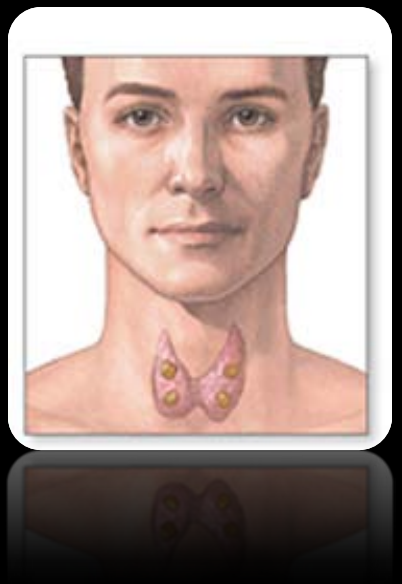
Primary hyperparathyroidism *and* indications for surgery

Jennifer L Marti, MD
Endocrine Surgery
Beth Israel Medical Center
Mount Sinai Health System
New York, New York

Overview

1. PHPT is underdiagnosed
2. Evidence for the guidelines
3. Are the guidelines absolute?



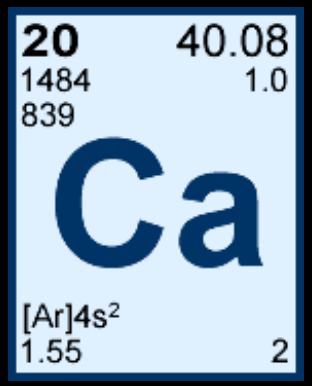
Diagnosis & initial evaluation

PHPT: blood test diagnosis

Excessive secretion of PTH inappropriate to the serum calcium concentration

10-20% of patients have normal serum calcium levels

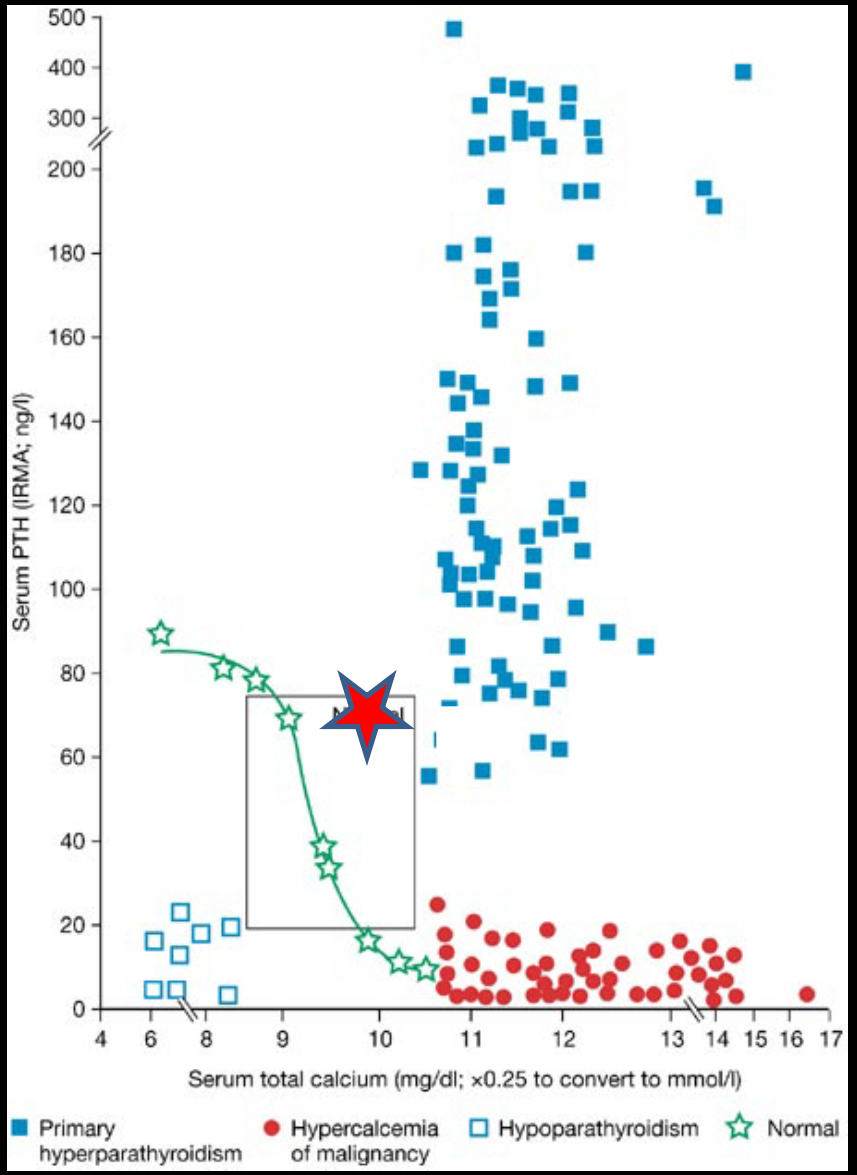
Calcium & PTH levels fluctuate… repeat labs



Maruani, JCEM 2003

Serum Ca/PTH relationship

Inverse relationship



Khairallah, Nat Clin Pract Nephrol 2007

PHPT epidemiology

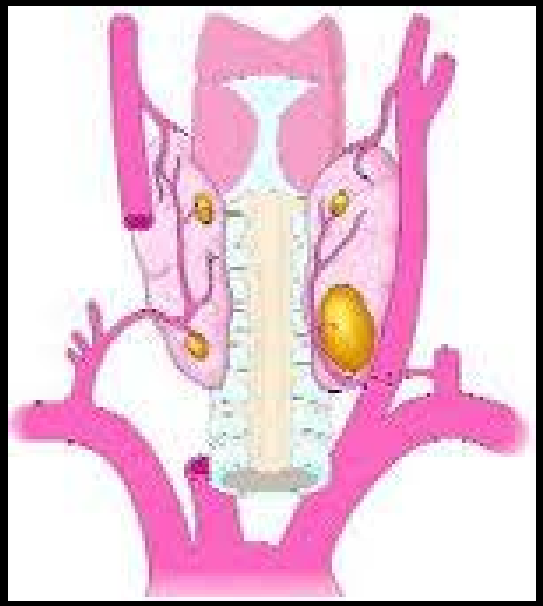
3 : 1 female : male

2% post-menopausal women (Swedish study)

80-90% single adenoma

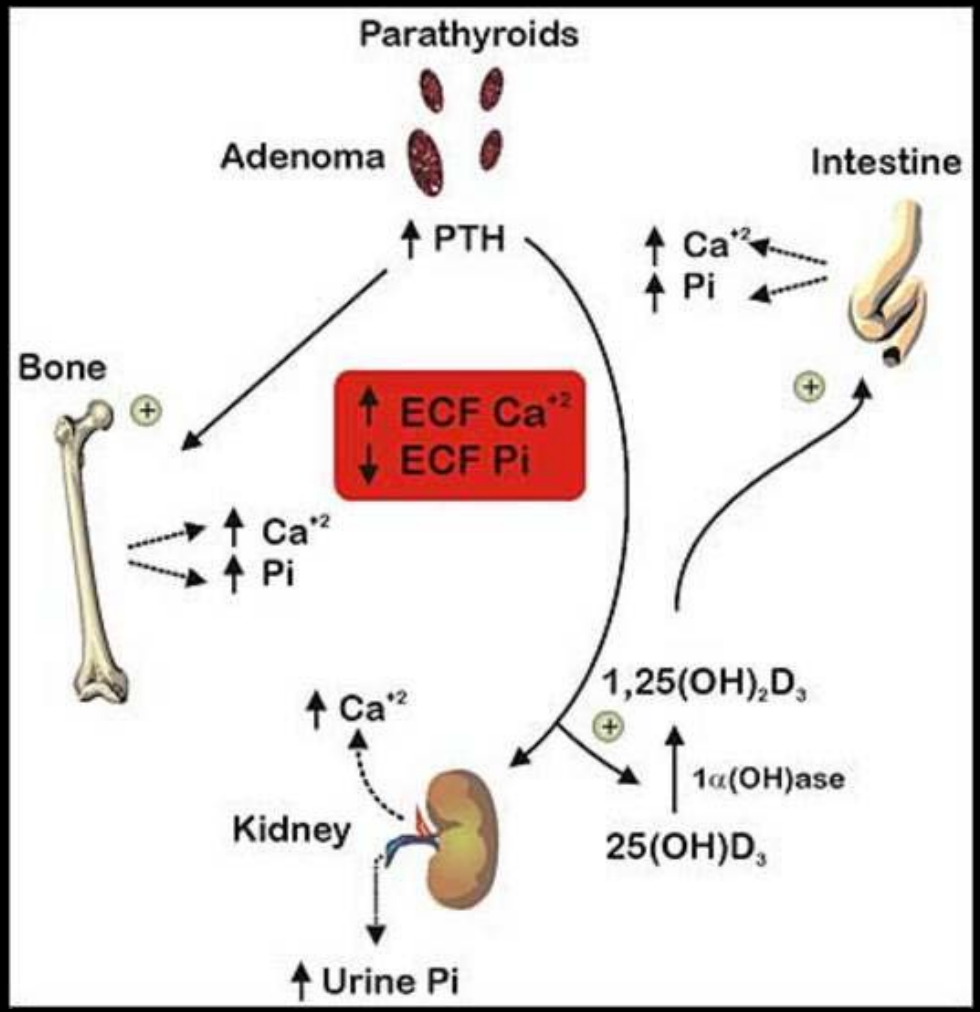
5% double adenoma

10-15% 4-gland hyperplasia



Silverberg, Nature Clin Prac Endoc & Metab 2006

Action of PTH



Pi: Phosphate

Goltzman, Diseases of Bone and Mineral Metabolism 2008

CASE

A 51 year old woman with osteopenia has bloodwork done:

calcium of 9.8 (nl 8.6-10.2),

PTH 82 (nl 10-65)

creatinine 0.8.

Differential Diagnosis? Is this HPT?

PHPT (normocalcemic or classic) or secondary HPT

Workup?

Check another Ca (levels can fluctuate), vitamin D level, 24h urine calcium

Types of hyperparathyroidism

- Primary (normal creatinine)
- Secondary (hypocalcemic or normocalcemic)
  - ESRD→*low vitamin D*, elevated PO4
  - Vitamin D deficiency
  - Malabsorption, short gut syndrome, gastric bypass
- Tertiary (hypercalcemic)
  - Classically described after renal transplant
  - Progression of secondary to autonomously hyperfunctioning glands

What is “asymptomatic HPT”?

Lack of specific symptoms or signs traditionally associated with PHPT, such as:

- Renal stones
- Myopathies
- Osteofibrosis cystica

Bilezikian, JCEM 2009

Incidental finding on "routine blood work"

- No longer the classic syndrome of "bones, stones, groans, and psychiatric overtones"
- Most patients are asymptomatic
- Use of multichannel blood autoanalyzer in 1970s

Table 1 The changing clinical profile of primary hyperparathyroidism.

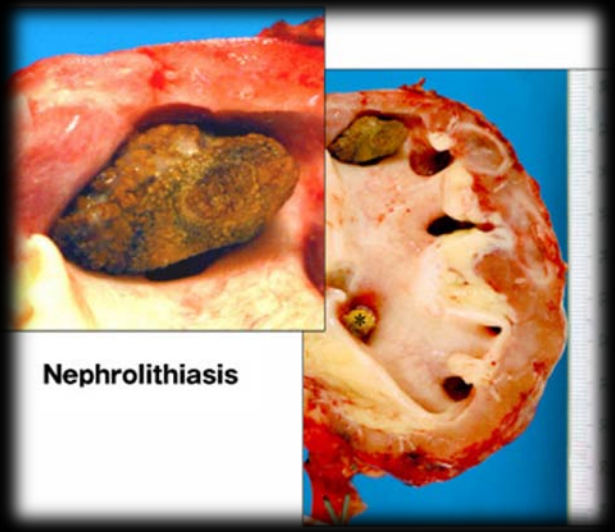
Researchers (study period)	Symptoms observed (% of patients)			
	Nephrolithiasis	Hypercalciuria	Overt skeletal disease	No overt symptoms
Cope (1930–1965)[81]	57	NR	23	0.6
Heath *et al.* (1965–1974)[2]	51	36	10	18
Mallette *et al.* (1965–1974)[82]	37	40	14	22
Silverberg, Bilezikian, and colleagues (1984–2006; various studies)	17	39	1.4	80 *

Abbreviation: NR, not reported.

St Goar, Ann Int Med 1957
Silverberg, Nature Clin Prac Endoc & Metab 2006

Ask about…

- Nephrolithiasis
- T score, history of fractures
- Neurocognitive symptoms



“But doc, I feel fine…”

Incidental hypercalcemia on “routine blood work” performed by PCP

Workup reveals PHPT

Who benefits from surgery?

CASE

55F with Ca 10.9, PTH 72, normal creatinine.

24h urine 420 mg

T -2.1 lumbar spine

Asymptomatic

Diagnosis?

PHPT

Does she meet consensus guidelines for surgery?

NO (but many would offer surgery)

What are the guidelines for surgery?

Rationale for guidelines

Majority of patients are asymptomatic

This led to the Consensus Development Conference on the

Management of Asymptomatic Primary Hyperparathyroidism

at the National Institutes of Health (1990)

Revised in 2002, 2008 & 2013 *(Florence, Italy, manuscript in press)*

Khan, JCEM 2009

Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Third International Workshop

John P. Bilezikian, Aliya A. Khan, and John T. Potts, Jr. on behalf of the Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism*

Bilezikian, JCEM 2009

Third international workshop on the management of asymptomatic hyperparathyroidism

Measurement	1990	2002	2008
Serum calcium (>upper limit of normal)	1–1.6 mg/dl (0.25–0.4 mmol/liter)	1.0 mg/dl (0.25 mmol/liter)	1.0 mg/dl (0.25 mmol/liter)
24-h urine for calcium	>400 mg/d (>10 mmol/d)	>400 mg/d (>10 mmol/d)	Not indicated[b]
Creatinine clearance (calculated)	Reduced by 30%	Reduced by 30%	Reduced to <60 ml/min
BMD	Z-score <−2.0 in forearm	T-score <−2.5 at any site[c]	T-score <−2.5 at any site[c] and/or previous fracture fragility[d]
Age (yr)	<50	<50	<50

Updated in 2013…

- Renal ultrasound to screen for kidney stones
- Additional skeletal testing
- Algorithm for treatment of normocalcemic HPT

Bilezikian, JCEM 2009

Evidence supporting the guidelines

Evidence supporting the guidelines

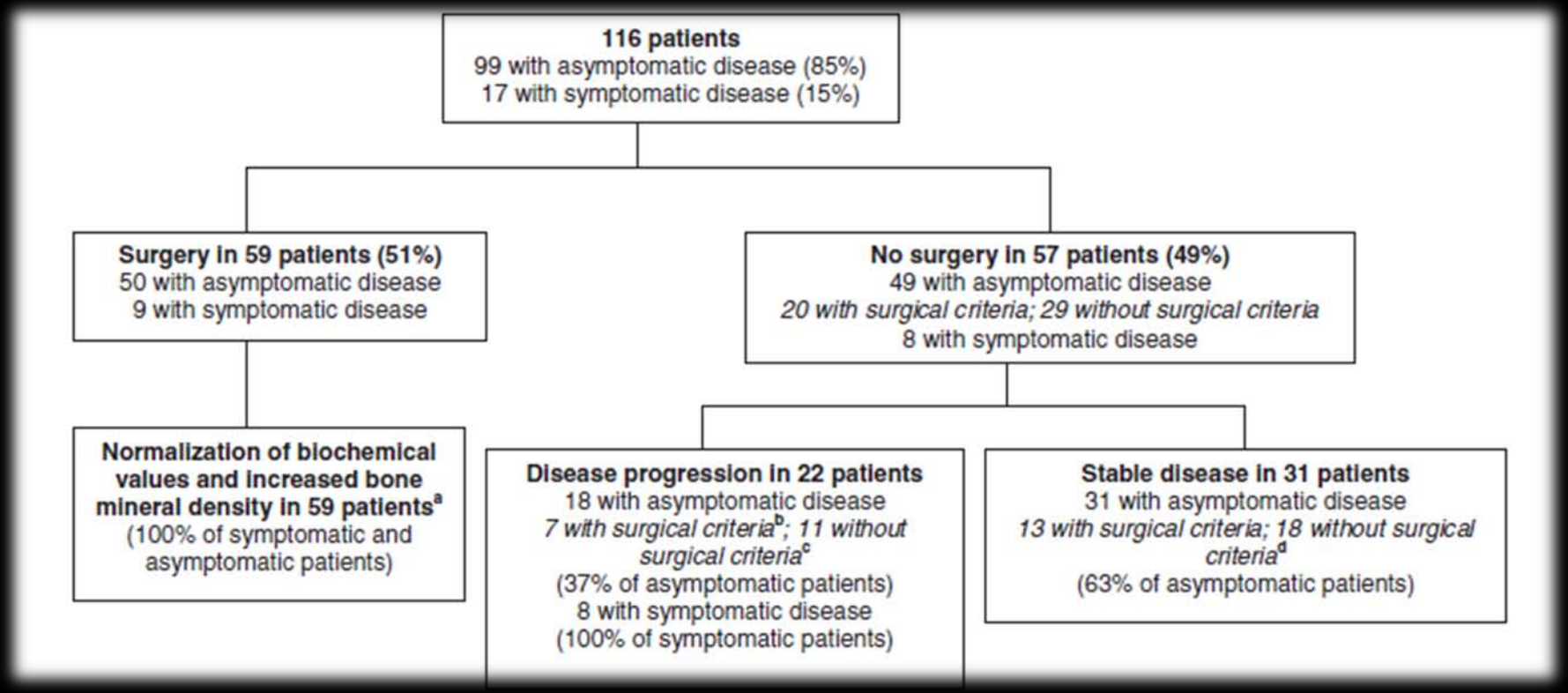
Exhibit A:
The natural history of primary hyperparathyroidism

The Natural History of Primary Hyperparathyroidism with or without Parathyroid Surgery after 15 Years

Mishaela R. Rubin, John P. Bilezikian, Donald J. McMahon, Thomas Jacobs, Elizabeth Shane, Ethel Siris, Julia Udesky and Shonni J. Silverberg

Rubin, JCEM 2008

15 year observational study of patients with primary HPT



Rubin, JCEM 2008

Observational study of patients with primary HPT

Calcium slowly increased over 15 years

Variable	Baseline (n = 49)	Yr 5 (n = 25)	Yr 10 (n = 11)	Yr 13 (n = 9)	Yr 15 (n = 6)
Serum calcium (mg/dl)	10.5 ± 0.1	10.7 ± 0.1	10.8 ± 0.2	11.0 ± 0.2[a]	11.1 ± 0.2[a]
PTH (pg/ml)	122 ± 10	119 ± 12	123 ± 14	124 ± 16	121 ± 18

Rubin, JCEM 2008

Observational study of patients with primary HPT

	Observed	Surgery	p
Number	57 (49%)	59 (51%)	
Kidney stones	Recurrence in 100% (of those with prior stones)	No recurrences	
Femur/radius BMD	-10%/-35% (in 59%)	**+10%/+7%**	0.002
Lumbar spine BMD	Stable	**+12%**	0.02

At 15 years, surgical patients **had increased** BMD despite expected age-related bone loss

These data argue for **early surgical intervention**

Rubin, JCEM 2008

Observational study of patients with primary HPT

- **37%** of asymptomatic patients eventually satisfy criteria for surgery (*1990 criteria*)
- This number would likely be higher by the 2008 criteria
- 60% of observed patients continued to lose BMD
- 100% of the surgical group had increased BMD

Rubin, JCEM 2008

PEAR study (Scotland)

The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study

N. YU[1], G.P. LEESE[2], D. SMITH[3] and P.T. DONNAN[1]

Yu, QJM 2011

PEAR study

1100 patients: mild primary hyperparathyroidism

Tayside, Scotland (1997-2006)

904 observed (median calcium 10.5 mg/dl, PTH 61 pg/mL)

200 had surgery

Followup: 4.7-5.8 years

15% with increasing calcium

- Age at diagnosis and baseline PTH were predictors of hypercalcemia

Yu, QJM 2011

PEAR study

Rates per 100 person-years

Other complications	Before surgery	After surgery	*P*-value
Cardiovascular disease	2.48	1.66	NS
Renal stones	3.10	0.38	0.01
Renal failure	4.96	0.90	<0.001
Osteoporosis fractures	1.56	0.76	NS
Cancer	1.86	2.30	NS
Psychiatric disease	0.32	0.12	NS

Surgery decreased the risk of:

Kidney stones (by 88%)

Fractures (by 50%, *not significant, underpowered*)

Yu, QJM 2011

Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism

Peter Vestergaard, Leif Mosekilde

- Danish cohort study (3213 patients; 1980-1999)
  - 1934 (60%) underwent surgery
  - 1279 (40%) were observed
- *Lower risk of fractures, ulcers and death in the surgical group*

Vestergaard, BMJ 2003

Randomized controlled trials for asymptomatic primary HPT

	N	Observation	Surgery
Henry Ford Hospital. Rao. JCEM. 2004.	53	**BMD loss:** 0.6% / year	**Increase in BMD:** 1.2% / year **Improved QOL** (at 2 yrs) Improved psych function
Pisa. Ambrogini. JCEM. 2007	50 with mild disease (did not meet 1990 criteria)	**BMD loss** (hip) 23% met criteria for surgery at 1 year	**Increased BMD** (at 1 yr) **Improved QOL** (at 1 yr)
Sweden. Bollerslev. JCEM. 2009.	191	**Decreased BMD Worse QOL**	**Increased BMD** (at 2 yrs)
Meta-analysis. Sankaran. 2010. JCEM 2010.	34 publications	**BMD loss:** 0.6-1.0% / year	**Increased BMD:** 2% L-spine 7% femur

Benefits to surgery are observed relatively soon
These RCTs argue for early intervention

What about fracture risk?

- Degree of osteoporosis predicts fracture risk
- Primary HPT → increased fracture risk in all patients
- Postoperative data conflicting; many studies underpowered

10 Year Fracture Free Survival Rates

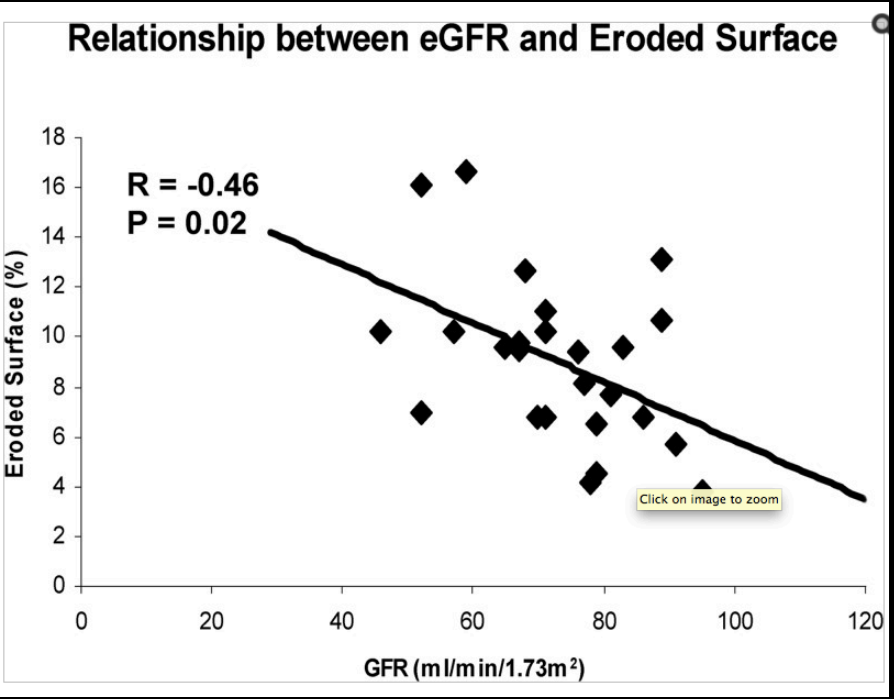
T score	Surgical group (n=159)	Observed (n=374)	Absolute risk reduction	p
> -1.0	98%	89%	9%	NS
-1 to – 2.5	92%	80%	12%	NS
<-2.5	82%	70%	12%	.02
All	**94%**	**81%**	**13%**	**.006**

Number needed to treat: 8

Vanderwalld, World J Surg 2009

GFR < 60 ml / min

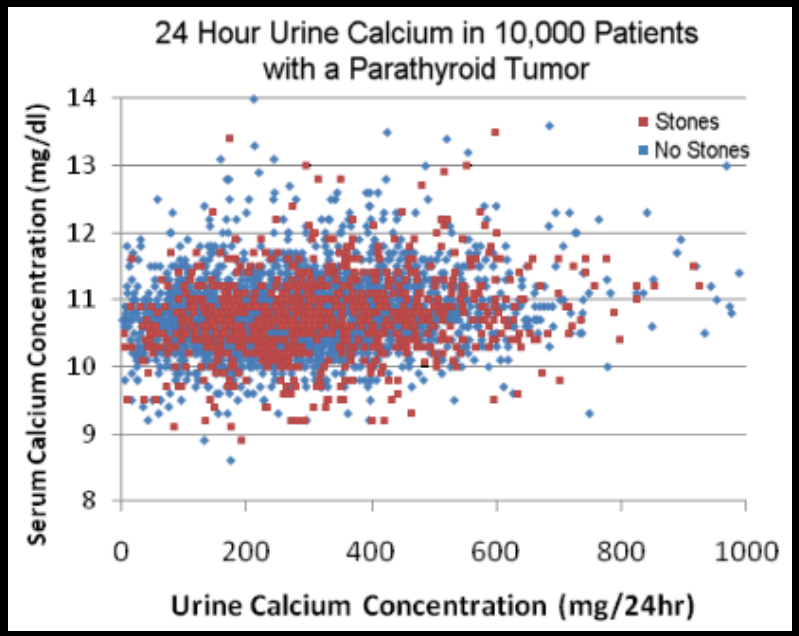
- PTH increases with decreased GFR
- This may worsen the primary hyperparathyroid state
- Recent data indicates that PTH increases at GFR < 30 ml/min
- Increased surface erosion of bone with decreased GFR



Fajtova, Calcif Tissue Int 1995
Tassone, JCEM 2009
Walker, JCEM 2012

24 hour urine: no longer a criterion

- Hypercalciuria is not a risk factor for nephrolithiasis in PHPT (if the patient has never had a kidney stone)
- Still helpful in initial evaluation, to rule out familial hypocalciuric hypercalcemia



Bilezikian, JCEM 2009
Peacock, J Bone Min Res 2002

Age < 50

Increased lifetime in which sequelae will occur

Young age (<50) is associated with increased risk of progression

Rubin, JCEM 2008
Bilezikian, JCEM 2009
Silverberg, Am J Med 2002

Are the guidelines absolute?

CASE

60 yo woman with calcium 10.9, PTH 65.

Symptoms: depression, memory loss, and fatigue.

Operate or observe?

Are 80% of patients really “asymptomatic”?

- With standardized questioning, 80-98% of patients with “asymptomatic HPT” are symptomatic
- Many of these “symptoms” are vague and non-specific

TABLE 1. SYMPTOMS AND ASSOCIATED CONDITIONS IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

Symptoms	*Associated conditions*
Fatigue	Osteopenia
Weakness	Osteitis fibrosa cystica
Depression	Nephrolithiasis
Loss of recent memory	Nephrocalcinosis
Polydipsia	Peptic ulcer disease
Polyuria	Pancreatitis
Nocturia	Gout
Musculoskeletal aches and pains	Pseudogout
Constipation	Hypertension
Abdominal or flank pain	

Clark, J of Bone and Min Res 1991
Eigelberger, Annals Surgery 2004

Are 80% of patients really “asymptomatic”?

- Several studies suggest that surgery improves neurocognitive symptoms in up to 80% of patients
- Reduced mood and anxiety symptoms and improved visuospatial working memory in a prospective study
- May be placebo effect; follow-up time is short
- The data *are not definitive*, and are not part of the guidelines

Clark, J of Bone and Min Res 1991
Eigelberger, Annals Surgery 2004
Roman, Sosa, Surgery 2005
Roman, Sosa, Ann Surg 2011

Are the guidelines cost-effective?

Parathyroidectomy is more cost effective than observation…

if life expectancy greater than 5 years

Zanocco, Surgery 2009

Are guidelines being followed?

- Kaiser Permanente (1995-2008, n=3388)
- Of patients who ***met*** guidelines, **< 50%** had surgery
- Of patients ***not*** meeting guidelines, **16%** had surgery
- Of patients with ***nephrolithiasis***, **only 50%** had surgery

- *Parathyroidectomy is underutilized*

Yeh, Annals of Surgery 2012

Why aren't the guidelines being followed?

- Lack of knowledge of the guidelines
- Lack of consultation with a surgeon
- ***Lack of localization*** *may incorrectly lead to continued observation*

- *Patients with biochemically-proven PHPT should be referred to a parathyroid surgeon for consultation*
- *A surgeon is the ideal individual to explain the risks, benefits and alternatives to operative intervention*

Yeh, Annals of Surgery 2012
Udelsman, JCEM 2009

Normocalcemic hyperparathyroidism

Normocalcemic PHPT

Rule out elevated PTH due to

- 25-OH vitamin D deficiency (<20-30 ng/mL)
  - Treat with vitamin D, PTH will decrease
- Primary renal calcium leak
  - Treat with HCTZ, PTH will decrease
- Impaired kidney function/ESRD
- Low calcium diet, malabsorption
  - Treat with calcium, PTH will decrease

Bilezikian, Arq Brs Endoc Metab 2010

Do patients with normocalcemic HPT benefit from surgery?

Controversial, probably yes

Cured of recurrent nephrolithiasis

Expect that patients with nephrolithiasis & osteoporosis would benefit

Johansson, Surgery 1975
Ljunghall, Acta Chir Scand 1980
Maruani, JCEM 2003

Do *asymptomatic* patients with normocalcemic HPT benefit from surgery?

Can we apply the 2008 consensus guidelines for patients with asymptomatic HPT to patients with NHPT?

Unclear…perhaps in a young patient with osteopenia

With normocalcemic HPT…

Is there an easy way to diagnose HPT?

Regression model for PTH levels

- Model helps distinguish primary vs secondary HPT
- Based on age, calcium, PTH and Vitamin D levels
- Expected PTH (pg/ml) =

  120– (6 * Ca mg/dl)– (0.52 x 25-OH Vit D ng/ml) + (0.26 x age)
- Validated on an independent cohort, successfully identified
  - 100% hypercalcemic PHPT
  - 96% normocalcemic HPT

Harvey, Endocrine Practice 2011

Secondary HPT

ESRD/HPT Indications for surgery

- Patients with severe HPT who fail medical therapy (Sensipar, Vitamin D, Phosphate binders) or cannot perform surveillance
- Persistently hypercalcemic
- PTH >800 pg/mL
- Calciphylaxis , fractures, bone pain or pruritis
- Ca * Po4 > 70

K/DOQI Clinical Practice Guidelines for Bone Metab and Disease in CKD. Am J Kidney Dis 2003
Dumasias, Oto Clinic N America 2010

Cinacalcet (Sensipar)

- Calcimimetic
- Increases the sensitivity of the calcium-sensing receptor to circulating serum calcium
- *Does not improve bone density*
- FDA approved for
  - HPT in patients with chronic kidney disease
  - severe hypercalcemia in patients with PHPT who cannot undergo surgery
  - Treatment of hypercalcemia in patients with parathyroid carcinoma

Duntas, Endocrine 2011
www.fda.gov

ESRD/HPT operative management

- Subtotal vs total with autotransplantation
- Often require calcium gtt & high doses of Rocaltrol post-op, due to hungry bone syndrome

K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003.
Dumasias. Oto Clinic N America. 2010.

SUMMARY

1. 80% of patients with primary HPT are asymptomatic
2. Parathyroidectomy results in increased BMD and perhaps QOL
3. Many observed patients would benefit from surgery
4. Low morbidity surgery will benefit the majority of patients
5. Patients with normocalcemic HPT may benefit from surgery

Contact information

Jennifer L Marti MD
Endocrine & Breast Surgery
Beth Israel Medical Center
Tel 212 844 6234
Email jmarti@chpnet.org

Beth Israel Medical Center
A Member of the Mount Sinai Health System