2016 Arizona AACE Meeting: Updated Guidelines for the Management of Primary Hyperparathyroidism (PHPT)

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Disclosures

• I have no personal disclosures

• All members of the AAES guidelines for the Management of PHPT submitted individual disclosures - none relevant
The American Association of Endocrine Surgeons (AAES) Guidelines for the Definitive Management of PHPT.


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PHPT Guidelines

• Condensed “Executive Summary” that reduces guidelines to essentials in a bullet point format (42 refs)

• “Online Supplement”: 174 online pages of recommendations, supporting evidence, tables, figures and pearls (712 refs)

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Existing Guidelines


Why create a new set of guidelines?

• Surgical treatment has undergone extensive change in the past 2 decades (MIP, IOPTH, Improved imaging, Definitions, etc.)

• Variation in practice generally implies variation in the quality of care, so efforts to standardize approaches to diagnosis, treatment, and surveillance are valuable.

• There has been disagreement regarding the best management approach and whether that should include surveillance, medical therapy, or surgery.

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Goals of the AAES Guidelines

1) Provide caregivers with a current background understanding of the epidemiology and pathogenesis of pHPT.

2) Outline the process for diagnosis of pHPT by laboratory studies and clinical manifestations (both subjective and objective) and once a diagnosis is established, examine the indications for surgical intervention.

3) Detail the pre- and intra-operative management of pHPT including creation of a “patient-specific operative plan” based on available resources, surgeon experience, and patient characteristics.

4) Delineate methods for safe and effective postoperative management including a definition of cure and an algorithm for managing operative failure.

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PHPT Guidelines

Objective:
• To develop evidence-based guidelines to enhance the appropriate, safe, and effective practice of parathyroidectomy.

Evidence Review:
• A multidisciplinary panel used PubMed to review the medical literature from January 1, 1985, to July 1, 2015.
  Limited to English language, Adults, and PHPT

• Levels of evidence were determined using the American College of Physicians grading system, and recommendations were discussed until consensus.

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ACP Grading

Grading designation

- Strong- Benefits outweigh risks/Should be applied to all pts.
- Weak- Benefits balance the risks
- Insufficient- not enough evidence to judge.

Strength of Recommendation

- High- RCT or overwhelming evidence
- Moderate- RCT with limitations, designed cohort studies, Large observational studies
- Low- potentially biased or small observational or case studies.

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PHPT Guidelines

• Formal feedback and suggestions were sought from an independent group of non-author experts
• Formal input from AAES members and other sources
• Peer Review
• E-publication in JAMA Surgery August 10, 2016
• Timeline: Jan 2014 to October 2016
• Cautions: These guidelines do not represent the only approach, are intended to be flexible, may require significant adaptation in practice settings characterized by barriers to implementation, and are not meant to replace individual physician judgment.

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Anatomical Relationships of Eutopic & Ectopic Parathyroid Glands
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Epidemiology and Pathogenesis of PHPT

- **Sporadic PHPT**: PHPT is primarily a sporadic disease process caused by abnormal iPTH production from a single adenoma, hyperplasia, and rarely carcinoma.

- **Acquired PHPT**: PHPT can be acquired as a result of environmental exposure—Lithium exposure, Ionizing radiation, Amiodarone.

- **Inherited PHPT**: PHPT can be seen in familial conditions such as MEN I, MENII-A, HPT-JT (Jaw tumor syndrome), FIHPT (Familial Isolated HPT), and other gene rearrangements such as PRAD-1.

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Epidemiology and Pathogenesis of PHPT

• **RECOMMENDATION 1-3:** In patients with suspected pHPT, a personal and family history should be performed. **Strong/Moderate**

• **RECOMMENDATION 1-6:** Genetic counseling should be performed for patients <40 years of age with pHPT and multigland disease (MGD), and considered for those with a family history or syndromic manifestations. **Strong/Low**

• **RECOMMENDATION 2-2:** Exposure-related and genotype-phenotype correlations are predictive of parathyroid anatomy and pathology, and should be considered as they may impact the planning and conduct of surgery. **Strong/Moderate**

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MEN I

- Primary HPT occurs in >90% of patients with MEN1
- MGD is the norm
- Recurrence rates up to 30% even with initial cure rate of 98%
- Surgical options include: Subtotal PTX, Total PTX with forearm autotransplant, Either with cervical thymectomy.

- RECOMMENDATION 9-1: In patients with MEN1-associated pHPT, subtotal parathyroidectomy is recommended as the index operation. Strong Recommendation - Moderate quality evidence

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Laboratory studies

Definitions:

• Hypercalcemic PHPT- serum calcium levels above the normal range with a concomitant inappropriately high PTH level.

• Normocalcemic PHPT- inappropriately high PTH levels and normal total and ionized serum calcium levels. In addition, causes of secondary HPT must be excluded.
Laboratory studies

• **Hypercalcemic PHPT**

  – **RECOMMENDATION 1-1**: The biochemical evaluation of suspected pHPT should include serum total calcium, PTH, creatinine, and 25-OH vitamin D levels. S/M

  – **RECOMMENDATION 3-2**: Parathyroidectomy is indicated when the serum calcium level is > 1 mg/dl above normal, regardless of whether objective symptoms are present or absent S/L

  – Agrees with the current guidelines
Laboratory studies

- **Normocalcemic PHPT**
  - Defined as, “inappropriately high PTH levels and normal total and ionized serum calcium levels” We must also exclude other sources of secondary HPT
  
  - Labs: Calcium, ionized calcium, iPTH, BUN/Cr, GFR, Vitamin D 25-OH. 24 hour urine collection for Calcium Clearance to exclude FHH.
Clinical Manifestations/Surgical Indication

- **No changes to traditional objective/symptomatic criteria:**
  - *Renal:* presence/suspicion of renal stones, Urine Ca > 400 mg/dL.
  - Agrees with the updated 4th International workshop that 24 hr Urine testing should be performed and if calcium is > 400 mg/dL for 24 hrs, surgery is indicated (This is an update in both guidelines from the 2008-3rd Int’l workshop)
  - Also agrees with 4th Int’l workshop that if renal stones are suspected Renal U/S or other imaging can be obtained.

- **RECOMMENDATION 3-3:** Parathyroidectomy is indicated for objective evidence of renal involvement including silent nephrolithiasis on renal imaging, nephrocalcinosis, hypercalciuria > 400 mg/dL with increased stone risk, or impaired renal function (GFR < 60 cc/min).

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Clinical Manifestations

• **No changes to traditional objective criteria:**
  - **Bone Related**- DEXA T score < -2.5, pathologic fracture, Diagnosis at age <50.
  - In a cohort of pts undergoing PTX vs. Observation- at 15 yrs
    - **PTX**- Increased Bone Density 14% at Femoral Neck at 10 yrs
    - **OBS**- Declined BD 10% Radius, 35% Fem neck at 15 yrs

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Surgical Indications-Symptomatic PHPT

- Ca > 1mg/dL above lab Upper normal
- Kidney stones- both symptomatic and Asx found on imaging.
- GFR <60, Urinary Ca > 400 mg/dL
- DXA- T score <-2.5, pathologic fx
- Age < 50
- Preferred treatment for those unable to comply with observation

**RECOMMENDATION 3-1**: Parathyroidectomy is indicated, and is the preferred treatment, for all patients with symptomatic pHPT.
Strong Recommendation - High quality evidence

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Asymptomatic/Non-traditional PHPT

- **Non-traditional Sx:** Neurocognitive, Cardiac, Muscular, GI, Sleep d/o. Current guidelines acknowledge that these sx “may be attributable to PHPT” but do not advise surgical intervention.

- **AAES Guidelines**
  - Neurocognitive: would argue that there are several high quality RCT’s that show that Neurocog sx do improve with PTX
Neurocognitive symptoms

- All 3 RCT’s utilized the SF-36
- Showed improvement in domains of: bodily pain, general health, vitality, and mental health, lower anxiety and phobia scores, and improvements in social and emotional role functioning.

- **RECOMMENDATION 3-8**: Parathyroidectomy is recommended for patients with neurocognitive and/or neuropsychiatric symptoms that are attributable to pHPT. **Strong/Low**
Asymptomatic/Non-traditional PHPT

• Cardiac
  – Increased incidence of myocardial infarction, hypertension, stroke, congestive heart failure, and diabetes has been observed in pHPT patients.
  – LVH appears to be related to PTH levels and may improve after parathyroidectomy

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Cardiac

- Overall survival was not affected, and indeed the relative risk of cardiovascular mortality was only decreased (RR 0.6).

- RCT data shows no improvement in HTN after PTX
Cardiac

• **RECOMMENDATION 3-9:** Parathyroidectomy may be offered to surgical candidates with cardiovascular disease who might benefit from mitigation of potential cardiovascular sequelae other than hypertension. *Weak Recommendation - Low quality evidence*

• Further study is required to determine if early parathyroidectomy can mitigate the cardiovascular morbidities of pHPT.

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Cost effectiveness of Parathyroidectomy

- The 4th Int’l Workshop for Management of PHPT does not currently outline information about the cost effectiveness of Observation vs Medical therapy vs Parathyroidectomy.

- Obs vs Cinacalcet vs Surgery (Asx PHPT)

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Observation vs Cinacalcet vs Surgery

- Operative intervention remained cost effective until cost increased from $4,778 per QALY (Quality adjusted life years) to > $14,650/QALY.
- Cinacalcet does not become cost effective when compared to surgery until annual cost decreases from estimated $7,406/yr to $221/yr.
- **Conclusion:** Parathyroidectomy is more cost-effective than observation for managing asymptomatic PHPT patients who do not meet National Institutes of Health criteria for parathyroidectomy.

- **RECOMMENDATION 3-12:** Operative management is more effective and cost-effective than either long-term observation or pharmacologic therapy. **Strong Recommendation – Moderate quality evidence**

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Preoperative planning

• Verify biochemical diagnosis and surgical indications

• **Localization**
  – Dr. John Doppman, who for many years led the endocrine radiology program at the National Institutes of Health, “the only localization study indicated in a patient with untreated primary hyperparathyroidism is the localization of an experienced endocrine surgeon”.
  – Imaging modalities have significantly improved and clearly impact operative choice: MIP vs. BNE
Imaging

• Imaging plays **NO ROLE** in the diagnosis of PHPT

• Imaging should be performed after the decision is made to proceed with surgical intervention

(Aimed at PCP’s- cost effective)

– **RECOMMENDATION 4-1**: Patients who are candidates for parathyroidectomy should be referred to an expert clinician to decide which imaging studies to perform based on their knowledge of regional imaging capabilities. Strong/Low

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Imaging

Sestamibi

Ultrasound

4D CT

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Imaging

• Imaging is not a criteria for patient referral for surgery
• Pts with negative imaging remain candidates for surgery
• Imaging is less accurate in the setting of MGD

• **RECOMMENDATION 4-2:** Patients who are candidates for surgery and have negative or discordant imaging should still be referred to a parathyroid surgeon for evaluation. **Strong Recommendation - Low quality evidence**
Preoperative planning

• **Surgeon introspection:**
  – Surgical Experience
    • surgeon volumes inversely correlate with complications, cost, and length of stay
    • Low hospital parathyroidectomy volume has also been correlated with higher complications, failed surgery, and the need for subsequent reoperation
  – **Patient Characteristics**- sporadic, single adenoma vs., MEN IIA pt vs. Reoperative PTX with limited imaging
  – **Hospital resources**- IOPTH, Imaging options (Sestamibi/SPECT, 4D-CT), frozen section, Cryopreservation

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Preoperative planning

- **Surgeon introspection:**
  - **RECOMMENDATION 3-11:** Parathyroidectomy should be conducted by surgeons with adequate training and experience in pHPT management. *Strong/Moderate*
  - **RECOMMENDATION 15-2:** Surgeons should choose an operative approach that in their hands carries a high cure rate, low risk profile, and comparable cost to other available techniques. *Strong/Low*
  - **RECOMMENDATION 17-2:** Patients with persistent or recurrent pHPT should be evaluated by an experienced parathyroid surgeon prior to the decision to proceed with surgery or nonoperative management. *Strong/Low*
Preoperative planning

• **Operative choice**
  – **Minimally Invasive PTX (MIP)**- currently over 75 definitions in the literature.

  – AAES defined the key components of MIP as:
    • Routine use of preop imaging
    • Short incision
    • Focused dissection (1 gland or at least unilateral)
    • An increased reliance on intraoperative technology and adjuncts such as IOPTH

  – **BE**- Bilateral neck exploration
MIP

- Generally utilized when preop imaging is suggestive of a solitary adenoma (80-85% of sporadic PHPT)
- Pt selection
  - Based on family hx- FIHPT, MEN, HPT-JT
  - Environmental history – Amiodarone and XRT hx heighten the chances of MGD. While Lithium toxicity can still affect solitary glands.
  - Pt age <30 may suggest higher rates of MGD.
- **RECOMMENDATION 7-1**: MIP, defined as a focused dissection, is ideally employed in patients who appear clinically and by imaging to have a single parathyroid adenoma. MIP is not routinely recommended in patients with known or suspected high risk of MGD. S/H

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Minimally Invasive Parathyroidectomy (MIP)

- **What is Minimally Invasive?**
  - Minimal incision parathyroidectomy
  - Radioguided parathyroidectomy
  - Video assisted parathyroidectomy
  - Endoscopic parathyroidectomy

- The current literature includes 75 different definitions for MIP. 
  
Radioguided Parathyroidectomy
Video Assisted Parathyroidectomy

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Video Assisted Parathyroidectomy
Video Assisted Parathyroidectomy

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Endoscopic parathyroidectomy

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MIP

- Intraoperative Parathyroid Monitoring (IPM) or use of IOPTH.
  - Rapid IPM testing became widely available in 1996
  - Leads to cure rates of 98% in experienced hands
  - Variety of techniques- Miami Criteria (50% rule), Dual Criteria (50% and in normal range), PTH decay curves.

- **RECOMMENDATION 6-2-** Surgeons utilizing IPM should employ a sampling protocol that is reliable in the local environment and should be familiar with the interpretation of PTH decay dynamics.

  *Strong Recommendation - Low quality evidence*

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Bilateral Neck Exploration

- BE still remains the Gold standard for parathyroidectomy
- Utilized in cases of expected MGD- Familial syndromes, XRT.
- Conversion to BE should be considered if MGD is encountered during exploration or failure of IPM to normalize.
- Utilize MGD if preoperative imaging is non-localizing

- **RECOMMENDATION 8-2**: Planned BE is the preferred operative strategy in situations of discordant or non-localizing preoperative imaging, when there is a high suspicion of MGD, when IPM is not available, or at the discretion of the surgeon. S/M
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Defining cure

- The goal of surgery is biochemical cure defined as durable normocalcemia.
- As such, the **only Postop laboratory study required** for hypercalcemic PHPT is a **Serum Calcium** level.
- iPTH levels in the setting of postop normocalcemia can be seen in up to 40% of pts due to hypocalcemia, Low Vit D, hungry bone syndrome, and mild renal insufficiency.
Cure of PHPT

- **RECOMMENDATION 15-1: a)** Cure after parathyroidectomy is defined as the reestablishment of normal calcium homeostasis lasting a minimum of 6 months. **Strong Recommendation - High quality evidence**

- **RECOMMENDATION 15-1: b)** Patients with normocalcemic pHPT who have persistently elevated PTH after parathyroidectomy should be evaluated and treated for causes of secondary HPT and if none are present, monitored for recurrent disease. **Strong Recommendation - Low quality evidence**

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Cure of Normocalcemic PHPT

- **Normocalcemic PHPT**: Inappropriately high PTH levels and normal total and ionized serum calcium levels. In addition, causes of secondary HPT must be excluded.

- Postop labs must include Calcium and iPTH

- **RECOMMENDATION 15-3**: In normocalcemic pHPT, the definition of cure must include normal calcium and PTH levels >6 months after surgery. **Insufficient**

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Defining Failure of Parathyroidectomy

- **RECOMMENDATION 15-4:** *Persistent* pHPT should be defined as a failure to achieve normocalcemia within 6 months of parathyroidectomy. *Recurrent* pHPT is defined by recurrence of hypercalcemia after a normocalcemic interval at >6 months after parathyroidectomy. **Strong Recommendation – High quality evidence**

- Distinguishing Persistent vs. Recurrent failure is important to understanding etiology of disease.

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Persistent PHPT

• Failure to achieve durable eucalcemia anytime in the first 6 mos after PTX.

• Causes
  – Missed gland or MGD
  – Error in initial dx: FHH, Secondary HPT- Vit D deficiency, CRI.
Recurrent PHPT

- Re-elevation of serum calcium levels beyond 6 mos of eucalcemia after PTX.
- Causes
  - Interval development of MGD, Remnant hypertrophy after MGD resection, parathyroid cancer, Capsular fracture-parathyromatosis or expected recurrence- MEN.

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Algorithm for Reoperation

- Reoperation requires stricter indications and greater surgeon experience
- Reported cure rates in reoperation range from 82–98%
- Higher rates of postoperative hypoparathyroidism and recurrent laryngeal nerve injury also occur with reoperation, 5-8%
- Higher threshold to indicate reoperation
  - Significant Symptomatology: fractures, severe or worsening osteoporosis, recurrent renal stones
  - Higher preop calcium levels
- Most surgeons require at least 1 positive imaging study

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Algorithm for the Evaluation and Management of Persistent or Recurrent PHPT

1. Patient with suspected persistent or recurrent pHPT
2. Confirmation of diagnosis
   - No → Continue routine follow-up
3. Review previous images, operative reports, pathologic test results, and vocal cord function examination results
4. Meets criteria for subsequent operation
   - No → Continue routine follow-up and nonoperative management
   - Yes → Patient is an operative candidate
5. Noninvasive imaging studies
   - Localizes → Subsequent parathyroidectomy (IPM suggested)
   - Does not localize → Consider invasive imaging
Medical Management after Failed PTX

- If no objective criteria are found (Fractures, worsening osteoporosis, Kidney stones)
- Patient co-morbidities outweigh reoperation
- PTX is **NOT** cost effective compared to medical management if patients have <5 years of “expected” remaining healthy life.

- **RECOMMENDATION 14-7**: At 6 months, surgeons individually or in conjunction with the multidisciplinary care team should assess post-parathyroidectomy patients for cure and evidence of long-term complications. **Strong/Low**

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Conclusion

• Because the surgical treatment of pHPT has undergone extensive change in the last 2 decades, the AAES determined the need to develop evidence-based clinical guidelines to enhance the safe, definitive treatment of pHPT. These evidence-based guidelines provide a broad-based approach to the clinical spectrum of pHPT and, although they do not represent the only acceptable approach, serve as a sound template for the effective surgical management of pHPT to achieve cure as safely as possible.

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Perception

- Frank Lloyd Wright- “Art Mimics Nature”