10%) patients in the entire cohort would have met the guideline criteria for surgery, respectively.

Conclusion: Expanding current guidelines for PHPT to include a broader age range, osteopenia, and neurocognitive symptoms may allow for earlier surgical referral and evaluation for definitive treatment.

Key Words: hyperparathyroidism, parathyroidectomy, indications, patient selection, hypercalcemia

Abbreviations: AAES, American Association of Endocrine Surgeons; AG, age group; BMD, bone mineral density; GERD, gastroesophageal reflux disease; GFR, glomerular filtration rate; IQR, interquartile range; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; QoL, quality of life.

Primary hyperparathyroidism (PHPT) is a condition that results in hypercalcemia due to inappropriate autonomous secretion of parathyroid hormone (PTH) by abnormal parathyroid gland(s). The diagnosis of PHPT is biochemical but remains underdiagnosed in patients with high serum calcium levels [1–3]. PHPT can negatively affect bone mineral density (BMD) and renal function, leading to fragility fractures, reduced glomerular filtration rate (GFR), and nephrolithiasis [4]. Symptoms associated with PHPT include musculoskeletal, gastrointestinal, and/or neurocognitive symptoms; the severity of these nonspecific, patient-reported symptoms can be highly variable. Parathyroidectomy is the only cure for PHPT, with reported cure rates greater than 95% and low rates of procedure-specific complications, such as recurrent laryngeal nerve injury and/or permanent hypoparathyroidism [5–8]. Parathyroidectomy has been

shown to improve sequelae of PHPT in nearly all facets of the disease [5, 9–17]. Parathyroidectomy is a procedure that is commonly performed in the outpatient setting with low rates of morbidity and rare mortality [7, 18–21]. Despite this, previous studies have shown that referral for surgery is likely guided by published societal clinical practice guidelines and PHPT remains underdiagnosed and undertreated [22–27].

Current consensus guidelines, which include those from the Fourth and Fifth International Workshops and the American Association of Endocrine Surgeons (AAES), classify PHPT into classic and asymptomatic categories based on specific disease features [22, 24, 28, 29]. Surgery is recommended for patients with symptomatic or “classic” PHPT (nephrolithiasis and fragility fractures), whereas other sequelae of PHPT, including reduced BMD, nephrocalcinosis, hypercalciuria, and reduced GFR, are considered “asymptomatic.” Indications

for parathyroidectomy in patients with asymptomatic disease per the Fourth International Workshop include (1) serum calcium greater than 1.0 mg/dL above the upper limit of normal; (2) BMD by dual-energy x-ray absorptiometry T score less than -2.5 at any site; (3) radiographic evidence of vertebral fracture; (4) 24-hour urine calcium greater than 400 mg/day and increased risk of stone formation; (5) presence of nephrolithiasis or nephrocalcinosis on imaging; and/or (6) age younger than 50 years [22]. The 2022 International Workshop revised recommendations for parathyroidectomy based on hypercalciuria to a threshold of greater than 250 mg/day for women and more than 300 mg/day for men [29].

It is important to note that parathyroidectomy should not be limited to symptomatic patients or asymptomatic patients who fulfill these guidelines. Justifications to support the current age recommendation of 50 years for patients with asymptomatic PHPT are largely based on potential consequences of long-term PHPT and data that suggest disease progression is more likely in younger patients than older patients [30]. Age 50 years has remained constant in recent guidelines, even as life expectancy in the United States has increased by almost 10 years in recent decades [31]. Increasing life expectancy may also have an effect on the progression of BMD in patients with PHPT, perhaps particularly those with osteopenia, given that BMD has been shown to decline at the hip and distal radius when no intervention has occurred for more than 10 years since onset of disease [13, 32-35].

In addition, while the presence of neurocognitive symptoms, including anxiety, depression, memory, concentration, and fatigue, were acknowledged both in the 2014 and 2022 International Workshop guidelines, they were not considered a strict indication for surgery [22]. Some studies, however, have demonstrated improvement in these symptoms following parathyroidectomy [12, 14, 36]. Based on these data, the AAES guidelines endorse a strong recommendation for parathyroidectomy in the setting of patients with neurocognitive symptoms “attributable to PHPT.” [24] Furthermore, in a recent systematic review of 31 studies that examined quality of life in patients with PHPT, the majority (87%) demonstrated significant improvement following curative parathyroidectomy [17, 22-24].

We hypothesized that among patients older than 50 years who underwent parathyroidectomy for asymptomatic PHPT, not all patients would meet the current guideline criteria, and that broadening the age criterion and criteria for other common sequelae of PHPT would increase the number of patients who may derive benefit from curative parathyroidectomy. Therefore, the aim of this study was to compare the demographic, biochemical, symptom profile, and indications for surgery in patients older than 50 years who underwent parathyroidectomy at our institution, to determine how changes to the current guidelines may affect recommendations for parathyroidectomy, as these findings may guide decision-making among patients and their health care team. Potential differences in symptom profile among patients who did not meet the guideline criteria and underwent parathyroidectomy also were assessed.

Material and Methods

This study was a retrospective review of an institutional, prospectively collected parathyroid database. Patients with sporadic PHPT who underwent initial parathyroidectomy

between January 1, 2012 and December 31, 2020, were included. Age was restricted to patients age 50 years or older since all patients younger than 50 years meet the current recommendations for surgery per societal guidelines [22, 24]. Patients with familial, secondary, or tertiary HPT were excluded. Patients with less than 6 months' follow-up also were excluded. This study was approved by an institutional review board at the Medical College of Wisconsin.

Demographic and clinical data were collected. Preoperative and postoperative laboratory data collected, based on our institutional protocol, included a comprehensive metabolic panel (including serum albumin), ionized calcium, PTH, 25-OH vitamin D levels, and 24-hour urine calcium and creatinine levels. Intraoperative PTH values and intraoperative findings, extent of surgery, final pathology, and long-term outcomes were also examined. Patients were classified into age groups at the time of surgery by decade and relatively equally distributed tertiles: 50 to 59 years, 60 to 69 years, and 70 years or older. Eight indications for parathyroidectomy were specifically examined based on the Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop and the AAES guidelines [22, 24]. Patients were categorized by indications for surgery (classic, asymptomatic, and no criteria met) based on the Fourth International Workshop Guidelines (Table 1), which were the existing guidelines for the majority of patients included in this study. Patients in the “no criteria met” group did not meet classic or asymptomatic criteria for parathyroidectomy.

Symptoms associated with PHPT were examined for the entire cohort and by indication grouping (classic, asymptomatic, and no criteria met). These data were collected by chart review of surgeon documentation of patient-reported symptoms. A composite variable was created for neurocognitive symptoms, which included fatigue, memory or concentration deficits, and mood swings. Other patient-reported symptoms included bone, joint, and muscle aches, polydipsia, nocturia, constipation, and pruritis. The earliest data used in this study were from patients who underwent surgery in 2012, which coincided with the documentation of patient-reported symptoms in our database.

All patients underwent parathyroidectomy with intraoperative PTH monitoring. The institutional protocol for parathyroidectomy and intraoperative PTH monitoring has previously been described [37, 38]. Postoperatively, for

Table 1. Definition of surgical indication groups based on published guidelines

Classic	Asymptomatic	No criteria met
Nephrolithiasis	Vertebral compression fractures	Biochemical diagnosis of PHPT
Fragility fractures	Osteoporosis (T score <-2.5)	
	Urine calcium >400 mg/24 h	
	Serum calcium >1 mg/dL above normal	
	Glomerular filtration rate <60 mL/min	

Abbreviation: PHPT, primary hyperparathyroidism.

patients who were admitted for observation, serum calcium, ionized calcium, and PTH were routinely obtained on postoperative day 1. Routine supplementation of calcium carbonate was performed per our institutional protocol in which patients with single-gland disease received 1000 mg of calcium carbonate twice daily and those with multigland disease received 2500 mg of calcium carbonate 3 times daily [20]. Calcitriol was prescribed for patients with PTH less than 5 pg/mL on postoperative day 1. Calcium supplementation was reassessed based on laboratory data at the postoperative visit 1 to 2 weeks after surgery.

Long-term outcomes were assessed at 6 months, 12 months, and every year after surgery with serum calcium, ionized calcium, and PTH in conjunction with the patient's endocrinologist and primary care provider. Biochemical cure was defined as normal serum and ionized calcium levels, with a PTH less than 40 pg/mL at 6 months postoperatively. Persistent disease was defined as serum calcium greater than 10.2 mg/dL (normal, 8.6-10.2 mg/dL) and PTH greater than 40 pg/mL (normal, 15-72 pg/mL) when present less than 6 months after surgery, while recurrent disease was defined as serum calcium greater than 10.2 mg/dL and PTH greater than 40 pg/mL 6 months or longer after surgery [20, 37]. Patients were considered to have permanent hypoparathyroidism if they required calcium and/or calcitriol supplementation for more than 6 months following surgery [20, 37].

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 28.0.0.0 (190) (IBM Corp). Mean is reported with SD, and median is reported with interquartile range (IQR). Continuous variables with a normal distribution were compared with *t* test or one-way analysis of variance, while comparison of continuous variables with a nonparametric distribution was performed with the Kruskal-Wallis test. Chi-square and Fisher exact tests were used to compare categorical variables. A *P* value greater than .05 was considered statistically significant.

Results

Demographic and Biochemical Profile of Entire Cohort

During the study period, 1182 patients met the criteria for inclusion in our study cohort (see Table 1). The mean age was 65 ± 8.5 years. The majority of patients were female (79%) and White (89%). The median serum calcium was 10.8 mg/dL (IQR 10.4-11.2) and median PTH was 93 pg/mL (IQR 70-124). The median 24-hour urine calcium was 273 mg per 24 hours (IQR 174-403). The remainder of the biochemical profile is summarized in Table 2.

Indications for Parathyroidectomy

When evaluated based on indications for surgery, the majority of patients (660; 56%) met the asymptomatic guideline criteria, 367 patients (31%) had classic PHPT, and 155 patients (13%) met no defined criteria for surgery (Fig. 1). Patients had a median of 2 indications for surgery (IQR 1, 2; range, 0-5). The most common indications for surgery in the cohort were extent of hypercalcemia (51%), osteoporosis (28%), and nephrolithiasis (27%). Patients with classic PHPT exhibited a range of 1 to 5 indications (median 2 [IQR 2-3]), while asymptomatic patients had 1 to 4 indications for parathyroidectomy (median 1 [IQR 1, 2; *P* < .001]).

For the patients with classic PHPT, 86% had nephrolithiasis, 49% were hypercalcemic, and 26% had osteoporosis. In the asymptomatic group, 65% were hypercalcemic, 36% had osteoporosis, and 30% had hypercalciuria. Hypercalciuria was more frequent in the asymptomatic group (30% vs 23%; *P* = .03; Table 3).

Comparison of Demographic, Biochemical, and Symptom Profile by Surgical Indications

The demographics and biochemical profile of patients were compared by indications for surgery (classic, asymptomatic, and no criteria met). The 155 patients who did not meet the guideline criteria were younger (mean 65 years vs 65 years vs 63 years; *P* < .001) and predominately female (79% vs 81% vs 89%; *P* < .001; see Table 2). Patients with asymptomatic PHPT had higher median serum calcium (10.7 vs 10.9 vs 10.5 mg/dL; *P* < .001) and PTH levels (93 vs 98 vs 81 pg/mL; *P* < .001), compared to the other 2 groups. There was no difference in ionized calcium, 25-OH vitamin D, serum albumin levels, or GFR between the groups. Patients with asymptomatic PHPT more frequently reported prior lithium use (1% vs 4% vs 3%; *P* = .02).

Potential sequelae of PHPT were compared for all patients based on indication group. Osteopenia was most frequent in patients who did not meet the guideline criteria (48% vs 39% vs 62%; *P* < .001; see Table 2). The presence of neurocognitive symptoms (81%), hypertension (62%), and bone/joint pains (53%) were reported in the majority of patients in each group, with no differences among the 3 groups. Additionally, there was no difference in presence of GERD or patient-reported constipation, nocturia, and pruritis. Polydipsia was more prevalent in patients with classic and asymptomatic PHPT, compared to those who did not meet the guideline criteria (17% vs 17% vs 6%; *P* = .008).

Analysis of Patients Who Did Not Meet Current Guidelines for Parathyroidectomy by Age Group

The 155 patients in the "no criteria met" group were categorized by decade: 39% were age 50 to 59 years (AG1), 41% were age 60 to 69 years (AG2), and 20% were 70 years or older (AG3; *P* < .01; see Fig. 1). There was no difference in sex, race, or body mass index across the age groups. There also was no difference in the biochemical profile, with similar serum calcium (10.5 mg/dL [IQR 10.1-10.8] vs 10.6 mg/dL [IQR 10.2-10.9] vs 10.6 mg/dL [IQR 10.3-10.9]; *P* = .19) and PTH (93 pg/mL [IQR 84-103] vs 101 pg/mL [IQR 91-110] vs 112 pg/mL [IQR 97-127]; *P* = .10) levels. When analyzed by presence of symptoms and sequelae potentially associated with PHPT, only hypertension was more common in older patients (AG1: 47% vs AG2: 57% vs AG3: 74%; *P* = .04). There was no difference in the incidence of osteopenia or any patient-reported symptoms across the age groups (Table 4).

Based on these findings, if guidelines were expanded in this cohort to include an age threshold of younger than 60, 65, or 70 years, an additional 61 (5% of entire cohort), 99 (8%), and 124 (10%) patients would have met the criteria for surgery. Regardless of age, if the presence of osteopenia was included, an additional 95 patients (8%) would have met the criteria for surgery. Similarly, if neurocognitive symptoms, as defined in this study, were an indication for surgery, an additional 118 patients (10%) would meet the criteria for surgery.

Table 2. Demographic, clinical characteristics, and symptom profile by indication group

Variable	Total		Classic		Asymptomatic		No criteria		P
	(n = 1182)		(n = 367)		(n = 660)		(n = 155)		
Age at surgery (mean ± SD)	65	±8.5	65	±8.6	65	±8.6	63	±7.8	<.001
Female sex	932	78.8%	261	71.1%	533	80.8%	138	89.0%	<.001
Race/Ethnicity									<.001
White	1047	88.6%	341	92.9%	565	85.6%	141	91.0%	
Black	98	8.3%	20	5.4%	66	10.0%	12	7.7%	
Asian	10	0.8%	2	0.5%	6	0.9%	2	1.3%	
Other	27	2.3%	4	1.1%	23	3.5%	0	0.0%	
Body mass index ^a	30.1	(25.6-34.9)	31.5	(26.3-35.6)	29.8	(25.3-34.6)	29.3	(25.6-34.3)	<.01
History of									
Radiation	55	4.7%	21	5.8%	30	4.6%	4	2.6%	.32
Radioactive iodine	25	2.2%	6	1.7%	14	2.2%	5	3.3%	.51
Lithium use	32	3.2%	3	1.0%	25	4.4%	4	3.0%	.02
Biochemical profile ^a									
Serum calcium, mg/dL	10.8	(10.4-11.2)	10.7	(10.3-11.1)	10.9	(10.5-11.4)	10.5	(10.2-10.8)	<.001
Ionized calcium, mmol/L	1.40	(1.36-1.46)	1.39	(1.35-1.45)	1.41	(1.37-1.47)	1.41	(1.34-1.41)	.08
24-h urine calcium, mg/TV	273	(174-403)	271	(173-398)	281	(174-429)	251	(183-328)	<.001
PTH, pg/mL	93	(70-124)	93	(67-128)	98	(74-130)	81	(60-101)	<.001
25-OH vitamin D, ng/mL	31	(24-39)	30	(24-39)	31	(24-39)	32	(26-41)	.56
Albumin, g/dL	4.4	(4.1-4.5)	4.3	(4.1-4.5)	4.4	(4.1-4.6)	4.4	(4.2-4.5)	.30
Creatinine, md/dL	0.9	(0.7-1.0)	0.9	(0.7-1.1)	0.9	(0.7-1.0)	0.8	(0.7-0.9)	<.001
GFR, mL/min	60	(60-60)	60	(60-60)	60	(58-60)	60	(60-60)	.02
Bone density									<.001
Normal	265	22.4%	84	22.9%	134	20.3%	47	30.3%	
Osteopenia	530	44.8%	175	47.7%	259	39.2%	96	61.9%	
Osteoporosis	333	28.2%	97	26.4%	236	35.8%	0	0.0%	
Unknown	54	4.6%	11	3.0%	31	4.7%	12	7.7%	
Hypertension	733	62.3%	226	61.6%	422	64.2%	85	55.6%	.13
Symptoms									
Neurocognitive symptoms	919	80.9%	291	81.5%	508	80.4%	120	81.6%	.88
Bony aches and pains	600	53.0%	198	55.6%	326	51.6%	76	52.4%	.47
Constipation	252	22.0%	91	25.3%	132	20.6%	29	20.0%	.18
GERD	511	44.2%	174	48.5%	280	43.3%	57	38.0%	.07
Nocturia	266	22.5%	88	25.2%	155	24.8%	23	16.1%	.07
Pruritus	71	6.8%	27	8.2%	40	6.8%	4	3.2%	.17
Thirst	159	15.6%	54	17.3%	97	16.7%	8	6.3%	<.01

Abbreviations: GERD, gastroesophageal reflux disease; GFR, glomerular filtration rate; PTH, parathyroid hormone.

^aIndicates median (interquartile range).

Clinical Outcomes by Indication Group

Among the 3 groups (classic, asymptomatic, and no criteria), there was no difference in presence of multigland disease (31% vs 26% vs 30%; $P = .20$). There also were no differences in rates of persistent or recurrent PHPT, permanent hypoparathyroidism, recurrent laryngeal nerve injury, or postoperative hematoma (Fig. 2).

Discussion

Current consensus guidelines for the management of patients with PHPT use a perceived age threshold of 50 years in the recommendation of parathyroidectomy for patients with otherwise asymptomatic disease [22, 24]. This study aimed to

assess the indications for parathyroidectomy among patients with PHPT who were 50 years or older, particularly those who did not meet any criteria per the current guidelines, with the hypothesis that at a high-volume center, parathyroidectomy is safely performed and these patients may derive benefit from normalization of serum calcium and PTH levels after successful surgery. In the present study, approximately one-third of patients age 50 years or older had classic PHPT and the majority (56%) met the criteria for asymptomatic PHPT. However, 13% of patients who underwent parathyroidectomy did not meet the classic or asymptomatic criteria and of these, more than three-quarters reported neurocognitive symptoms, and more than half had evidence of osteopenia and/or hypertension. Our findings add valuable information

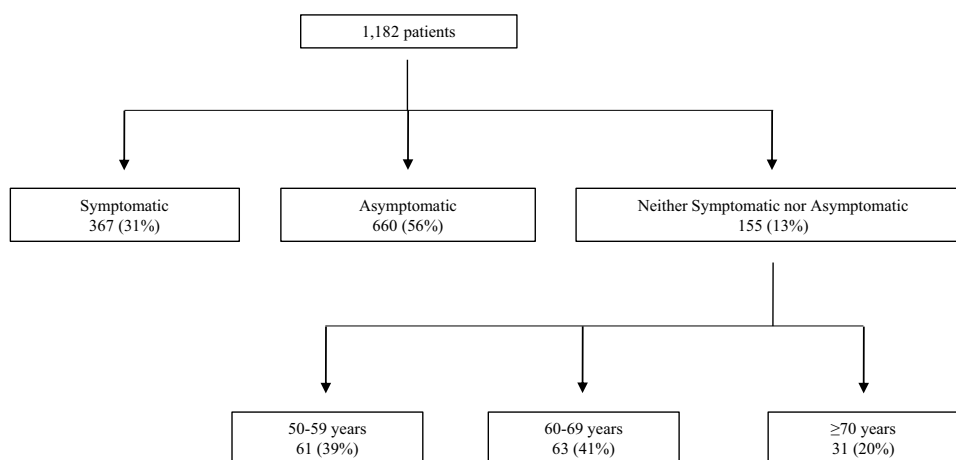


Figure 1. Flow diagram of patient classification for study purposes.

Table 3. Indications for surgery in the classic and asymptomatic groups

Variable	Classic		Asymptomatic		P
	(n = 367)		(n = 660)		
Kidney stones	315	85.8%	0	0.0%	<.001
Nontraumatic fractures	62	17.2%	0	0.0%	<.001
Vertebral compression fractures	8	2.2%	24	3.6%	.198
Bone density					.005
Normal	84	22.9%	134	20.3%	
Osteopenia	175	47.7%	259	39.2%	
Osteoporosis	97	26.4%	236	35.8%	
Urine calcium >400 mg/24 h	86	23.4%	196	29.7%	.03
Serum calcium >1 mg/dL above normal	180	49.0%	427	64.7%	<.001
Glomerular filtration rate <60 mL/min	87	23.7%	189	28.6%	.09

Table 4. Clinical characteristics and symptom profile for the “no criteria met” group

Variable	Total		50-59 y		60-69 y		>70 y		P
	(n = 155)		(n = 61)		(n = 63)		(n = 31)		
Bone density									.43
Normal	47	30.3%	23	38.3%	16	25.8%	7	22.6%	
Osteopenia	96	61.9%	32	53.3%	42	67.7%	21	67.7%	
Hypertension	85	55.6%	27	46.6%	35	56.5%	23	74.2%	.04
Symptoms									
Neurocognitive symptoms	120	81.6%	49	87.5%	48	81.4%	21	70.0%	.14
Bony aches and pains	76	52.4%	33	60.0%	29	50.0%	13	43.3%	.30
Constipation	29	20.0%	14	25.0%	9	15.8%	5	16.1%	.41
GERD	57	38.0%	26	46.4%	23	37.7%	7	22.6%	.09
Nocturia	23	16.1%	11	19.6%	7	12.7%	4	12.9%	.54
Pruritus	4	3.2%	3	5.9%	0	0.0%	1	3.6%	.26
Thirst	8	6.3%	4	8.2%	0	0.0%	2	7.1%	.13

Abbreviation: GERD, gastroesophageal reflux disease.

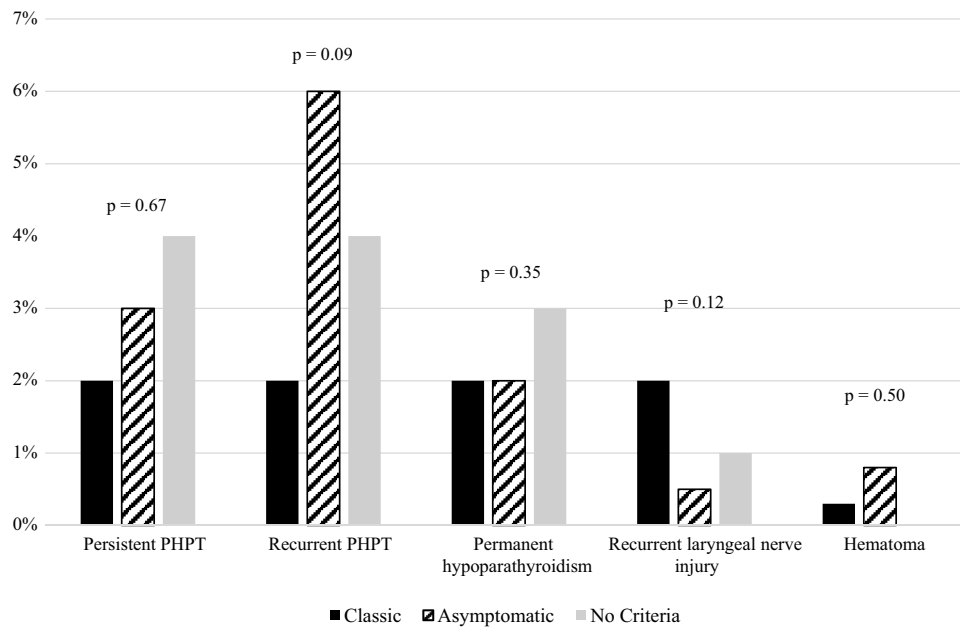


Figure 2. Long-term outcomes for patients following parathyroidectomy.

to the literature about a group of patients not frequently studied—patients with PHPT who do not meet the guideline criteria for parathyroidectomy but report symptoms that are associated with PHPT—and highlight the importance of patient education, discussion, and shared decision-making by patients and their health care team regarding potential benefits of parathyroidectomy.

When the initial guidelines for management of asymptomatic PHPT were published in 1991 by the National Institutes of Health, the justification for selecting age younger than 50 years as an indication for surgery was the risk of long-term PHPT and concern for progression of disease [23]. However, at that time, the average life expectancy in the United States was 71.8 years for a man and 78.8 years for a woman [39]. The average life expectancy in 2017 increased to 77.3 years for a man and 82 years for a woman, with projected increases in life expectancy to 83.9 years for a man and 87.3 years for a woman by the year 2060 [40]. Given increases in average life expectancy, we considered whether the age threshold as an indication for parathyroidectomy should increase. Prior studies of patients who have undergone parathyroidectomy after surgical consultation have demonstrated that parathyroidectomy is safe without increased risk of surgical complications in the older population [19, 20, 41]. There are sparse data to support age younger than 50 as the specific threshold for parathyroidectomy, although data do suggest that PHPT in younger patients is more likely to progress than in older patients [30]. Additionally, menopause and estrogen deficiency may play a role in disease progression in women, especially skeletal sequelae [30, 42, 43]. If age criteria were expanded to age younger than 60 years in this study, an additional 61 (5%) patients would have met the criteria for surgery.

Fatigue, changes in mood, sleep, memory and concentration, and other symptoms associated with a poorer quality of life (QoL) are commonly reported in patients with PHPT [9, 10, 14]. The findings of this study are consistent with other studies regarding the prevalence of reported neurocognitive symptoms in this patient population. Previous studies have

used general health QoL tools as well as a validated parathyroid-specific QoL tool to assess neurocognitive symptoms in patients with PHPT [36, 44-46]. However, there are few randomized controlled trials and, to date, many of the existing studies have had small sample sizes, have used different tools to assess patient QoL, and have not always included a control group of patients, resulting in mixed findings with respect to true improvement in neurocognitive symptoms following parathyroidectomy [5, 28, 45, 47-50]. As a result, to date, consensus guidelines have not included the presence of neurocognitive symptoms as an indication for surgery in patients with otherwise asymptomatic PHPT [22]. However, there is evidence to support improvement in patient-reported fatigue, depression, and symptoms of anxiety following parathyroidectomy, even with the previously mentioned limitations [36, 45, 47]. Improvement in social functioning and vitality have reliably been demonstrated in patients following parathyroidectomy in randomized controlled trials using the Short Form Health Survey [5, 45, 50]. In multicenter, prospective, observational studies that used nontoxic patients who underwent thyroidectomy for comparison, parathyroidectomy patients reported improvement in fatigue, depression, mood swings, and memory, whereas patients who underwent thyroidectomy did not [36]. Another multicenter, prospective, observational QoL study that compared parathyroidectomy to observation in patients with PHPT demonstrated marked improvement in a different primary hyperparathyroidism QoL questionnaire after surgery, especially when serum calcium was reduced by more than 1 mg/dL [51]. In light of these data, if neurocognitive symptoms were considered an indication for surgery, 118 (10%) additional patients would have met the criteria for parathyroidectomy. Earlier surgical referral would offer patients more information about surgery as an option and a chance for shared decision-making between the patient and surgeon.

Fractures in older adults can have devastating consequences, particularly hip fractures, which are associated with increased morbidity and mortality in older populations [34].

Parathyroidectomy has been shown to stabilize or improve BMD in patients with PHPT [5, 32, 33, 45]. Studies have demonstrated mixed results as to whether BMD worsens without surgery [5, 33, 45]. Osteopenia is not currently considered an indication for surgery unless worsening BMD on subsequent imaging is demonstrated [22]. Newly published studies show there likely is a benefit to parathyroidectomy in patients with PHPT even in the absence of osteoporosis. A recent study from Seib et al [35] demonstrated a reduced risk of any fracture (adjusted risk ratio 5.1% [4.6%-5.5%]) and hip fracture (adjusted risk ratio 2.3% [2.0%-2.6%]) among patients with PHPT 10 years after parathyroidectomy compared to those who underwent observation. These benefits were observed in patients with and without osteoporosis. If osteopenia was an indication for surgery, 95 (8%) additional patients would have met the criteria for parathyroidectomy. Surgical consultation should be considered in any patient with reduced BMD, especially those at increased risk of fracture, so that patients can have a discussion regarding the risks and benefits of parathyroidectomy vs potential fracture.

Underdiagnosis and treatment of PHPT continues to be a problem nearly 30 years after the first guidelines from the National Institutes of Health were published despite multiple iterations and societies endorsing these guidelines [1-3, 22-26]. Studies examining adherence to published guidelines demonstrate underutilization with greater likelihood of referral to surgery when patients are evaluated by an endocrinologist [52, 53]. Delays in diagnosis, referral, and treatment may partly explain the higher prevalence of osteoporosis, and the higher serum calcium and PTH levels that were observed in patients in the asymptomatic group compared to the classic group.

There are several limitations to this study, including the lack of long-term data regarding changes in bone health, fracture rates, and mixed evidence with respect to improvement in neurocognitive symptoms following parathyroidectomy. While neurocognitive symptoms are documented preoperatively in our institutional parathyroid database, postoperative documentation of symptom improvement has not been as rigorous to date. This remains a limitation of a single-institution study, and multi-institutional studies are needed. There also is likely a selection bias in this study, as our database captures only patients who have undergone parathyroidectomy. As a result, we are not able to determine if those patients with PHPT who are not referred or who do not choose to undergo parathyroidectomy meet the current guideline criteria for surgery or have sequelae of PHPT, as described in this study, although this is likely, given evidence to suggest undertreatment of PHPT [54]. Lastly, we are not able to assess reasons why providers of or patients with PHPT do not pursue a surgical referral or to determine whether strict adherence to clinical guidelines are driving referral patterns. Despite these limitations, a strength of this study includes the large cohort of consecutive patients with PHPT who underwent parathyroidectomy by a single group of fellowship-trained endocrine surgeons, the low rates of endocrine-specific complications of persistent/recurrent PHPT and hypoparathyroidism, and the longitudinal tracking of patients in our institutional database.

Conclusion

At our institution, 13% of patients who underwent parathyroidectomy for PHPT did not meet the criteria for surgery

based on current societal guidelines. These patients frequently experienced neurocognitive symptoms (81%) and/or had osteopenia (62%). These data further emphasize the importance of education of clinical care teams that current guidelines are not meant to be stringent criteria for consideration of surgery, and that the benefits of parathyroidectomy should be discussed with patients who may not meet these guidelines, such as those with neurocognitive symptoms and/or osteopenia and a 10-year FRAX calculation greater than 3% at the hip or greater than 20%, as these patients may benefit from reduced fracture risk after parathyroidectomy [55]. Furthermore, with the increased longevity of the general population and the potential for improvement in neurocognitive symptoms following parathyroidectomy, consideration of the expansion of current consensus guidelines in the criteria for parathyroidectomy in patients with otherwise asymptomatic PHPT to include a broader age range, osteopenia, and neurocognitive symptoms would potentially allow for earlier surgical referral, evaluation for definitive treatment, and earlier discussion between patients and their multidisciplinary team of clinicians (primary care providers, endocrinologists, and surgeons) regarding the potential short-term and long-term risks and benefits of parathyroidectomy.

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Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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