

Current Investigation for Primary Hyperparathyroidism



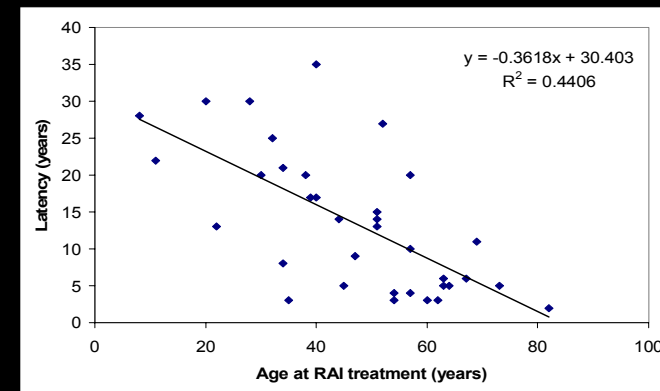
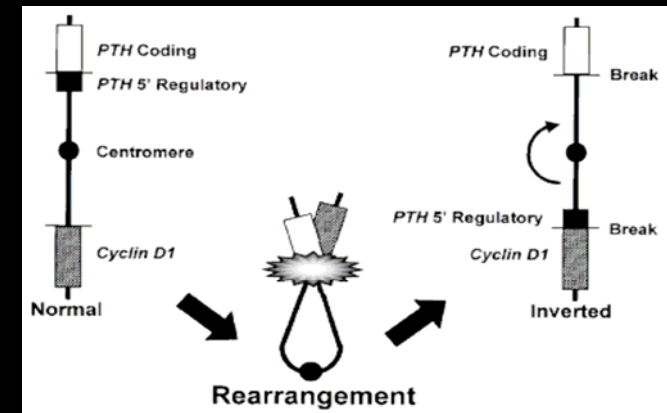
8th Postgraduate Course in Endocrine Surgery
Capsis Beach, Crete, September 22, 2006

Quan-Yang Duh, Professor of Surgery, UCSF

What Causes Primary
Hyperparathyroidism?

What Causes Primary Hyperparathyroidism?

- Menin (MEN 1)
- Cyclin D1 (PRAD1)
- Radiation
 - Radiation to tonsil before age 16 2.9x risk Cohen *et al. JAMA* 1990;264:581-4.
 - RAI for thyroid
- Parafibromin (HRPT-2)



HRPT2 Mutations:

Parathyroid cancer & (HPT-JT) syndrome

- *HRPT2* (1q25–q32) encodes parafibromin.
- Hyperparathyroidism–jaw tumor (HPT-JT) syndrome: 1 HPT, ossifying fibromas of the maxilla and mandible, renal cysts and solid tumors.
- Germ-line inactivating mutations of *HRPT2* found in about half the kindreds with HPT-JT syndrome
- Somatic and germ-line mutations in 2/3 (10 of 15) of sporadic parathyroid carcinomas.

N Engl J Med. 2003 Oct 30;349(18):1722-9 , Shattuck TM, Valimaki S, Obara T, Gaz RD, Clark OH, Shoback D, Wierman ME, Tojo K, Robbins CM, Carpten JD, Farnebo LO, Larsson C, Arnold A.

NIH Consensus Conference on the
Indications for Parathyroidectomy for
Primary Hyperparathyroidism:
1990, Revised 2002

NIH Consensus Statement: Indications for Parathyroidectomy

- Markedly elevated serum calcium
- Episodes of life-threatening hypercalcemia
- Reduced creatinine clearance
- Kidney stone(s) by radiography
- Markedly elevated 24 hr urinary calcium excretion
- Substantially reduced bone mass

1990 (2002) NIH Consensus Statement: Indications for Parathyroidectomy

- Serum calcium > 11.4-12.0 mg/dl (>11.4)
- Creatinine clearance reduced by 30%, (abnl cr)
- 24 hr urinary calcium excretion > 400 mg (not)
- Bone density Z score, age match < -2 (to T score)

NIH Consensus Statement: Indications for Parathyroidectomy

- Patients request surgery
- Consistent follow-up is unlikely
- Coexisting illness complicates management
- Patient is young (< 50 years old)

Why Parathyroidectomy?

Primary Hyperparathyroidism: Symptoms & Associated Conditions

- “Stones, Bones, Moans and Groans”
- Bone: osteitis fibrosa cystica, osteoporosis
- Kidney: stones, renal failure
- Abdominal pain: PUD, pancreatitis,
- Fatigue, weakness, lethargy
- Depression, memory loss
- Hypertension, gout, pseudogout

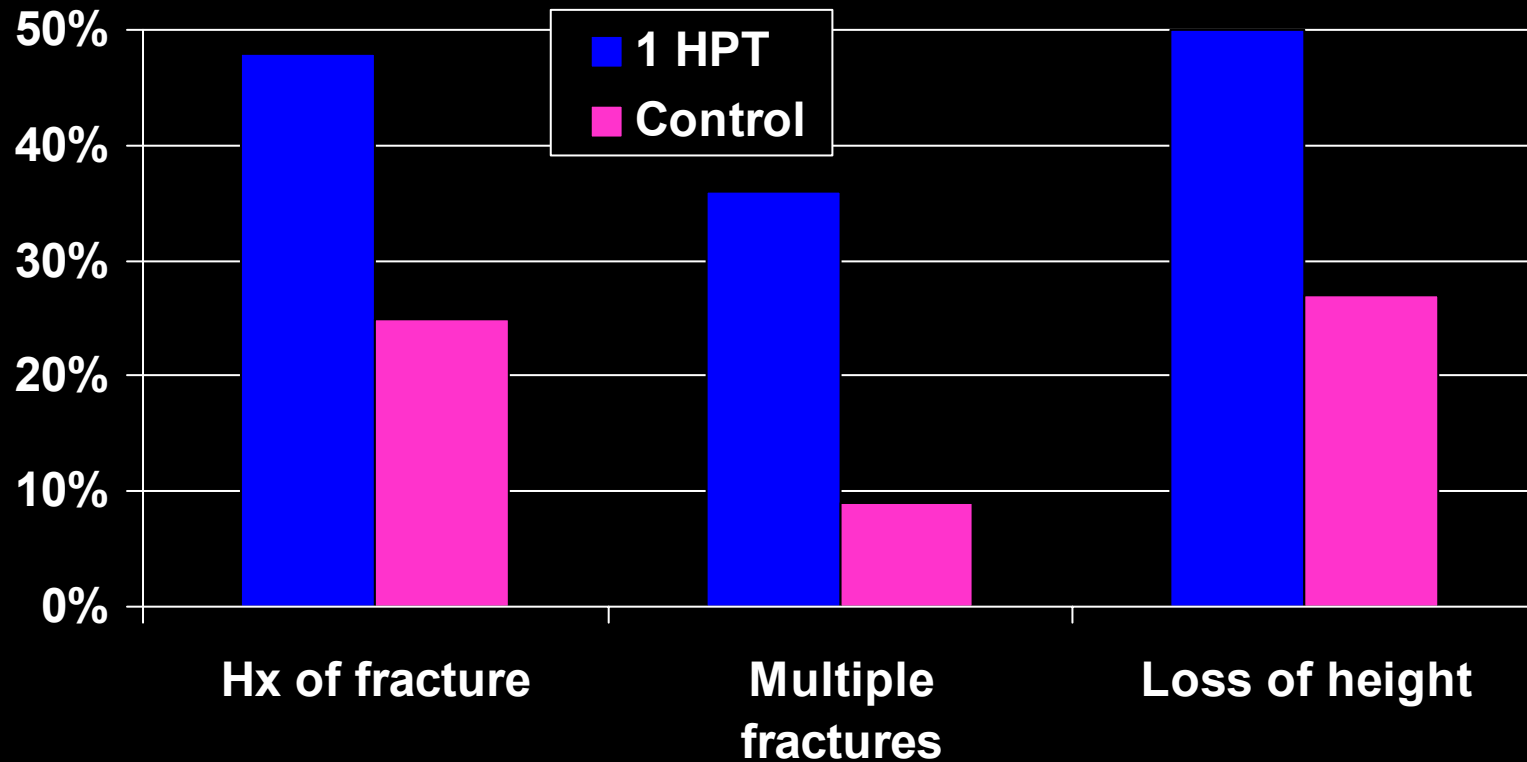
Increased Risk of Death from Untreated Primary Hyperparathyroidism

- Increased risk of death
 - Mainly from CV disease and cancers
 - Actuarial curve like smoking 1 pack per day
- Risk correlated with tumor size
 - But not serum calcium level
- Reverse the risk by parathyroidectomy
 - in younger patients.

Primary Hyperparathyroidism: Symptoms in Screened Patients

- Swedish screening mammography study
- More psychic complaints
 - lassitude, fatigue, irritability
 - lack of sexual and emotional interests.
- Lower bone density, visited physicians more often
- More sick leave used (odds ratio 12) for the 5 years before diagnosed, due to cardiovascular diseases.

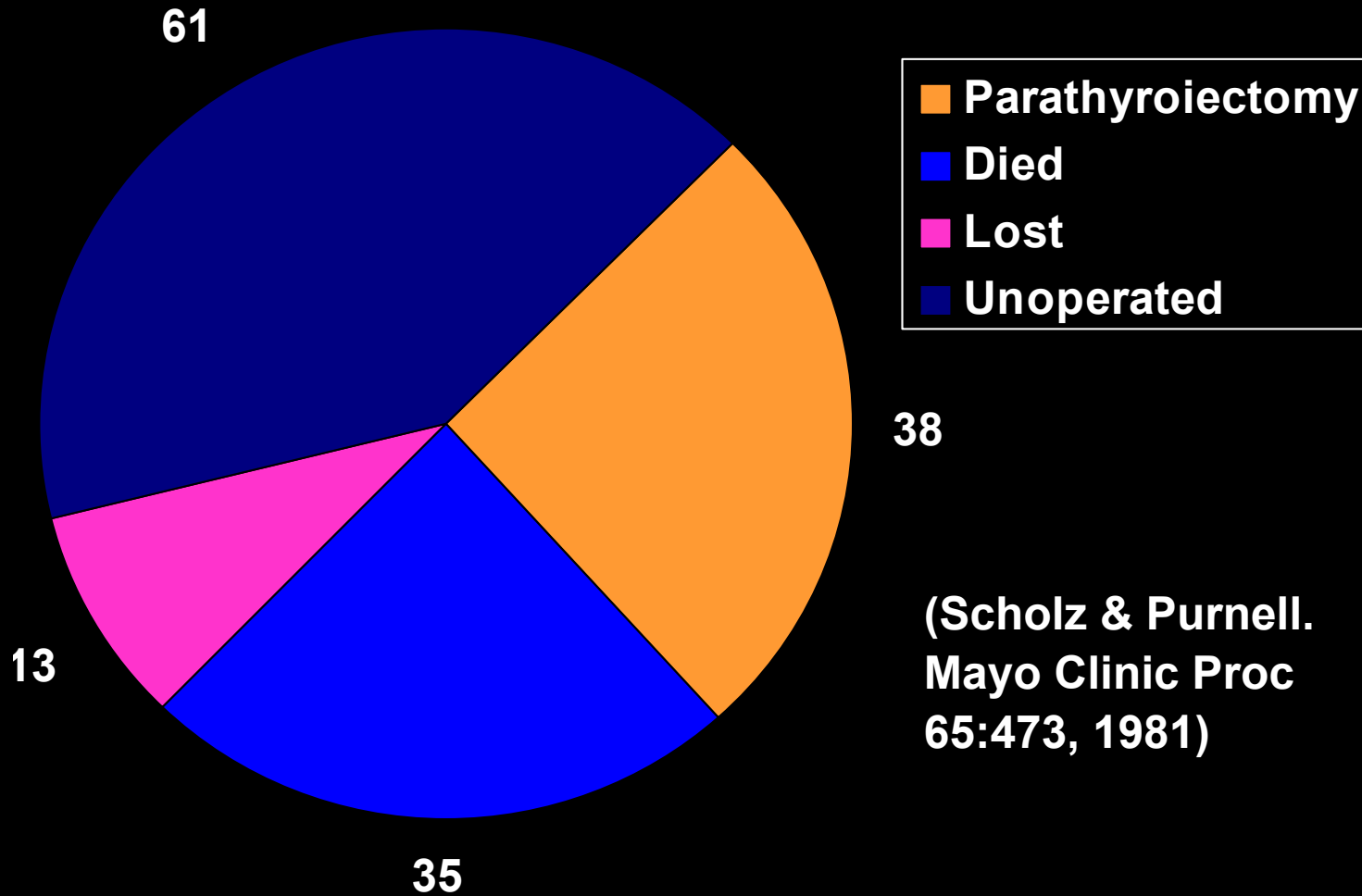
Bone Disease in Postmenopausal Women with Primary Hyperpara



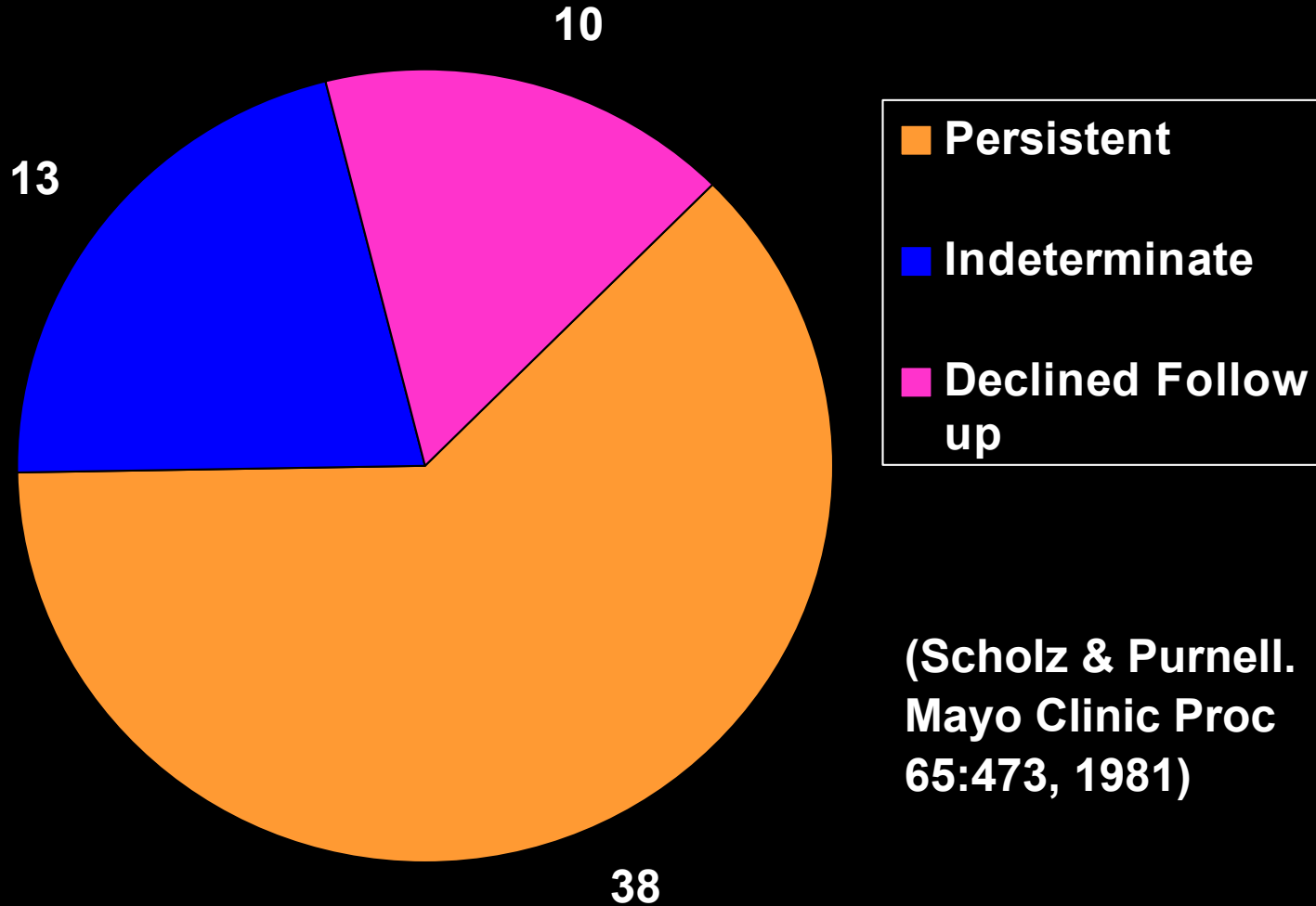
Kenny AM, et al: Surgery 118:109-14, 1995

Minimal Hyperparathyroidism
“asymptomatic hyperparathyroidism”

Minimal Hyperparathyroidism



Minimal Hyperparathyroidism



(Scholz & Purnell.
Mayo Clinic Proc
65:473, 1981)

“Asymptomatic” Hyperparathyroidism

- 5% (7/152) truly asymptomatic
 - prospective questionnaire
 - non-specific symptoms including fatigue, exhaustion, weakness, polydipsia, polyuria, nocturia, joint pain, bone pain, constipation, depression, anorexia, nausea, and heartburn
- 95% have some improvement postop
 - 55% feels better overall (vs 30% thyroid control)
- Serum calcium does not predict improvement.

Minimal Hyperparathyroidism

- Rochester Epidemiology Project: 1965 to 1992, 435 diagnosed with primary hyperpara, only 126 (29%) had parathyroidectomy.
- Maximal serum Ca: an independent predictor of mortality (**RR=1.3 per mg/dL**) by age-adjusted multivariate analysis.
- Survival not affected in patients with mild primary hyperpara

Improvement after Parathyroidectomy

Improvement after Parathyroidectomy

- Improve strength and fine motor, 1 month.
 - Chou et al: Surgery 117: 18, 1995
- Improve psychiatric symptoms, 1 month.
 - Solomon et al: Am J Med 96:101, 1994
- Improve renal colic (66% to 2%/yr), 1 year.
 - Jabbour: SG&O 172:25, 1991
- Improve LVH, 1 year and continue beyond.
 - interventricular septum (-6%), posterior wall (-19%)
 - Stefenelli: Am J Med 95:197, 1993; Surgery 121:157-61, 1997; JCEM 82:106-12, 1997
- Improved health status (SF36), 2 months
 - Burney RE, et al: Surgery 124:987-91, 1998

Improved Bone Mineral Density (BMD) after Parathyroidectomy

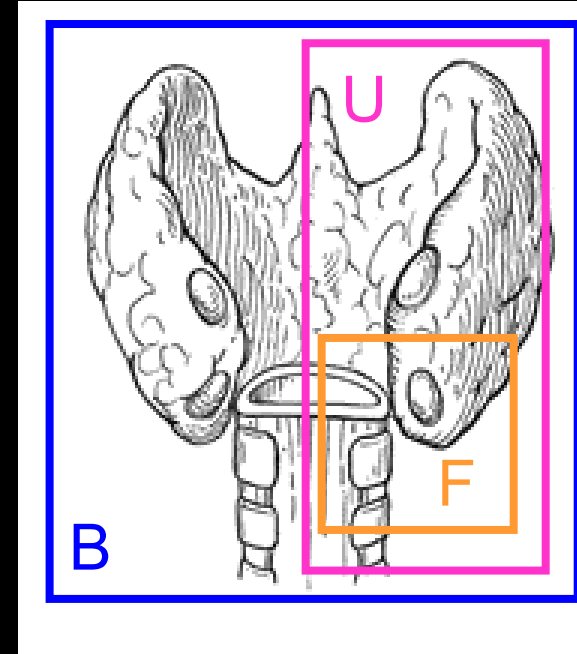
- Improved BMD, 15% (1 yr) 21% (4 yr) postop, in the lumbar spine of those with vertebral osteopenia.
 - Silverberg et al: JCEM 80:729, 1995; 81:4007-12, 1996
- Improved BMD in spine and hip. Improved serum alkaline phosphatase and osteocalcin.
 - Thorsen K et al: Surgery 122:882-7, 1997
- Improved BMD to an extent that restores the preoperative bone loss.
 - Abdelhadi M et al: JCEM 83:3845, 1998

Improve Health Status (SF36) after Parathyroidectomy

- SF-36 health status assessment tool
 - (140 pts, 110 followed at 2 m, 82 at 6 m)
- Preop: marked impairment in 7 of 8 domains
- 2 m postop: improvement in 5 of 8 domains
- 6 m postop: improvement in 6 of 8 domains
- Improvement in: limitations caused by physical and emotional role function, social function, bodily pain, and vitality.

Parathyroidectomy: Extent of Exploration

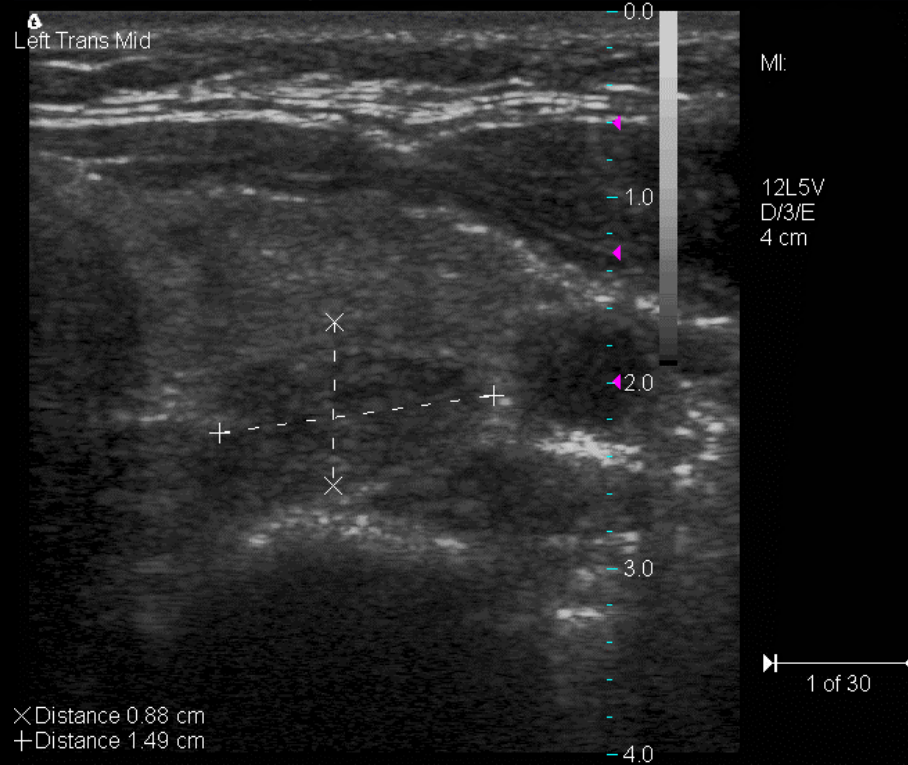
- Bilateral exploration
 - 4 glands or more identified
- Unilateral exploration
 - 1 tumor and 1 normal gland identified
- Focused exploration
 - “limited”, “targeted”, “concise”
 - 1 tumor identified
 - Adenomaectomy without full exploration



Successful Parathyroidectomy: Focused (vs General) Exploration

- Know where to start
 - Preoperative localization studies (MIBI or US)
 - *Intraoperative localization studies*
- Know when to stop
 - Intraoperative quick assay for hormones
 - Bayesian analysis
 - *Intraoperative radio-guidance*

45 year-old woman, had gastric bypass, Ca 11, PTH 78, Left upper 2.6 cm parathyroid adenoma



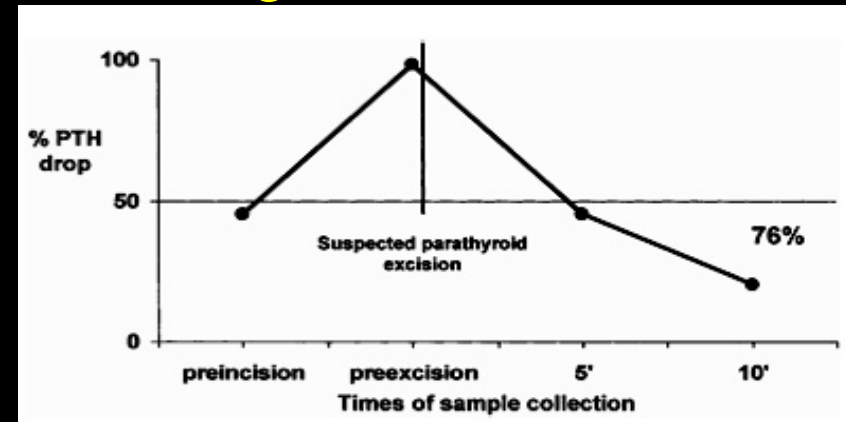
Intraoperative PTH for Parathyroidectomy

University of Miami Protocol

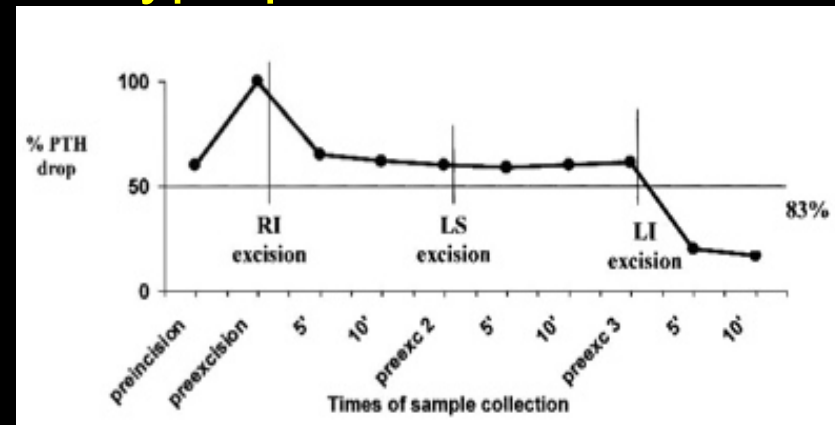
Samples taken:

- Pre Incision (skin incision)
 - Pre Excision (prior to cross clamping pedicle)
 - 5 minutes
 - 10 minutes
- 50% decrease from highest Pre value predictor of eucalcemia at ≥ 6 months

Single Adenoma



Hyperplasia



University of Miami: 294 consecutive patients

| Initial Operation | | Calcium Level at 6 months | |
|-----------------------|------|---------------------------|--------------------|
| | | <10.3 | >10.3 |
| Drop in 10 minute PTH | ≥50% | TP:279/294 (95%) | FP:1/294 (0.4%) |
| | <50% | FN:7/294 (2.7%) | TN:4/294 (1.5%) |

Double adenomas: more than half of the time IOPTH is wrong

| Study | Institution | No Patients | <50% drop TN | ≥50% drop FP |
|-----------|-----------------------------|-------------|--------------|--------------|
| Gauger | Univ Michigan/ Australia | 20 | 9(45%) | 11(55%) |
| Haciyanli | UCSF | 21 | 8(40%) | 13(60%) |

How much does a parathyroidectomy cost? (UCSF charges for self-pay, 2004)

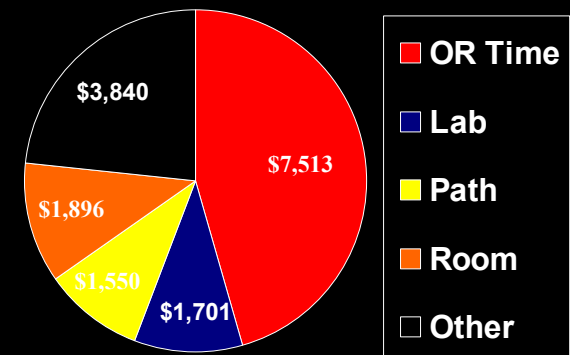
UCSF billing data

- Neck ultrasound \$544
- Sestamibi scan: \$1,100
- CT with and without contrast: \$2,500
- MRI with gadolinium: \$4,100
- PET scan: \$4,700
- Selective venous cath: \$18,000
 - *IR pro fee: \$10,000 + \$8,000 hospital charge*

- IOPTH \$318 for 1 pre and post. \$284 each addtl post.
- 99Tc Sestamibi for Gamma probe \$398
- Frozen section: \$388 first block. Each addtl \$184.
- Serum PTH + Ca: \$214 (Ca only: \$35)
- Serum Phos: \$33
- Surgeon's fee: \$3,473
- Semi-private room: \$1,896 per day
- OR cost: base level \$2,200. First 30 min \$1,800.
 - *Each addtl 15 min ~\$900*
- Anesthesiologist pro fees: 1.5hr \$950, 2.5hr \$1,250

Total inpatient bill for
focused PTX with
overnight stay
(*professional fees and
preoperative localization
not included*)

\$16,500



Charges for Parathyroidectomy

| | Japan | US (UCSF'04) |
|----------------|--------------|----------------------|
| ■ Mibi | \$631 | (\$1100) |
| ■ Ultrasound | \$47 | (\$544) |
| ■ CT | \$118 | (\$2500) |
| ■ MRI | \$193 | (\$4100) |
| ■ IOPTH | \$19 | (\$600) |
| ■ Surgeon | \$1237 | (\$3500+\$1900 Hosp) |
| ■ Anesthesia | \$566 | (\$950+\$5800 OR) |
| ■ 15 more min. | \$0 | (\$150+\$900) |

How much does a parathyroidectomy cost? (UCSF charges for self-pay, 2004)

| Localization + OR + Anesthesia charges only | Focused | Bilateral | Failed Focused |
|---------------------------------------------|-------------------|---------------------|---------------------|
| US | \$544 | \$0 | \$544 |
| MIBI | \$1,100 | \$0 | \$1,100 |
| IOPTH (3 samples) | \$602 | \$0 | \$0 |
| OR charge | \$5,800 (1 hr) | \$9,400 (2 hr) | \$9,400 (2 hr) |
| Anesthesia fees | \$950 (1.5 hr) | \$1,250 (2.5 hr) | \$1,250 (2.5 hr) |
| Total | \$8,996 | \$10,650 | \$12,294 |

1 hr focused (vs 2 hr bilateral) approach saves **\$3900** in OR and anesthesia fees!
(net savings **\$1,654**)

15 min in OR = \$1,000

Standard preop localizing studies add **\$1,644!**



Imaging directed parathyroidectomy (imaging selected parathyroidectomy)

- +MIBI alone
 - 90% success with focused approach
- +US alone
 - 85% success with focused approach
- +MIBI and +US
 - 96% success with focused approach
- Positive MIBI and US selected those likely to have a solitary adenoma

“Kebebew Score” of 3 or more predicts single adenoma

9:00–10:15 am

SCIENTIFIC SESSION I

1

Predictors of Single Versus Multigland Parathyroid Disease in Primary Hyperparathyroidism: A Simple and Accurate Scoring Model

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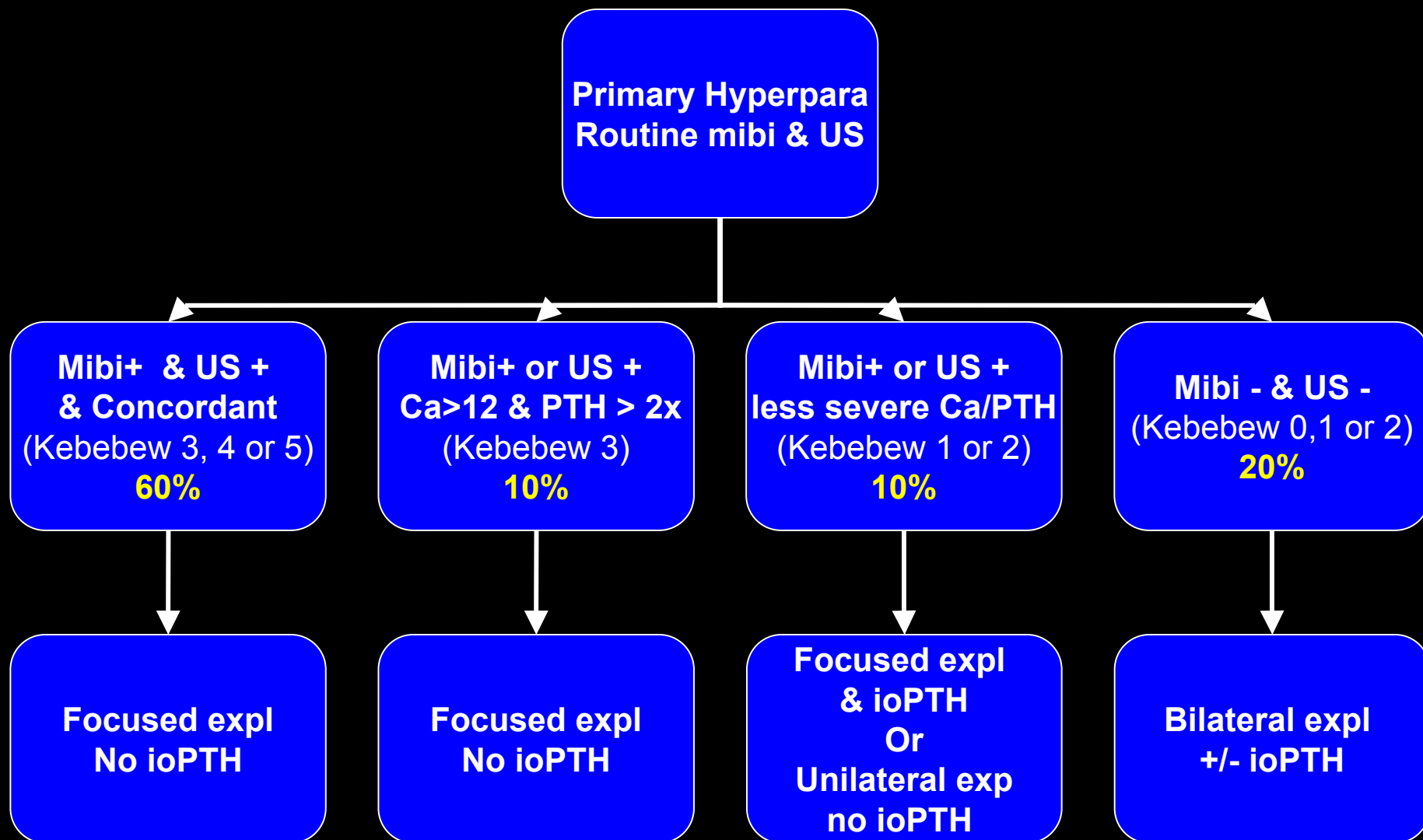
PRESENTED BY

Electron Kebebew, MD

- Sestamibi
- Ultrasound
- Concordance
- Ca > 12 mg/dl
- PTH > 2x upper nl

3 or more predicts
single gland disease

Recommendations



Changing Approach for Primary Hyperparathyroidism: Conclusions

- Parathyroidectomy:
 - successful, beneficial, and minimal risks
 - NIH criteria too conservative?
- Routine preoperative sestamibi and ultrasound
 - even for first-time operation and reoperation
 - Save time and money by shorten operation?
- Focused exploration possible in most patients
 - Most are known preoperatively (“Kebebew Score”)
 - Selective use of intraoperative PTH?