



**Asymptomatic Primary
Hyperparathyroidism
and Parathyroid incidentaloma**
Verona - October 28, 2006



Focus on the problem

Giorgio Borretta

S.C. di Endocrinologia e Malattie del Ricambio

Ospedale S. Croce e Carle, Cuneo

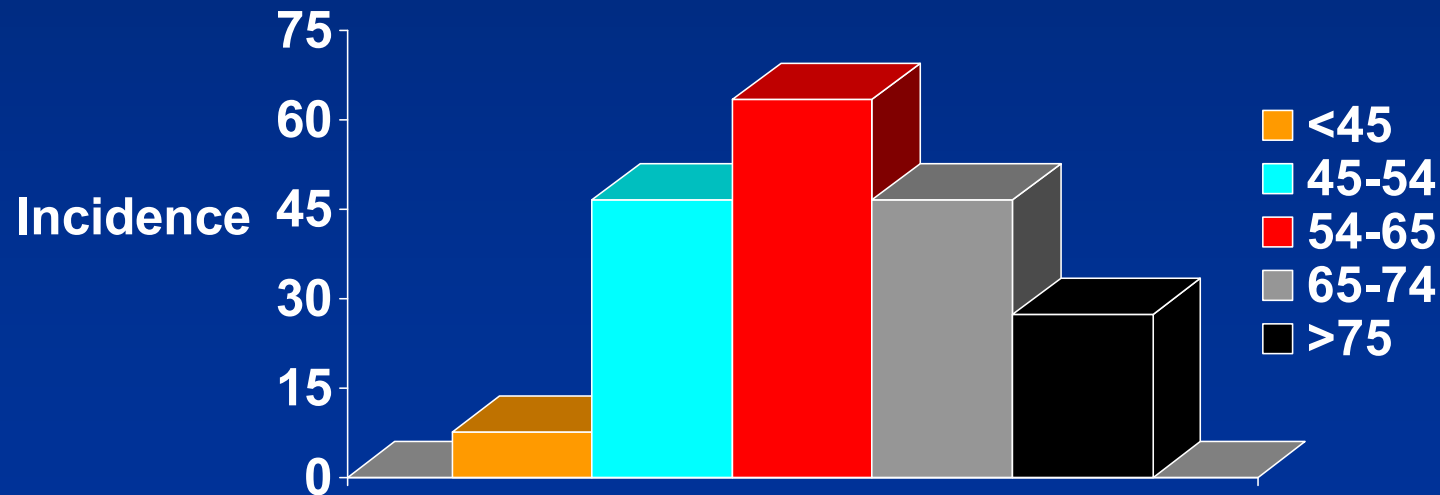
Pathogenesis

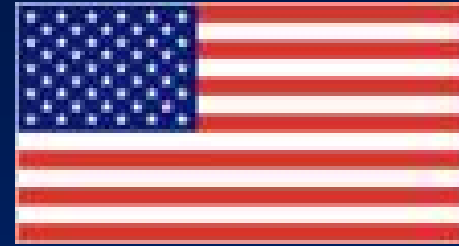


pHPT sporadic, single adenoma	80-85%
pHPT sporadic, multiglandular disease	10-12%
pHPT carcinoma	1%
pHPT genetic syndromes <i>MEN type 1 – type 2</i> <i>Familial hypocalciuric hypercalcemia (FHH)</i> <i>Post natal severe hyperparathyroidism</i> <i>HPT- jaw tumors syndrome</i>	2- 8%

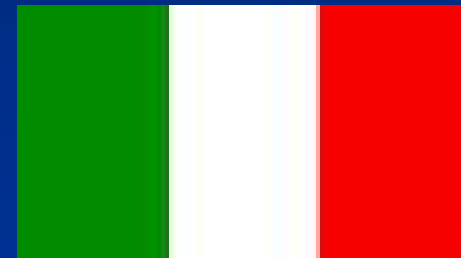
Epidemiologic Profile

- Incidence: **20-30:100000/year**
- Prevalence: **1-4/1000**
- F:M = **3 : 1**
- More common **after age 55 years**



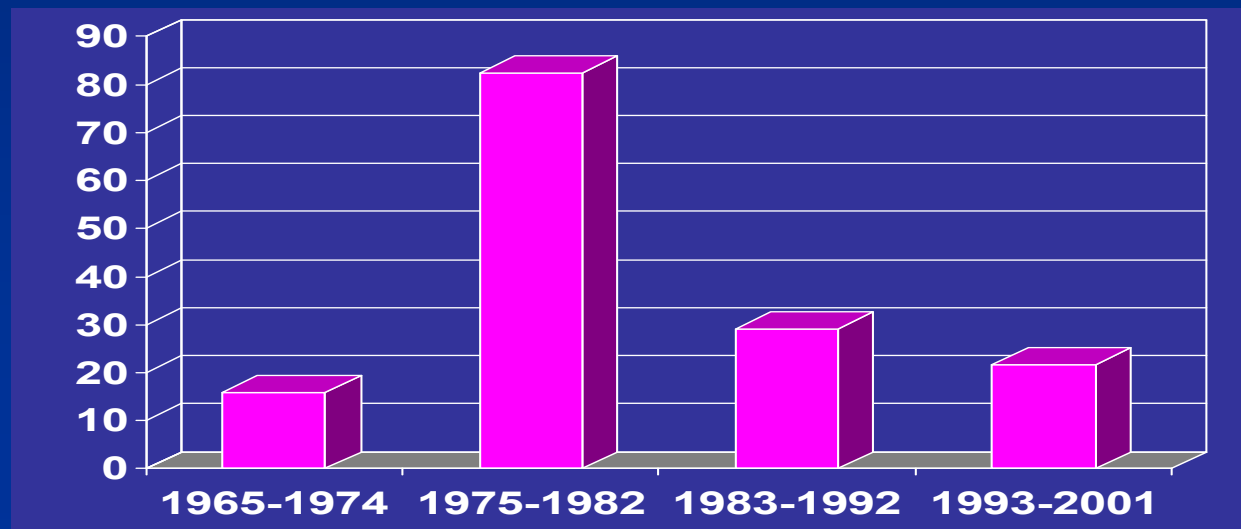
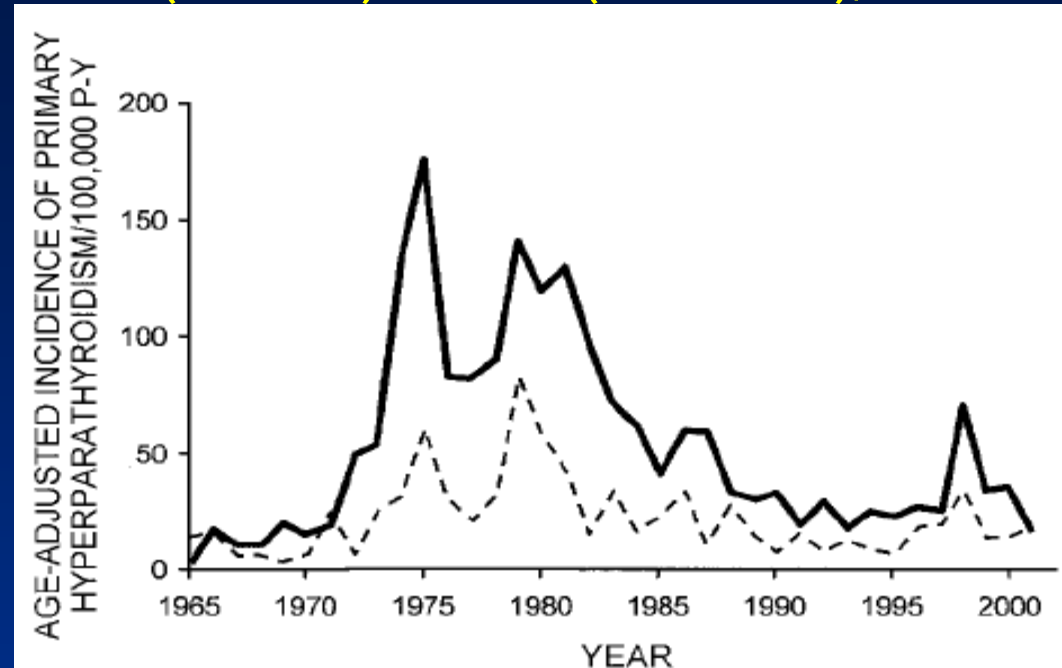


500.000-1.250.000 pt
50.000-100.000 new cases/year



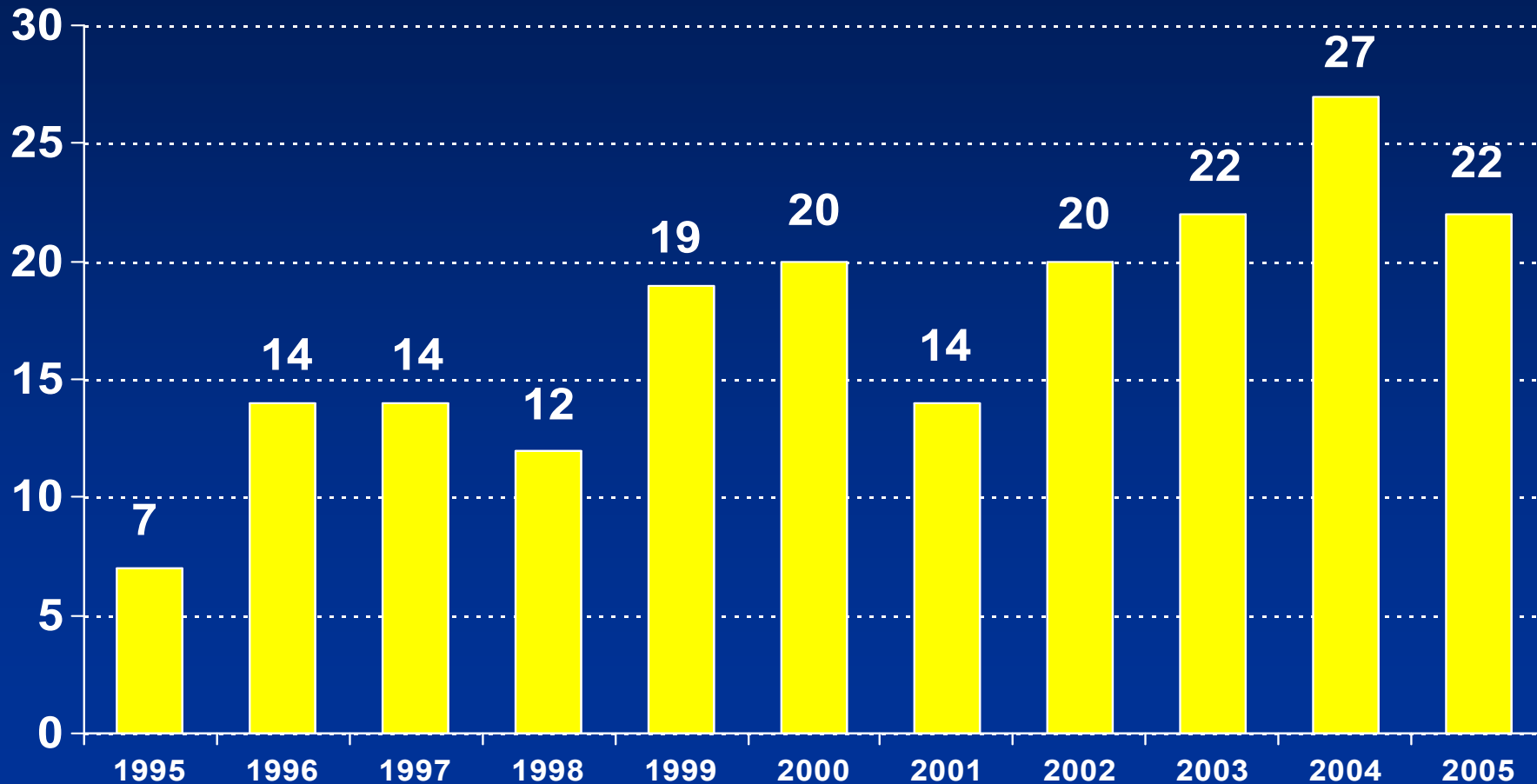
120-300.000 pt
12.000-24.000 new cases/year

Age-adjusted (to 2000 U.S. whites) incidence (per 100,000 person-years) of definite plus possible primary hyperparathyroidism among Rochester women (solid line) and men (dashed line), 1965–2001.



New diagnosis per year in our pHPTseries

1995-2005, n=191
(Cuneo, Italy)



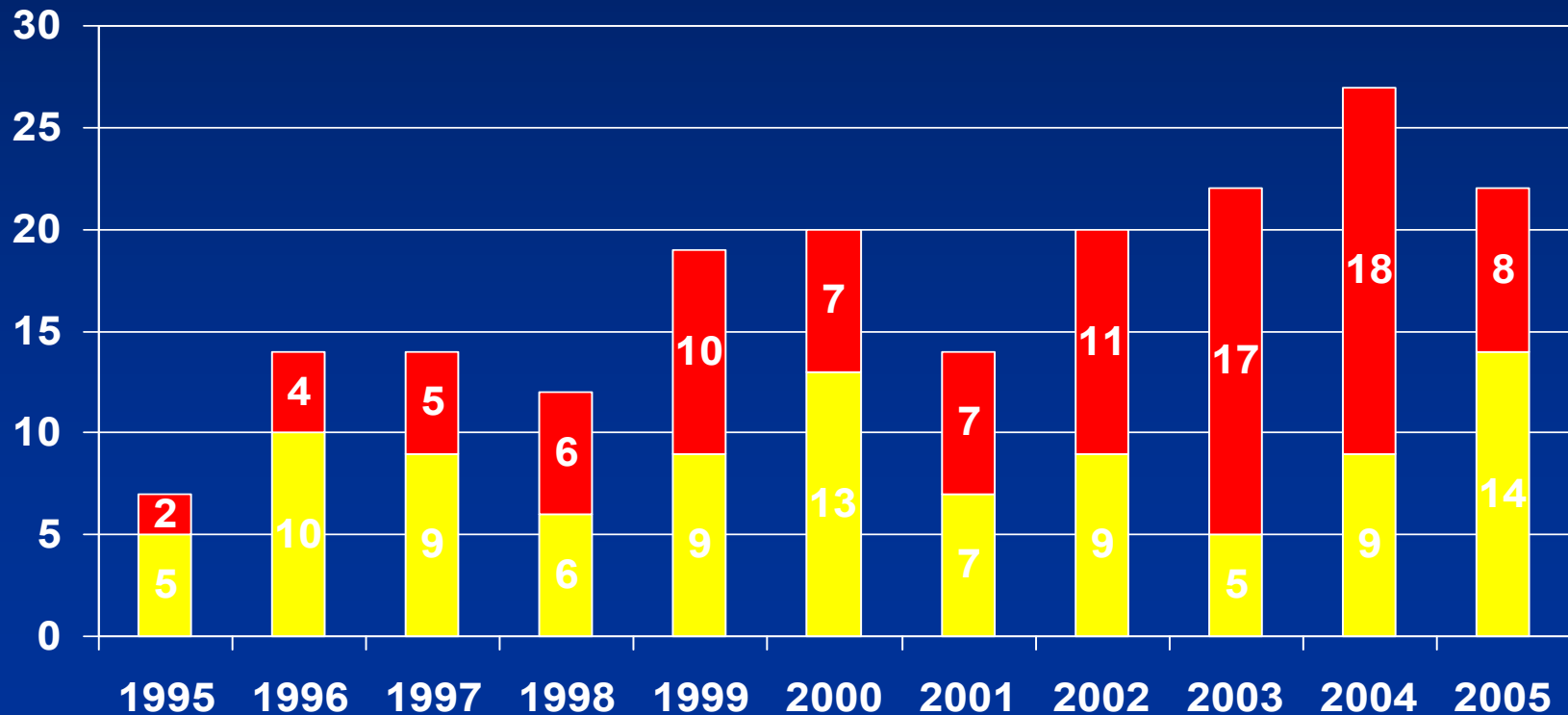
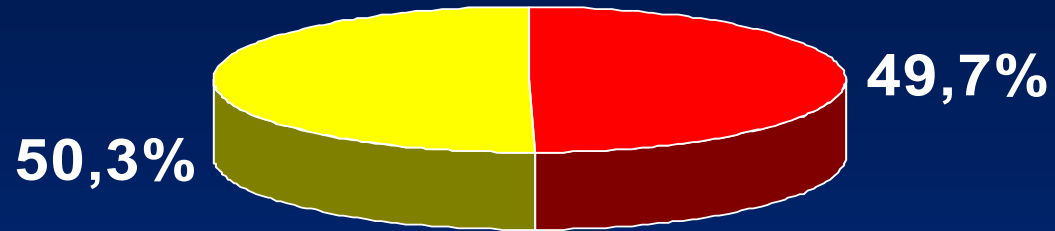
The changing clinical profile of primary hyperparathyroidism

	Cope et al. 1930-1945 %	Heath et al. 1965-1974 %	Mallette et al. 1965-1974 %	Silverberg et al., 1984-2002 %
Nephrolithiasis	57	51	37	17
Hypercalciuria	n.d.	6	40	39
Overt skeletal disease	23	10	14	1.4
Asymptomatic	0.6	18	22	80

Bilezikian & Potts, 2002

New diagnosis per year in our series 1995-2005 (n=191) according to clinical presentation (Cuneo, Italy)

Symptomatic
Asymptomatic



“Non Classical” (Aspecific) Clinical Manifestations of pHPT

NEUROMUSCOLAR

- Weakness
- High fatigability
- Muscular atrophy
- Paresthesias, cramps

GASTROINTESTINAL

- Peptic ulcer disease
- Pancreatitis

Neuropsychiatric

- Attention deficit
- Depression or psychosis
- Neurocognitive deficit

CARDIOVASCULAR

- Arterial Hypertension
- Cardiac Hypertrophy
- Valvular and myocardial calcifications

METABOLIC

- IGT, DM
- Insulin resistance
- Hyperlipidaemia
- Increased serum levels of urate

Parathyroid adenomas and cardiovascular risk

N Garcia de la Torre, J A H Wass and H E Turner

Table 3 Proposed causes of increased cardiovascular risk associated with primary hyperparathyroidism

1. Hypertension
 2. Left ventricular hypertrophy
 3. Valvular and myocardial calcification
 4. Dysfunction in vascular reactivity:
 - Endothelial vasodilatory response altered
 - Vascular smooth muscle reactivity altered
 5. Vascular structural changes
 6. Arrhythmias
 7. Insulin resistance and diabetes mellitus
 8. Hyperlipidaemia
 9. Increased body mass index and body fat mass
 10. Increased serum levels of urate
-

Mortality studies among pHPT patients

	N pz	Ca ++	Follow-up (years)	RR death	Risk ratio for CVD
Hedbäck	896	12.1	12.9	1.67	1.66
Uden	282	11.6	8	NP	1.18
Palmer	172	10.9	14	2.21	1.43
Wermers	435	10.9	NP	0.69	0.60

The different ways leading to the diagnosis of pHPT in a series of 123 consecutive patients (Reggio Emilia, 2000-2004)

- Occasional hypercalcemia 36
- Screening for osteoporosis 32
- Screening for urolithiasis 10
- **Parathyroid incidentaloma** 11
- Clinical suspicion for hyperparathyroidism 8
- Clinical suspicion for MEN 3

Criteria for Diagnosis

- Hypercalcemia in the face of increased levels of PTH
- PTH levels in the normal range, but inappropriately high (in the upper range of normal), relative to the hypercalcemia
- Increased PTH levels in normocalcemic patients who show no evidence of a secondary hyperparathyroid state (*so-called “normocalcemic” pHPT*)

If urinary calcium excretion is very low, *familial hypocalciuric hypercalcemia* (FHH) should be ruled out

Localization techniques in pHPT

❖ Preoperative, noninvasive

^{99m}Tc /sestamibi

Sestamibi with single-photon emission (SPECT)

Ultrasound

C
M
❖ **Parathyroid imaging has no role in the diagnosis of pHPT, but should be used for operative planning.**

S
D
❖ **If the imaging techniques localize an adenoma, this information facilitates a focused or minimally invasive surgical approach.**

γ 1100c

SURGICAL OPTIONS IN PRIMARY HYPERPARATHYROIDISM

**..... none of these technologies is a
substitute for an experienced surgeon**

Intraoperative Aids

- Technetium^{99m} Sestamibi**
- Parathyroid hormone level**

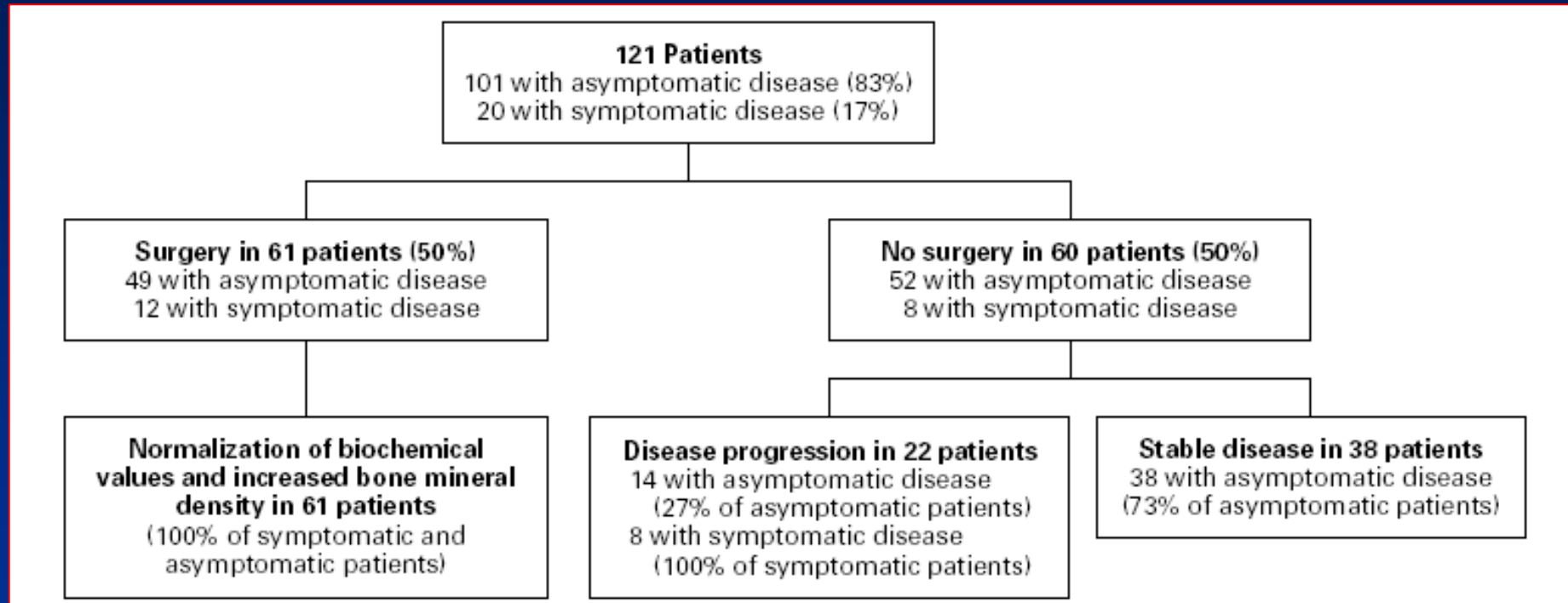
Therapy

- Operative management is currently the only curative therapy for patients with pHPT
- Surgical therapy is clearly indicated for all patients with symptomatic pHPT
- The recommendation of surgical treatment for asymptomatic patients with pHPT remains controversial

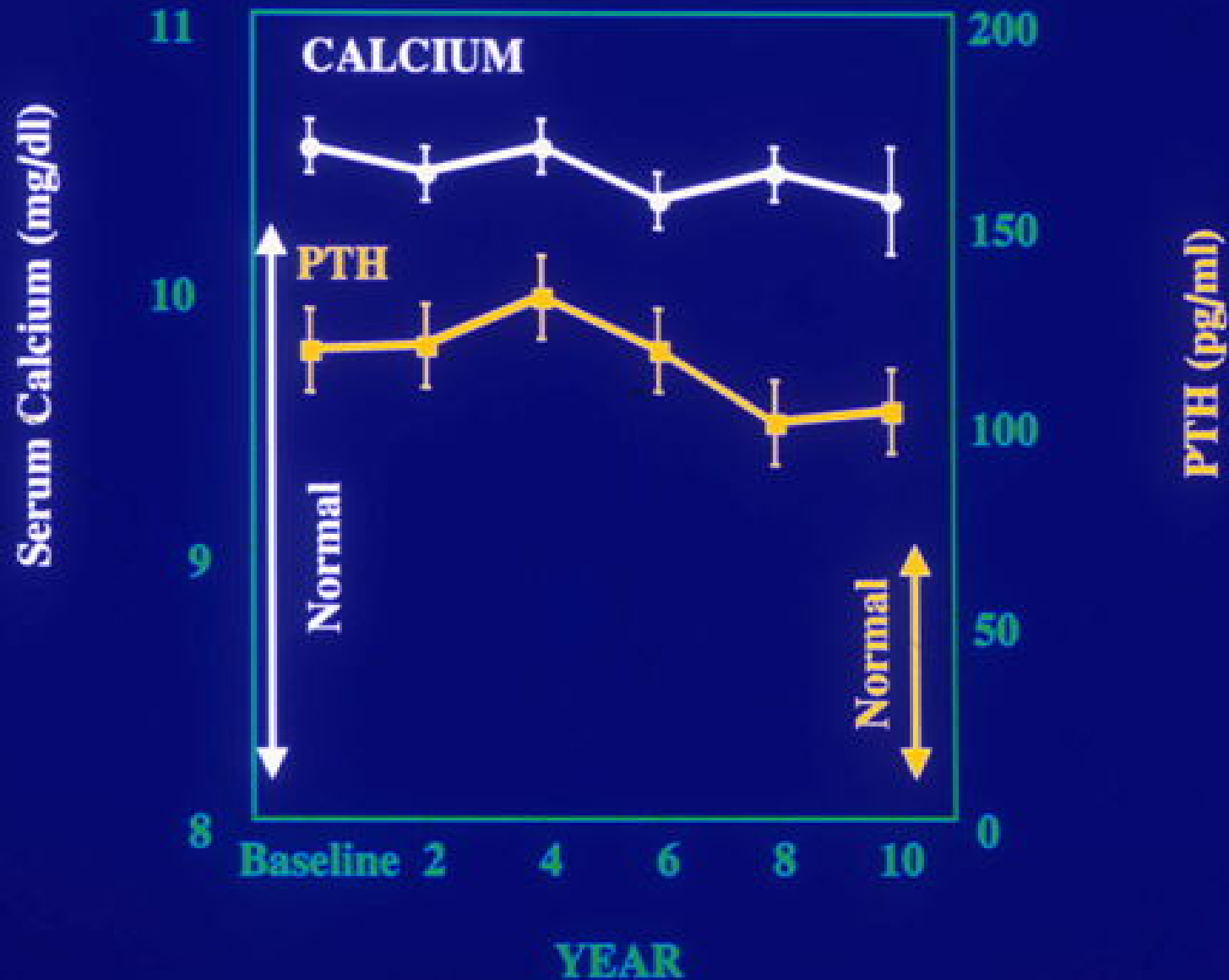
**TO CUT IT OUT OR
TO LEAVE IT IN...**

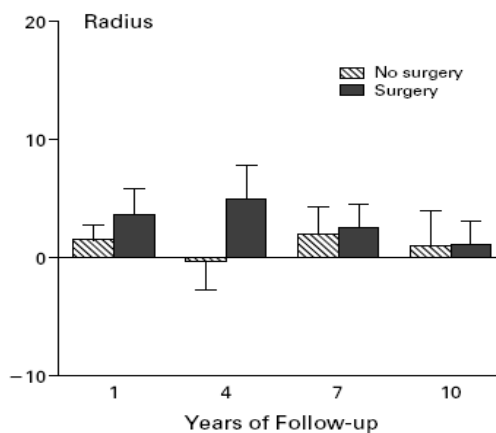
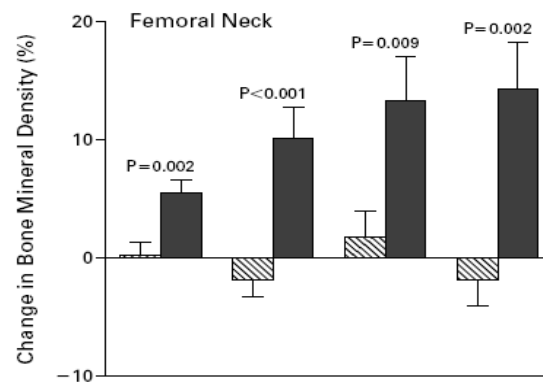
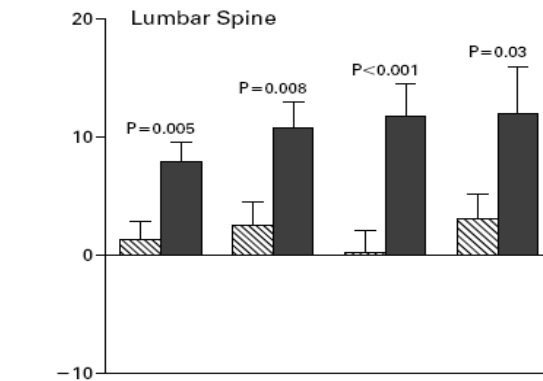
THESE ARE THE QUESTIONS!

A 10-YEAR PROSPECTIVE STUDY OF PRIMARY HYPERPARATHYROIDISM WITH OR WITHOUT PARATHYROID SURGERY



Calcium & PTH: Patients Followed without Surgery





	1	4	7	10
No. of Patients				
No surgery	44	28	21	14
Surgery	39	24	17	17

Silverberg SJ et al, NEJM 1999

A comparison of new and old *consensus NIH guidelines* for parathyroid surgery in asymptomatic primary hyperparathyroidism

Measurement	Guidelines (1990)	Guidelines (2002)
Serum calcium	1-1.6 mg/dl	1.0 mg/dl
24-h urinary calcium	> 400 mg/dl	> 400 mg/dl
Creatinine clearance	Reduced by 30%	Reduced by 30%
Bone mineral density	Z score <-2.0 (forearm)	T-score < -2.5 (at any site)
Age	<50	<50

Bilezikian et al., 2002

A Slight Decrease in Renal Function Further Impairs Bone Mineral Density in Primary Hyperparathyroidism

Laura Gianotti, Francesco Tassone, Flora Cesario, Anna Pia, Paola Razzore, Giampaolo Magro, Alessandro Piovesan, and Giorgio Borretta

Division of Endocrinology and Metabolism (L.G., F.T., F.C., A.Pia, P.R., G.M., G.B.), S. Croce and Carle Hospital, 12100 Cuneo, Italy; and Division of Endocrinology and Oncology (A.Pio.) S. G. Battista Hospital, 10126 Turin, Italy

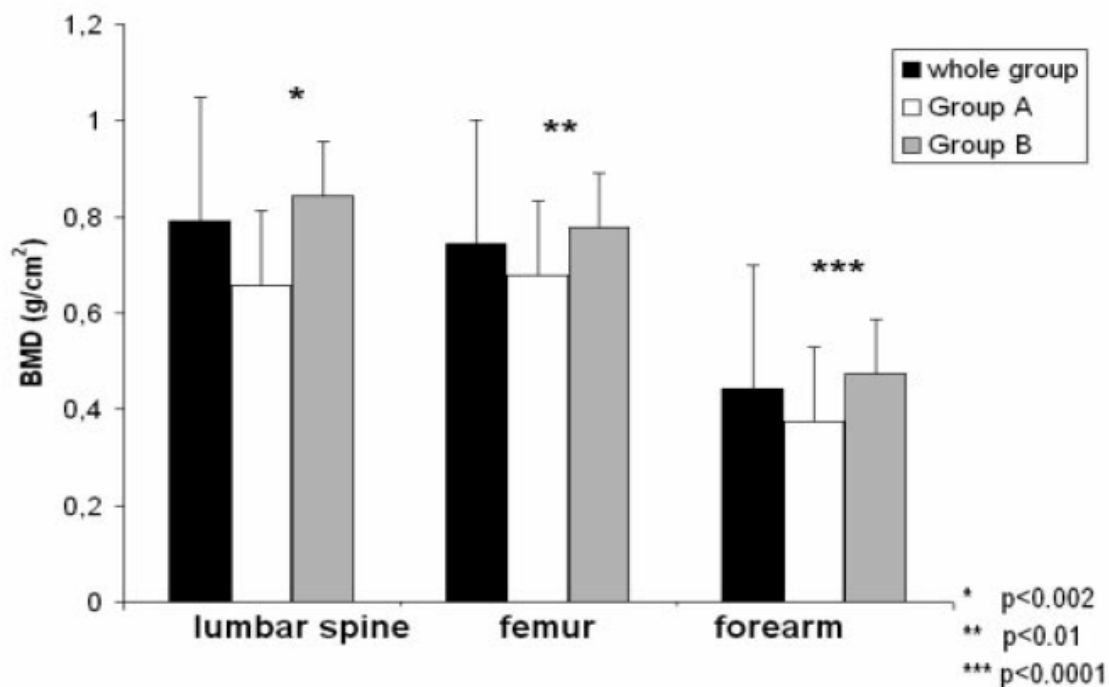
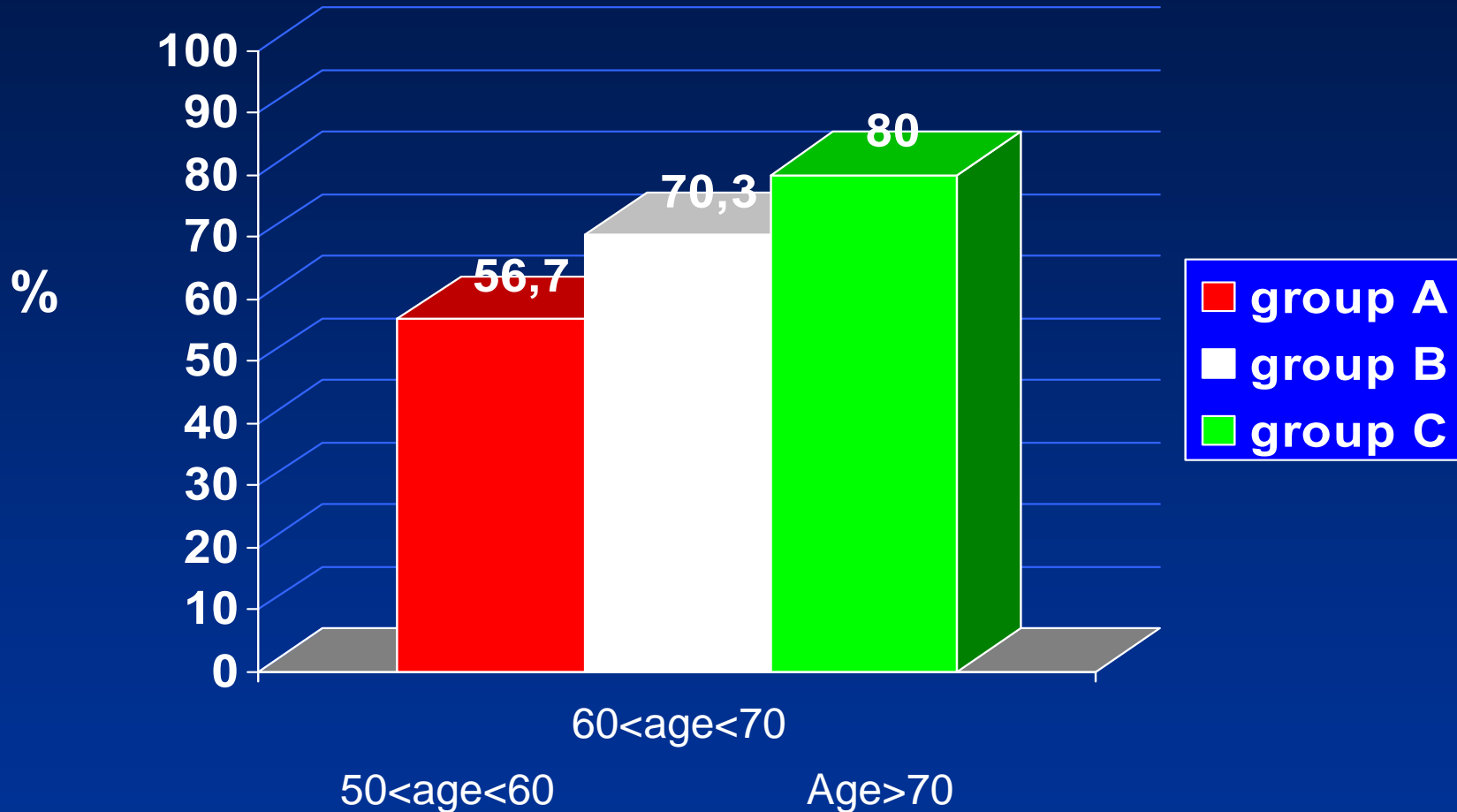


FIG. 1. Mean (\pm SD) levels of BMD (grams per square centimeter) at lumbar spine, femur, and forearm of the whole group of PHPT patients (black columns), PHPT patients with lower Ccr (group A, white columns), and PHPT patients with higher Ccr levels (group B, gray columns). *P* values refer to comparisons between groups A and B.

A = Ccr \leq 70 ml/mn
B = Ccr > 70 ml/mn

What about asymptomatic PHPT ?..... patients with Ccr \leq 70 ml/min had lower forearm BMD than patients with higher Ccr (p < 0.00001).

SURGERY INDICATIONS ACCORDING TO 2002 NIH CRITERIA IN OUR SERIES OF ASYMPTOMATIC pHPT



Group C:	T-score < -2.5	→ 68.8%
	reduced CCR	→ 56.0%

**THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND
THE AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS
POSITION STATEMENT ON THE DIAGNOSIS AND MANAGEMENT
OF PRIMARY HYPERPARATHYROIDISM**

Operative management should be considered and recommended for all asymptomatic patients with pHPT who have reasonable life expectancy and suitable operative and anesthesia risk factors.





Asymptomatic Primary Hyperparathyroidism and Parathyroid incidentaloma

Verona - October 28, 2006



Thompson G (USA) and Frasoldati A (Italy)

- ❖ When and why to treat asymptomatic hyperparathyroidism
- ❖ Preoperative imaging in primary hyperparathyroidism: choice of the procedures
- ❖ What kind of treatment?
- ❖ Parathyroid incidentaloma with normal calcium: how do you manage it?

Clinical case 1.

- 55 year old woman
- Serum calcium 11.8 mg/dl
- Phosphorus 2.3 mg/dl
- PTH 320 pg/ml
- BMD evidence of osteoporosis. PT scintiscan (sestamibi) is equivocal

What's your nex step?

1. Follow-up with periodic biochemical tests
2. Repeat PT scintiscan and perform neck MRI
3. Proceed with cervical exploration and PT surgery
4. Perform US and FNA-PTH (needle washout)

Cinical case 2.

- 60 yr. Old woman
- serum calcium 10.1 mg/dl,
- phosphorus 3.8 mg/dl,
- Alk Phosph. 50 U/l
- PTH 110 pg/ml.
- Urinary calcium 240 mg/24 h
- BMD normal

Your management?

1. Parathyroid Imaging
2. Parathyroid Surgery
3. Treat 1000 mg calcium daily
4. Vit. D measurement

Clinical Case n.3

- 67 yr old woman with
- Serum calcium 10.6 mg/dl
- Phosphorus 4.0 mg/dl
- Alk Phosph 60 U/l
- PTH 105 pg/ml

Your management?

- 1. No treatment; follow-up (1 year)
- 2. Immediate Parathyroid Surgery
- 3. Obtain BMD and recommend treatment based on results
- 4. Add calcium + vit D

Clinical Case n.4

- 67 yr.old woman
- Same data as before
- BMD spine T score = - 1.9
- BMD femur T score = - 1.5

Your management?

1. Parathyroid Surgery
2. Continue follow-up

Clinical case n. 5

- 52 yr. Old man
- Serum Calcium 11.2 mg/dl
- Phosphorus 2.3 mg/dl
- PTH 270 pg/ml
- History of renal stones and hypertension

Your management?

- 1. Parathyroid Imaging to localize tumor
- 2. No further test necessary. Proceed with surgery
- 3. Measure BMD to help with management
- 4. Refer to psychiatrist!

Asymptomatic Primary Hyperparathyroidism and Parathyroid Incidentaloma



Geoffrey B. Thompson, MD
Professor of Surgery
Mayo Clinic College of Medicine

Educational Objectives

- A problematic HPT likely does not exist
- Parathyroid Surgery is Safe and Efficacious
- MIP is as successful as standard surgery and simplifies surgery for the pt.
- Pts with "mild hpt" benefit from early surgical intervention
- Parathyroid incidentalomas

Symptomatic HPT (<20%)

- Nephrolithiasis
- Fractures, osteitis fibrosa cystica
- Hypercalcemic Crisis
- Pancreatitis

NIH Consensus Conference for Parathyroidectomy in Patients with HPT

- Age < 50 years
- Nephrolithiasis
- Markedly elevated serum calcium level : >1.0 mg/dl above normal
- Osteitis fibrosa cystica
- Creatinine clearance 30% less than that of age-matched normal subjects
- History of hypercalcemic crisis
- Urinary calcium > 400mg/day
- Bone density more than 2 std dev below controls
- Documented neuromuscular symptoms
- Medical surveillance not desirable or possible

Primary Hyperparathyroidism

- Over 90% of our operated patients meet the new NIH criteria
- Over 80% of patients have a myriad of non-classical, subclinical signs and symptoms at presentation
- Primary HPT offers something (bad) for everyone if you look for it

Asymptomatic Hyperparathyroidism

IT DOES NOT EXIST !

Or at least **aproblematic** hpt does not exist

Excess Mortality from HPT

- 896 pts operated between 1953 and 1982
- Increased relative risk for premature death
- Risk ameliorated by successful surgery
- Return to normal risk occurred more quickly in milder cases

Excess Mortality

- Seen in mild and severe hpt
- Diminished by surgery (Palmer, 1987; Ronni-Sivula, 1985)
- Mayo-Wermers 1998: Increased risk of death in more severe untreated cases

BONE DISEASE

- Often clinically silent until fractures occur
- \$14 billion dollar medical expense in U.S.

Risk of Fracture in HPT

- 407 patients with HPT at Mayo
- Observed increase of 30% over expected in hpt group
- Parathyroid surgery may have protective effect

Effect of Surgery on Bone

- 10-year follow-up study
- ALL symptomatic, non-operated, patients progressed
- After surgery all pts had improved BMD
- No difference in symptomatic vs asymptomatic pts
- No reliable predictors for who will progress

Editorial Comment-R. Utiger

“Asymptomatic does not necessarily mean unharmed”

“Surgical Treatment....should now be recommended for (nearly) all hpt pts.”

PTx vs. Antiresorptive Agents

- Increase in BMD less than 10% over 3 years (Lieberman, 1995,1996) with ARA's
- PTx increases BMD 8-12% in 1-3 years (Silverberg, 1999)

Neuropsychiatric and Musculoskeletal Symptoms

- Joborn (1989)
- Numann (1984)
- Chan (1985)
- Lundgren (1998)
- Burney (1996,1998,1999)
- Pasieka (2002)

Burney

- SF-36 Questionnaire
- 140 pts: $Ca < 10.9$, $Ca > 10.9$
- 8 domains: physical function, physical role limit, bodily pain, general health, vitality, social function, emotional role limit, mental health

Burney

- Much lower scores in preops compared to pts without hpt
- Great improvement over 2-6 months post-op in 7 of 8 categories irrespective of calcium level pre-op
- Operate sooner rather than later

Pasieka

- QOL tool based on a visual analog scale
- Given pre- and post-op
- Validated in prospective study
- Pts fulfilling and not fulfilling NIH criteria
- Thyroidectomy pts as controls

Pasieka-----Conclusions

- Sx's just as severe in pts not fulfilling NIH criteria for operation
- These pts achieved significant improvement in symptoms with parathyroidectomy
- NIH guidelines need to be broadened

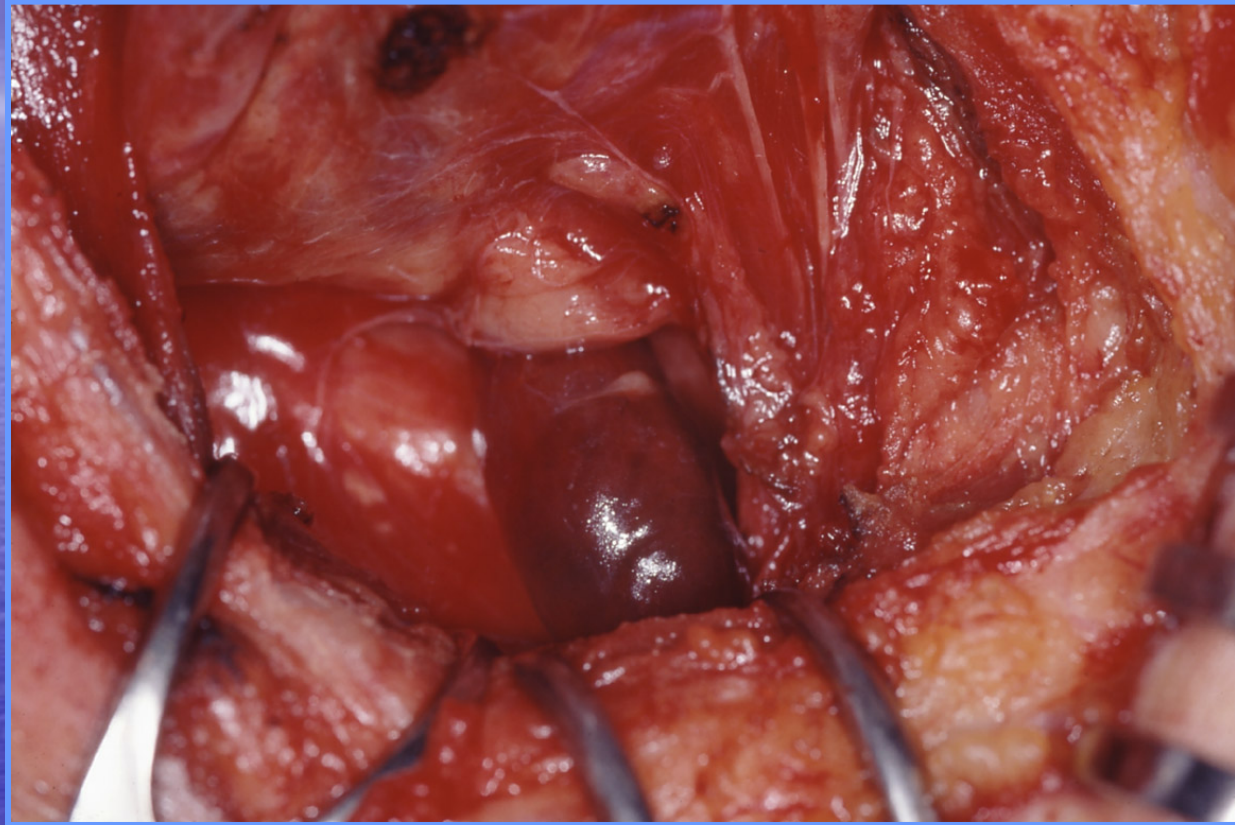
Standard Cervical Exploration



Success: >98%

Complications: <1%

Reoperative Parathyroid Surgery



Success: 88%

RLN injury: 1%

Hypoparathyroidism: 13%

“New” Outcome Measures

- Patient-Focused
 - General anesthesia after-effects
 - Nausea & vomiting
 - Clouded sensorium
 - Incisional pain
 - Outpatient dismissal
 - Postoperative convalescence

MIP

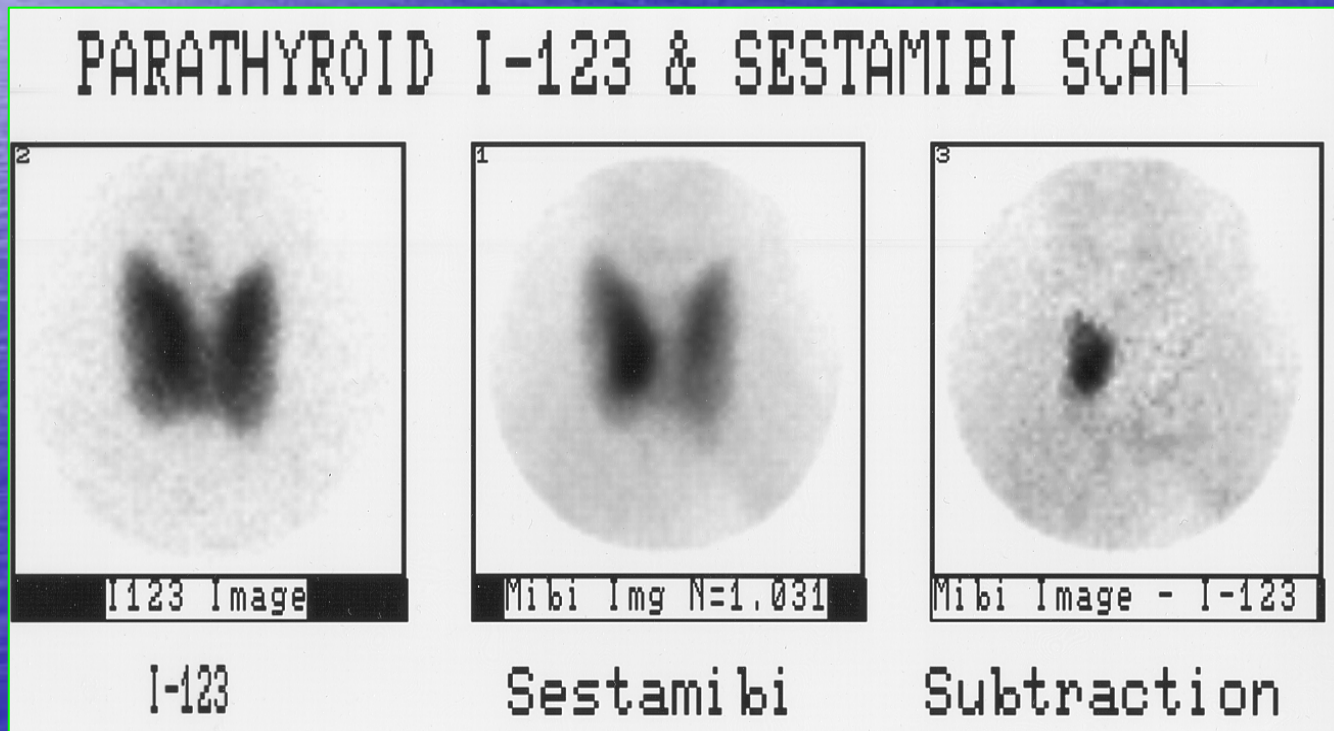
- Image-guided MIP
- Radioguided MIP
- Endoscopic or video-assisted MIP

Minimally Invasive Parathyroid Surgery

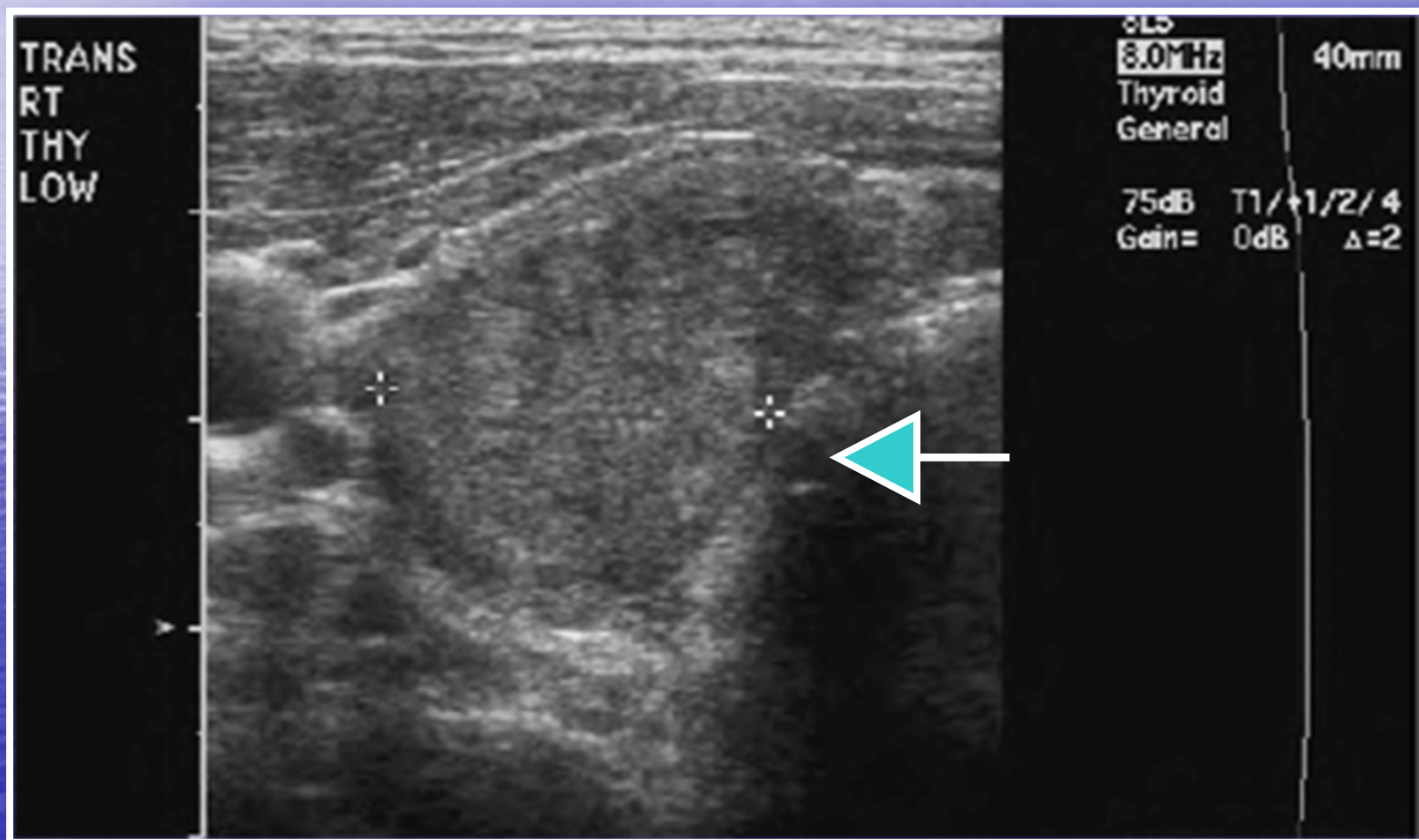
- Sestambi parathyroid scanning
- Ultrasound
- Intraoperative PTH monitoring

Sestamibi Parathyroid Scan

- Dual photon, Subtraction scans
- With Planar, Oblique and SPECT imaging

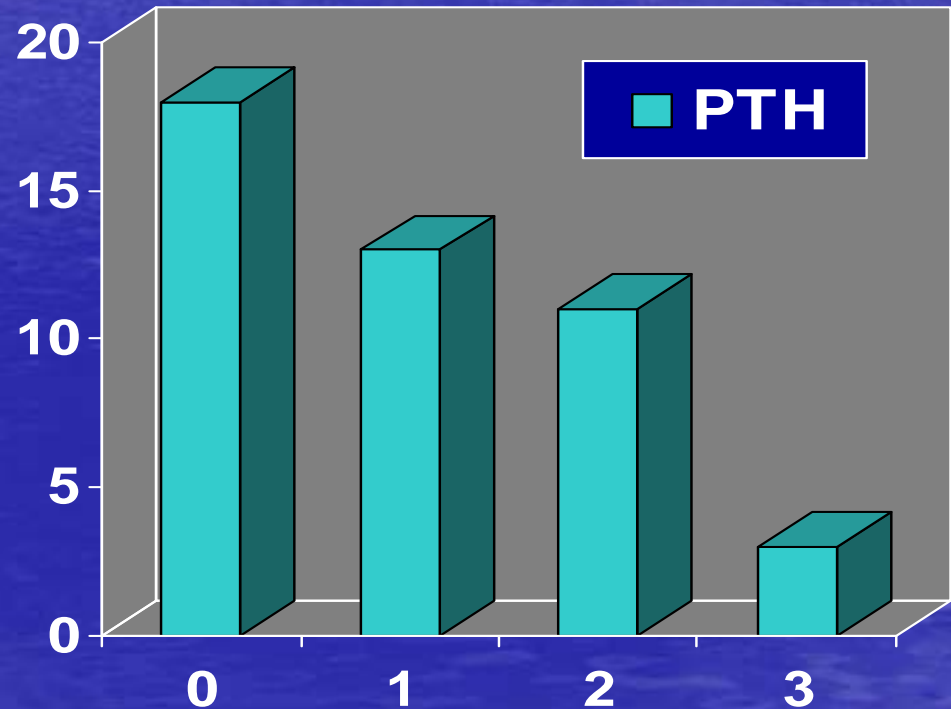
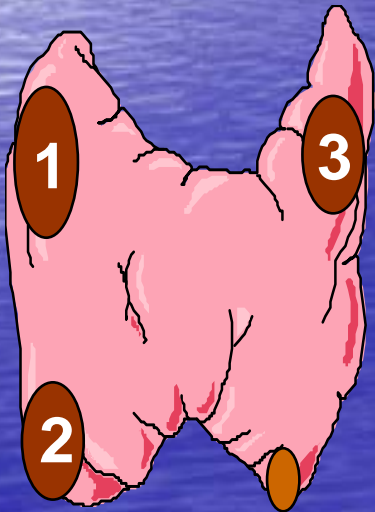


Parathyroid Ultrasound

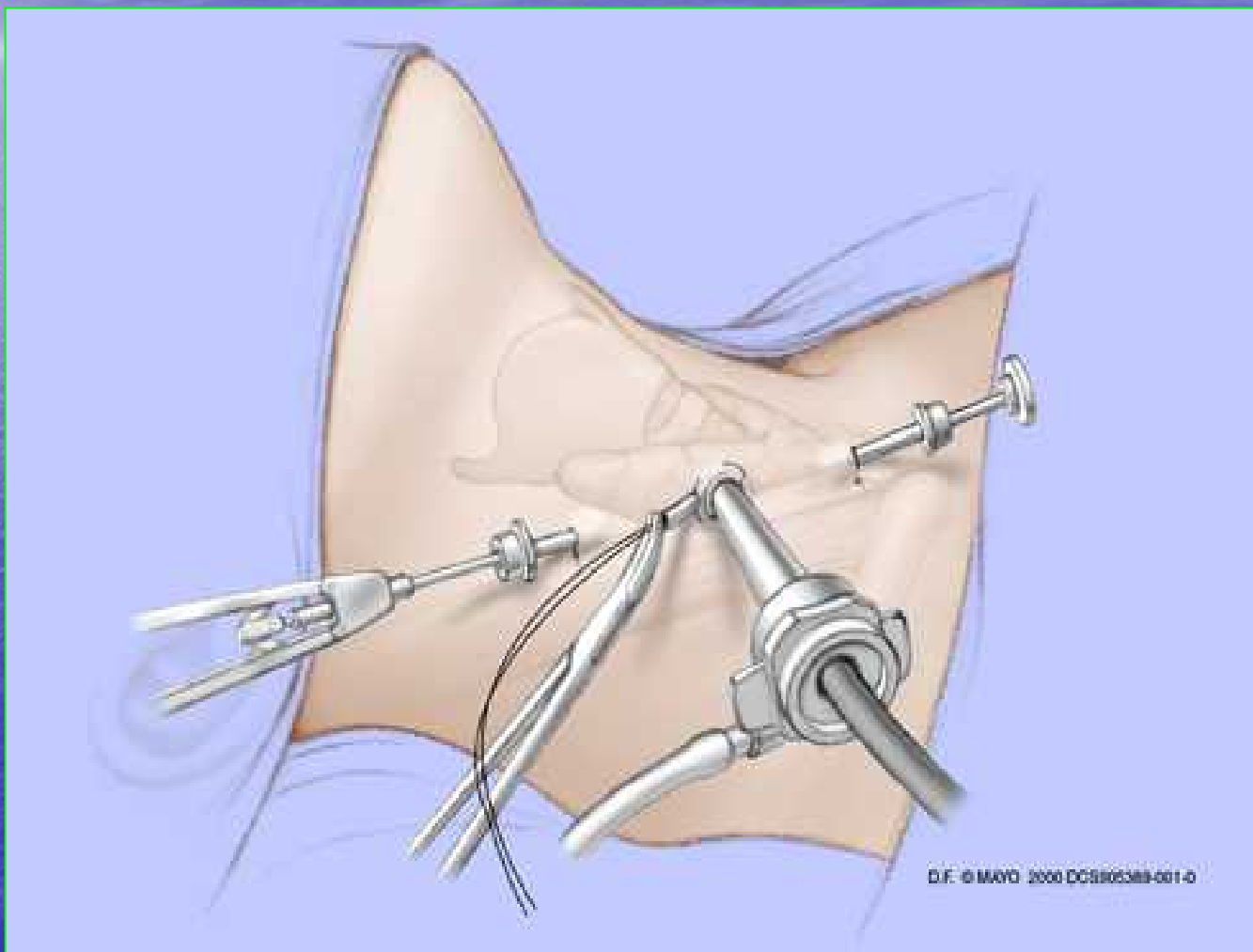


IOPTH

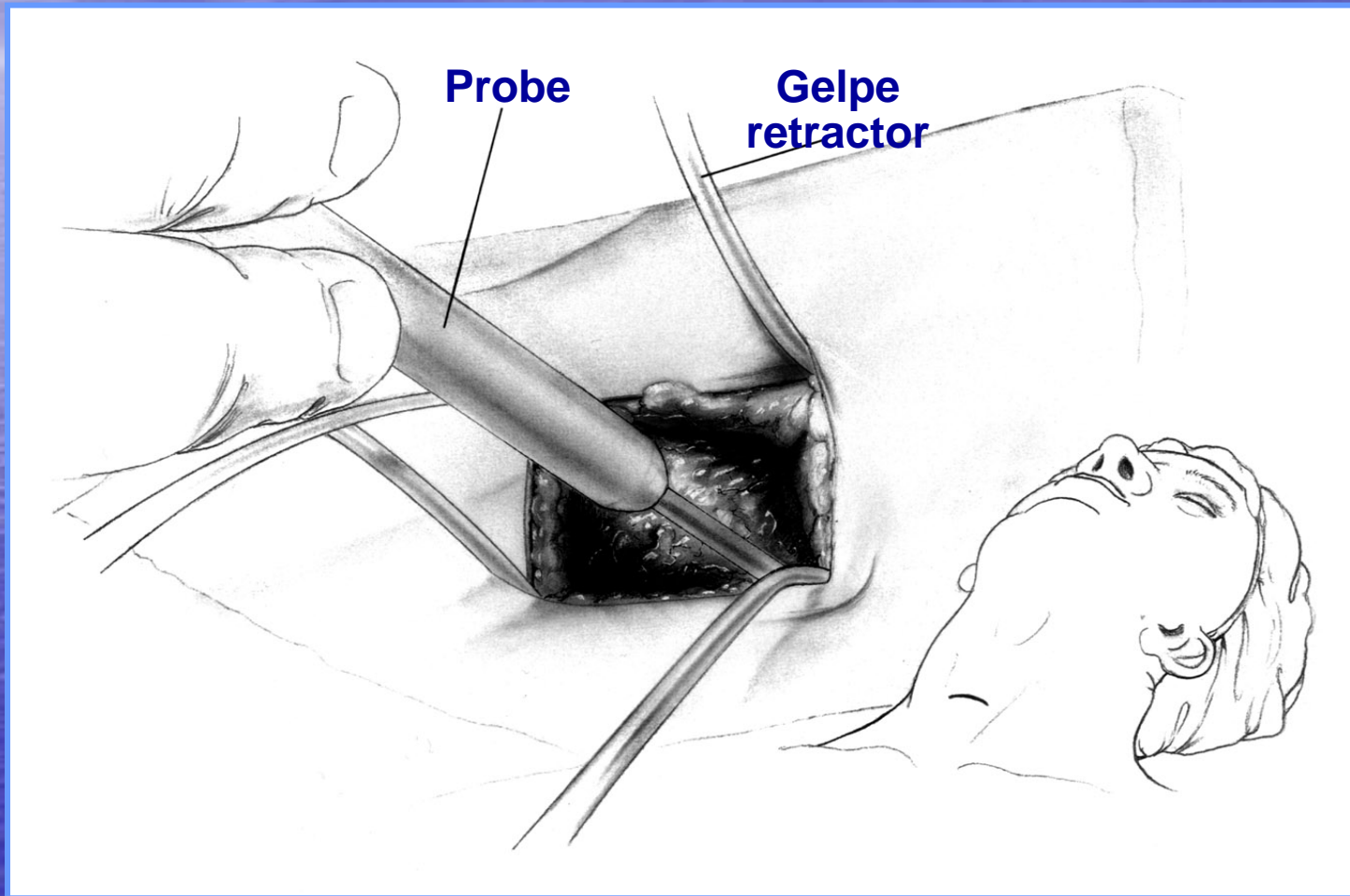
- Rapid results
- Highly reliable: SGD & MGD
- Cost: \$1,000/patient?
- Immulite: \$500



Endoscopic Technique



Radioguided MIP

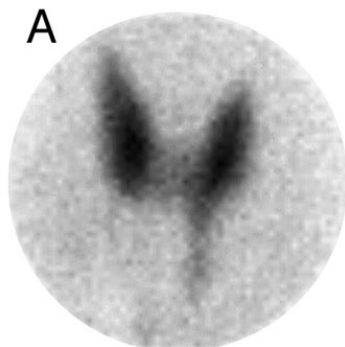


33% failure rate at Mayo Clinic

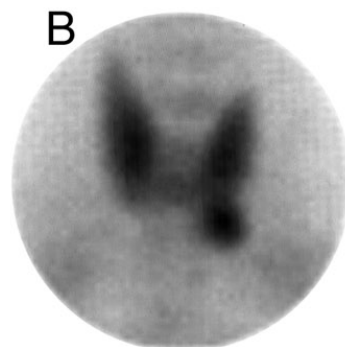
Image-Guided MIP

- Based on highly accurate preop SPS or US images
- IOPTH

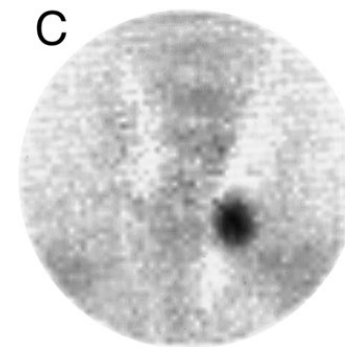
SPS



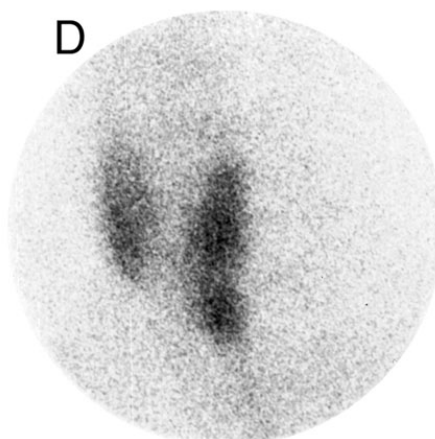
Perchnetate



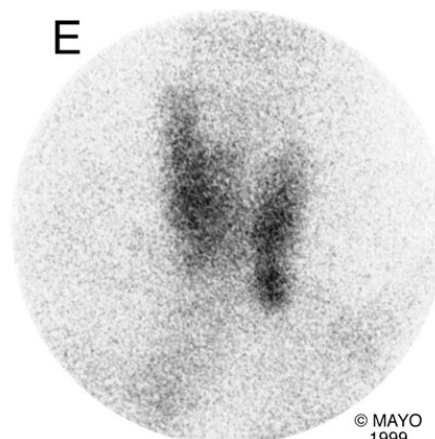
Sestamibi



Subtraction



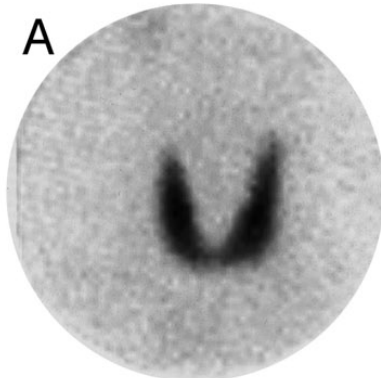
LAO



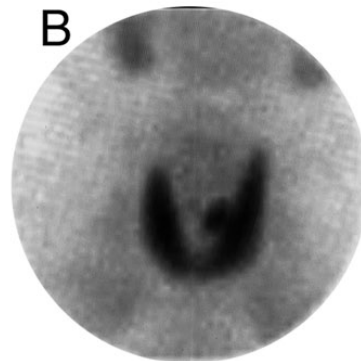
RAO

© MAYO
1999

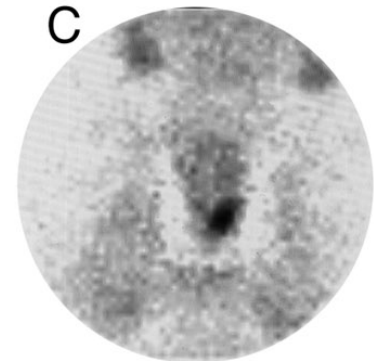
SPS



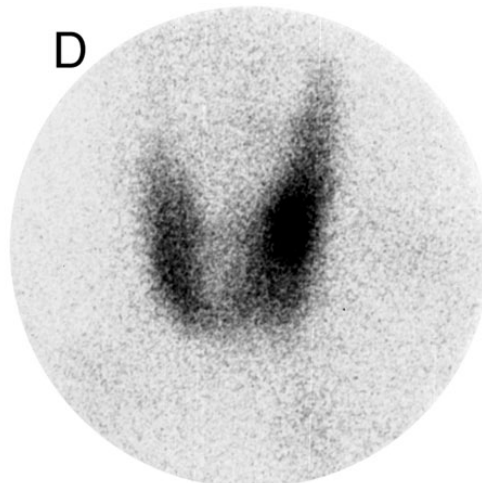
Pertechetate



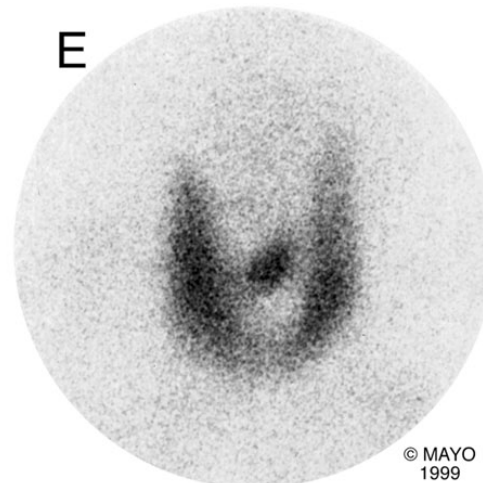
Sestamibi



Subtraction



LAO



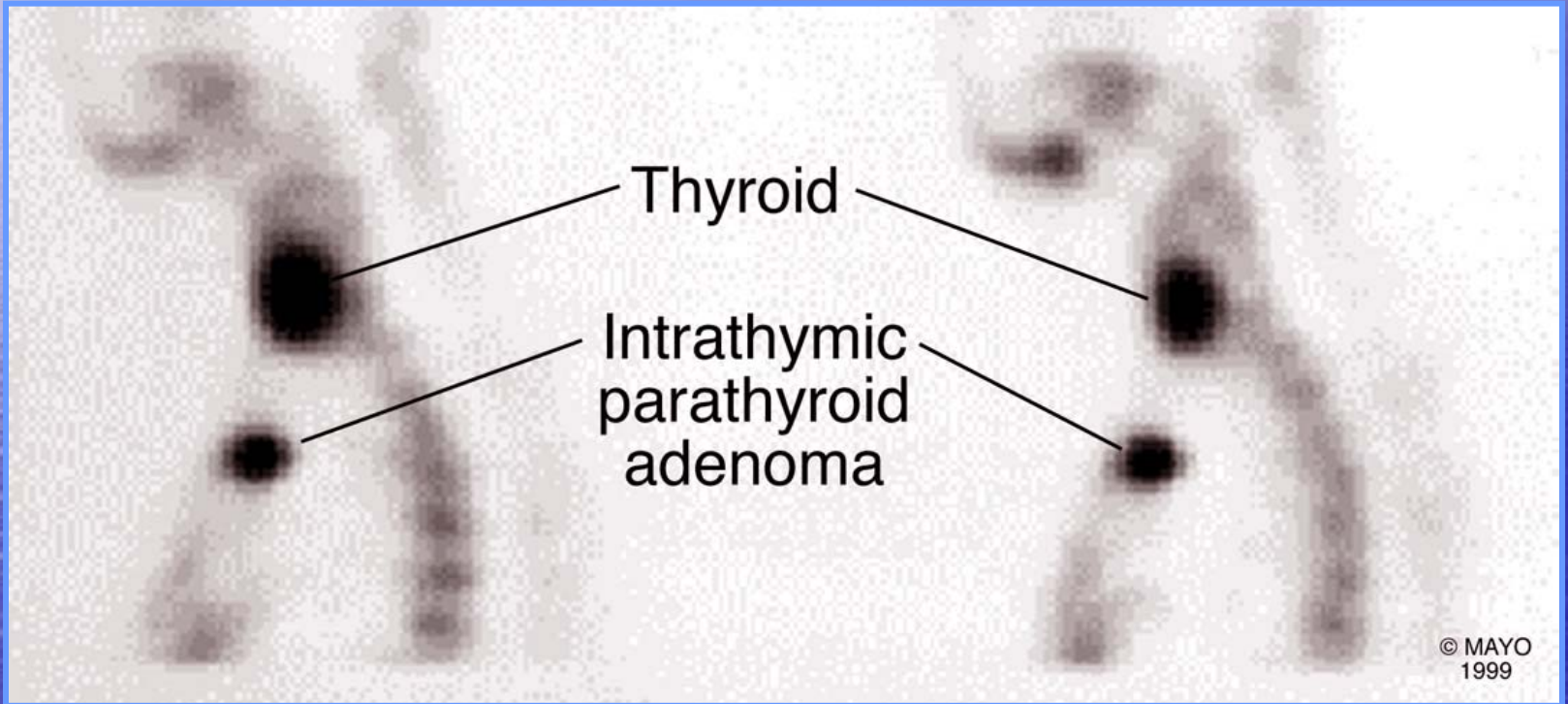
RAO

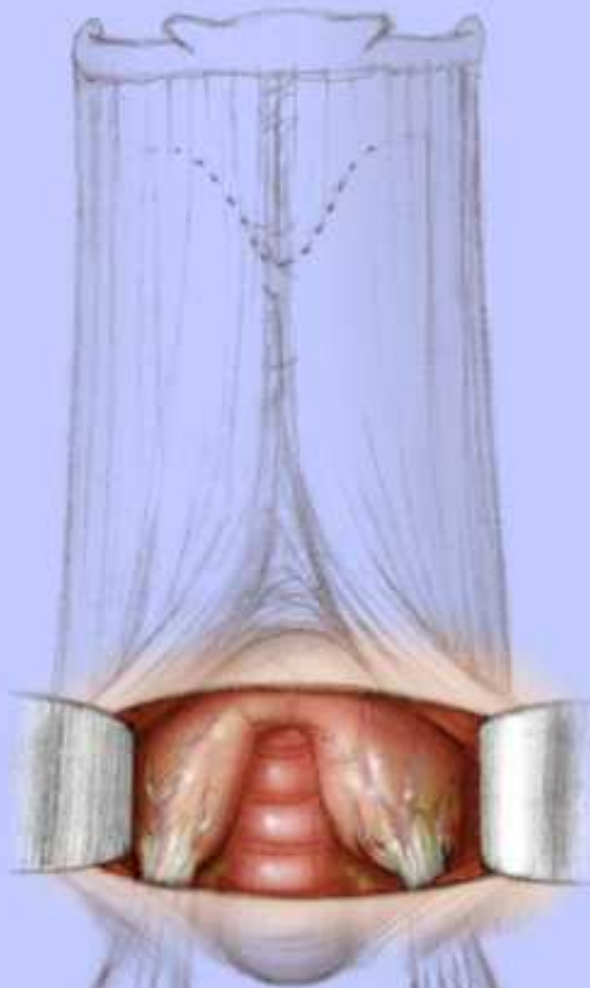
© MAYO
1999

Image-Guided MIP

- 3-cm collar incision/unilateral exploration
- Local anesthesia*/general anesthesia
- Outpatient setting
- Less nausea, pain
- Confirm results with IOPTH

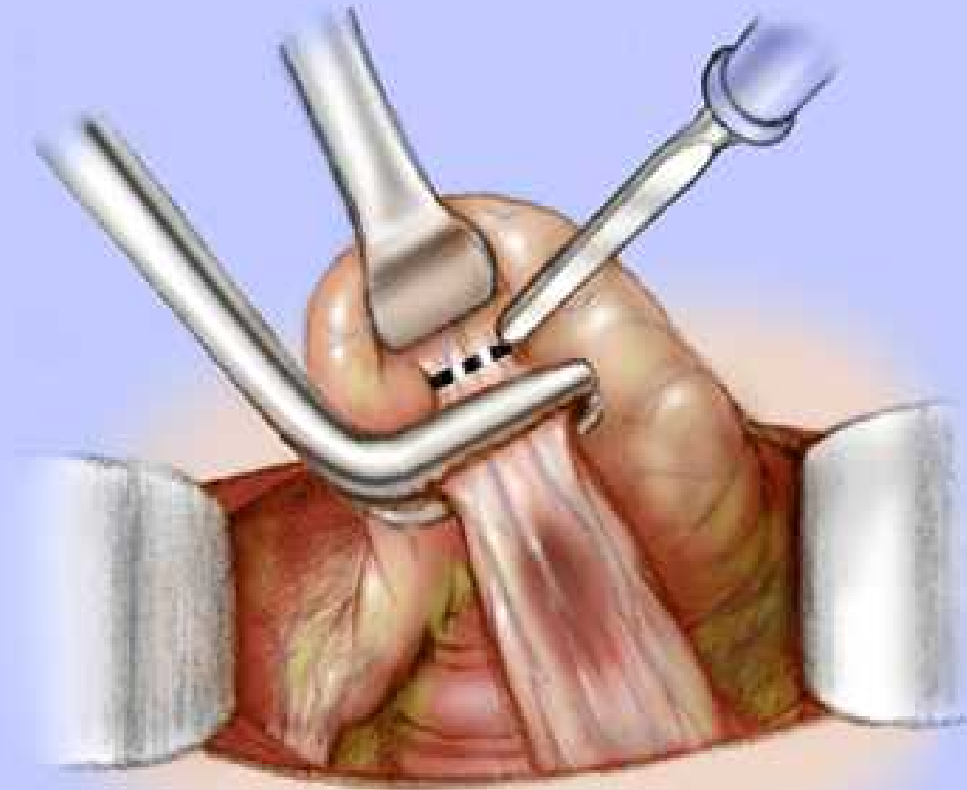
* preferred



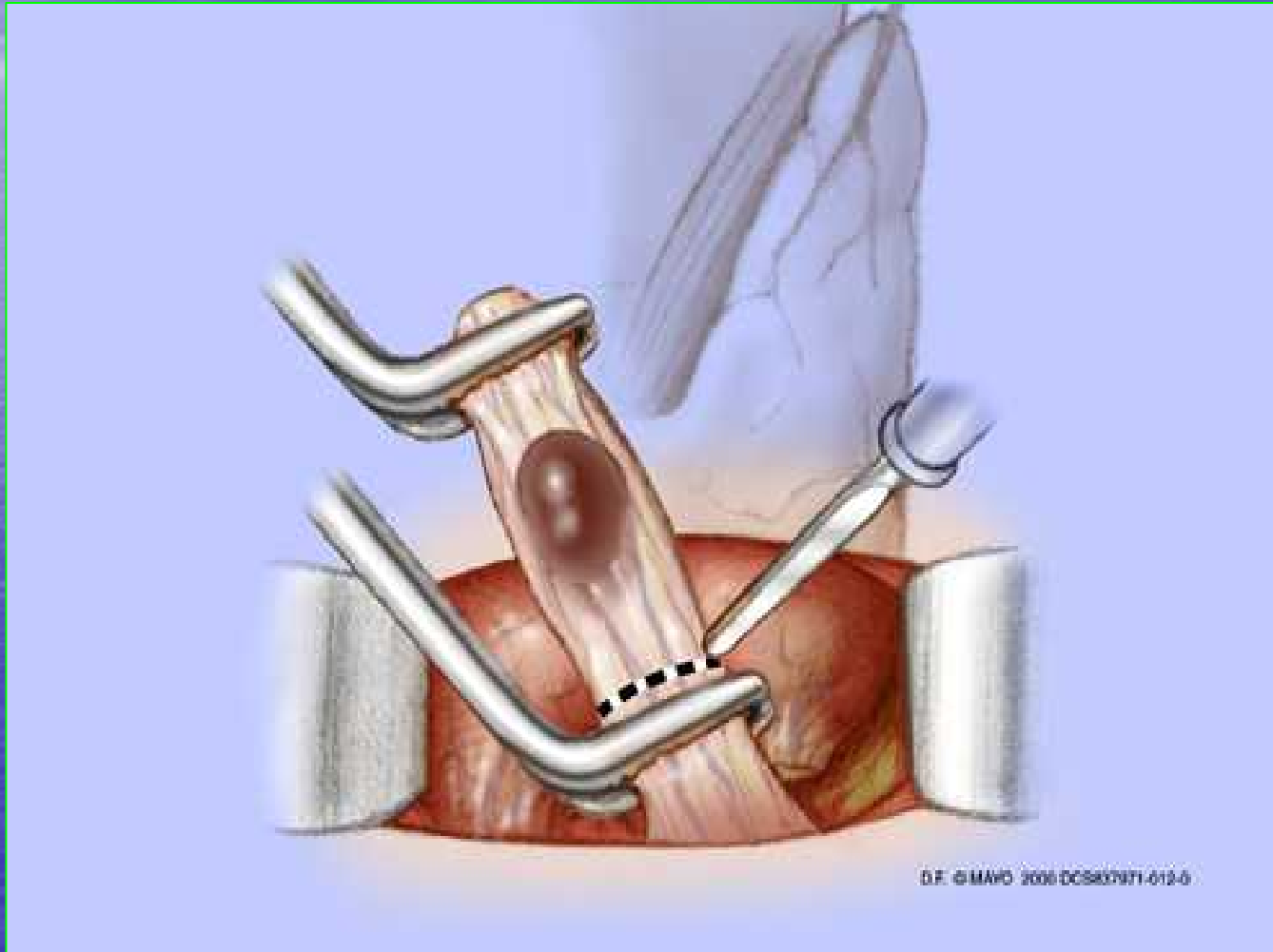


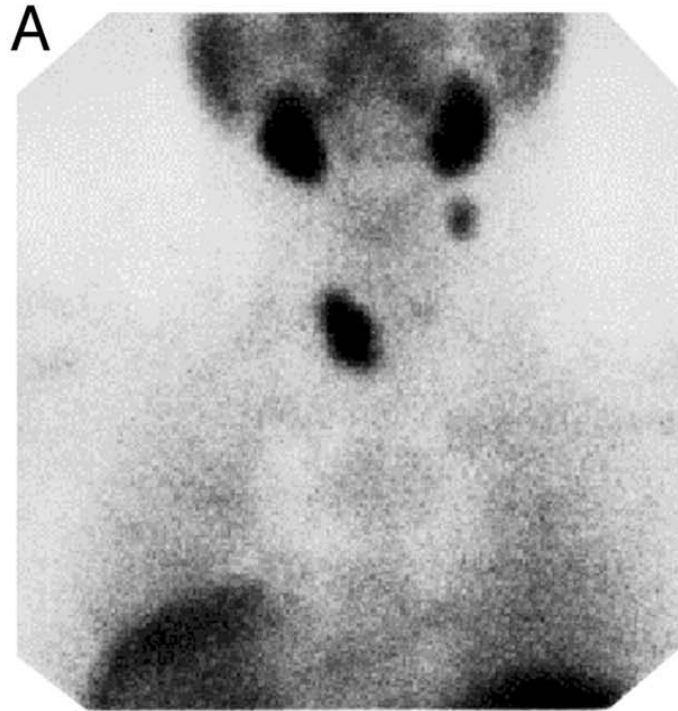
Intrathyroid
parathyroid
adenoma

MIP Technique

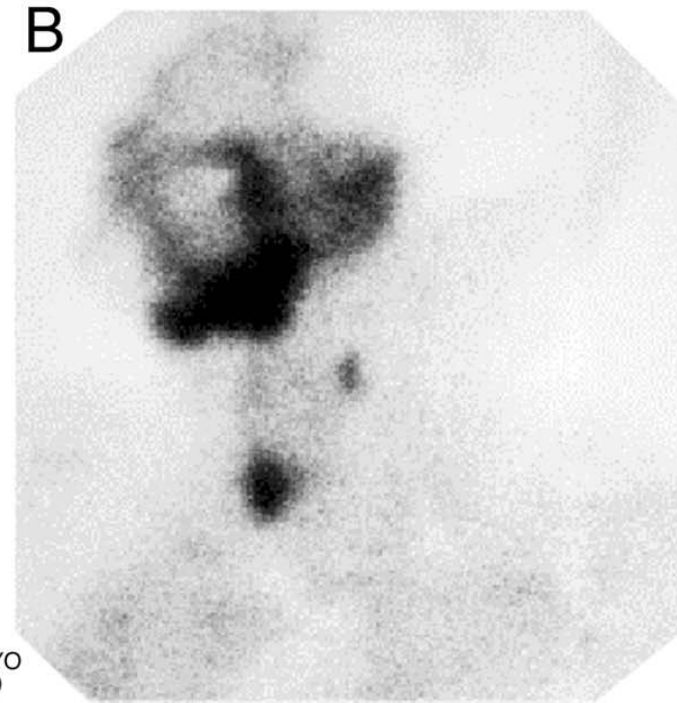


MIP Technique





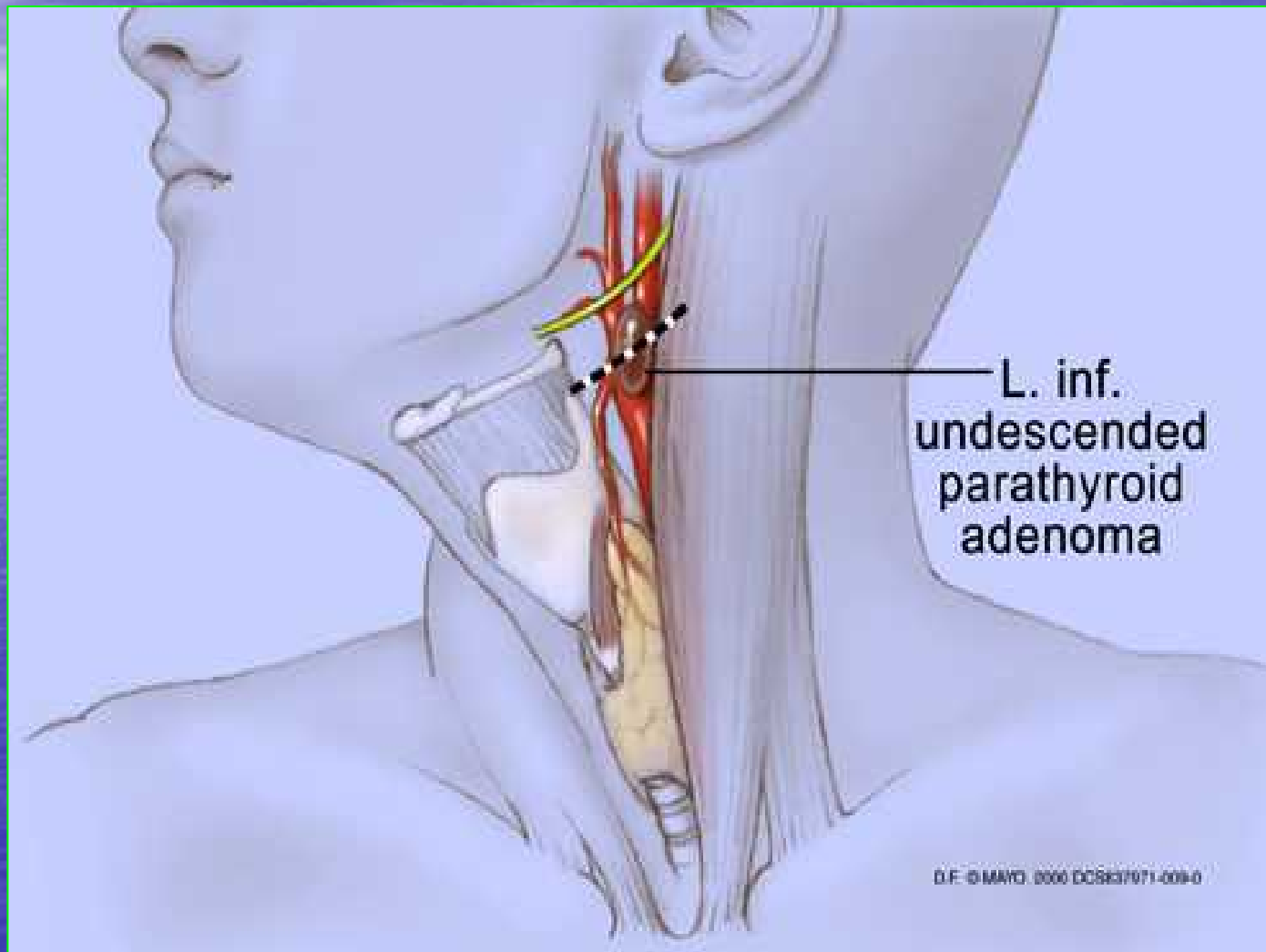
Right Anterior Left



Ant Left Lateral Post

© MAYO
1999

MIP Technique



First Fifty Patients

- Outcomes similar
- Morbidity <1%
- Return to normal
- Overall satisfaction
- Scar satisfaction

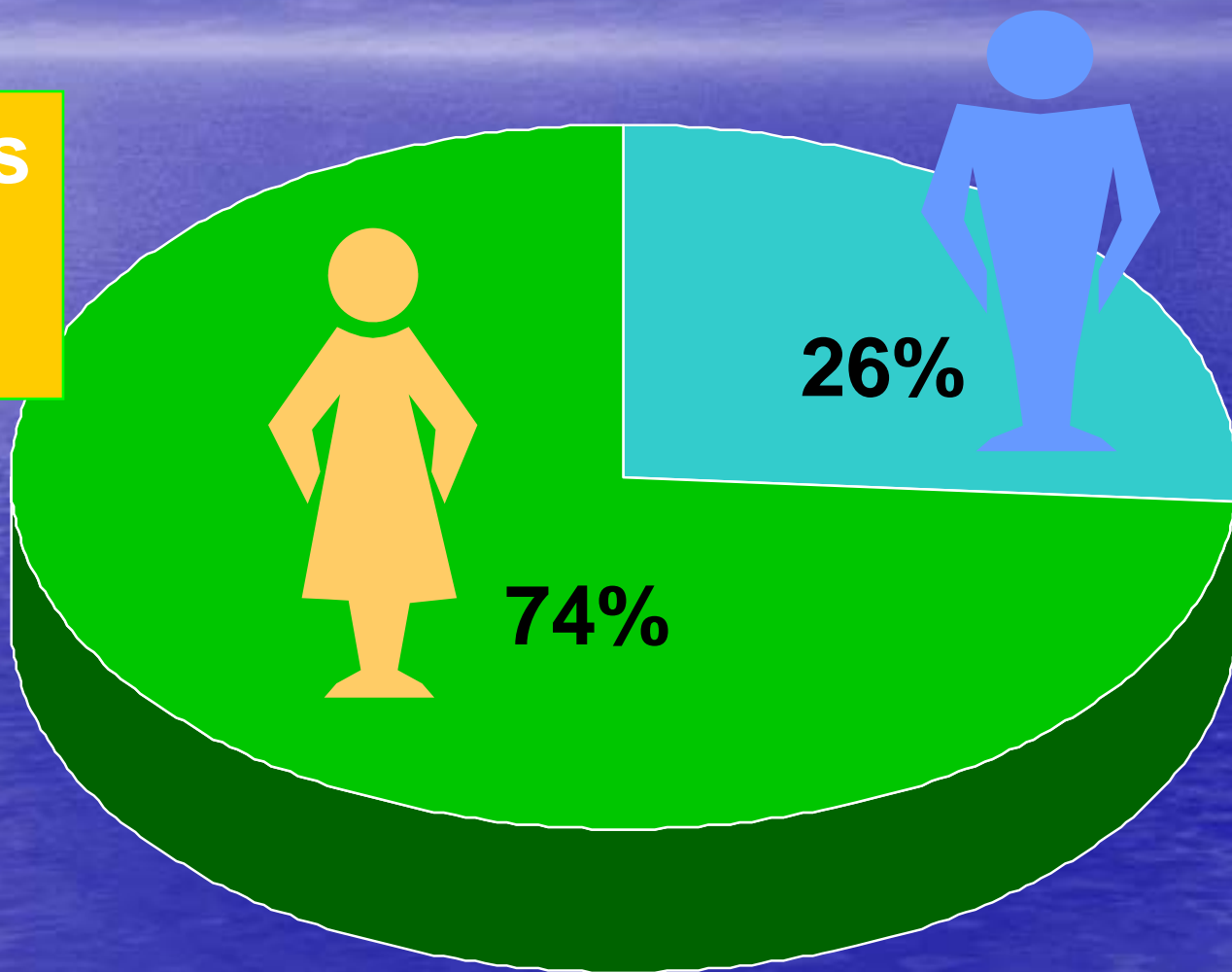
Similar

- Pain and nausea* less in MIP group
- Cosmesis better?

*When performed under local anesthesia

HPT: Mayo 6/98-12/05

2,052 pts
Age 61
(11-97)

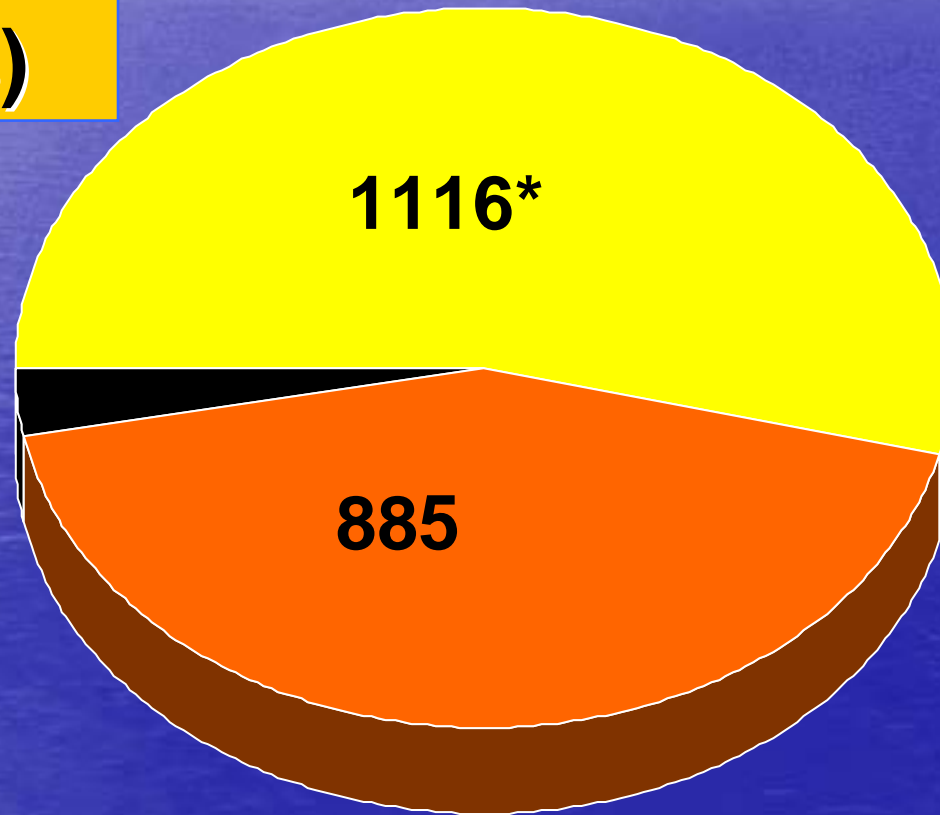


HPT: Mayo Clinic Experience

2,052 pts
(2,065 ops)

Conventional

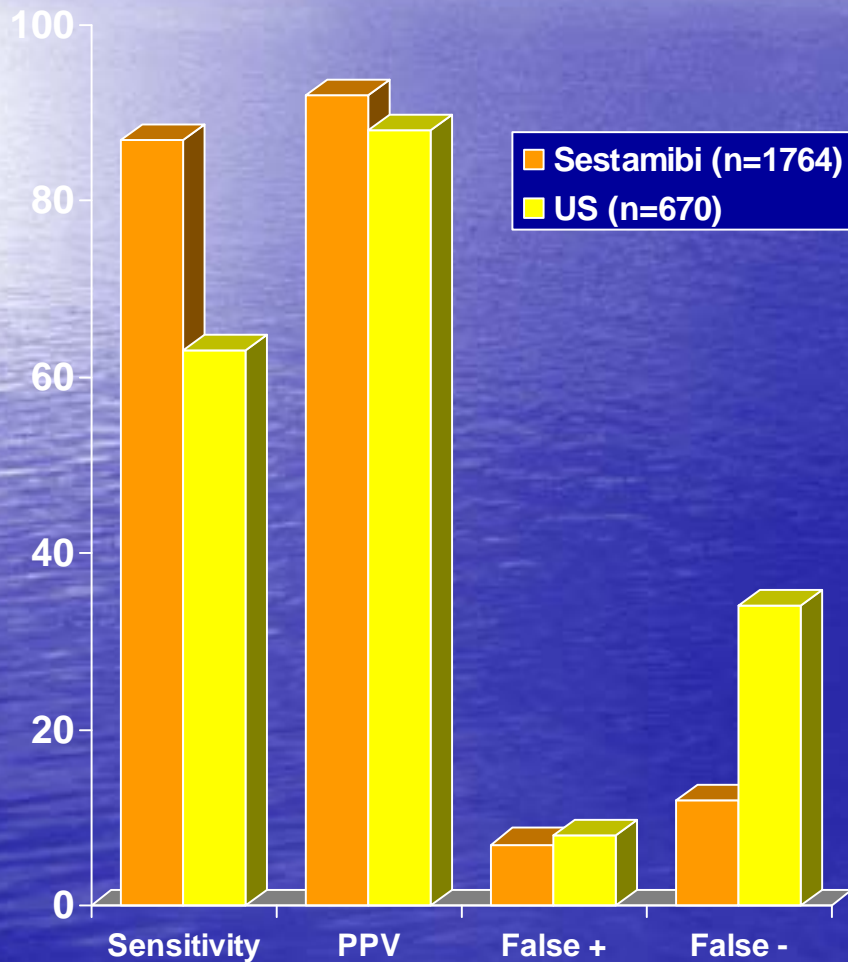
MIP
converted-51



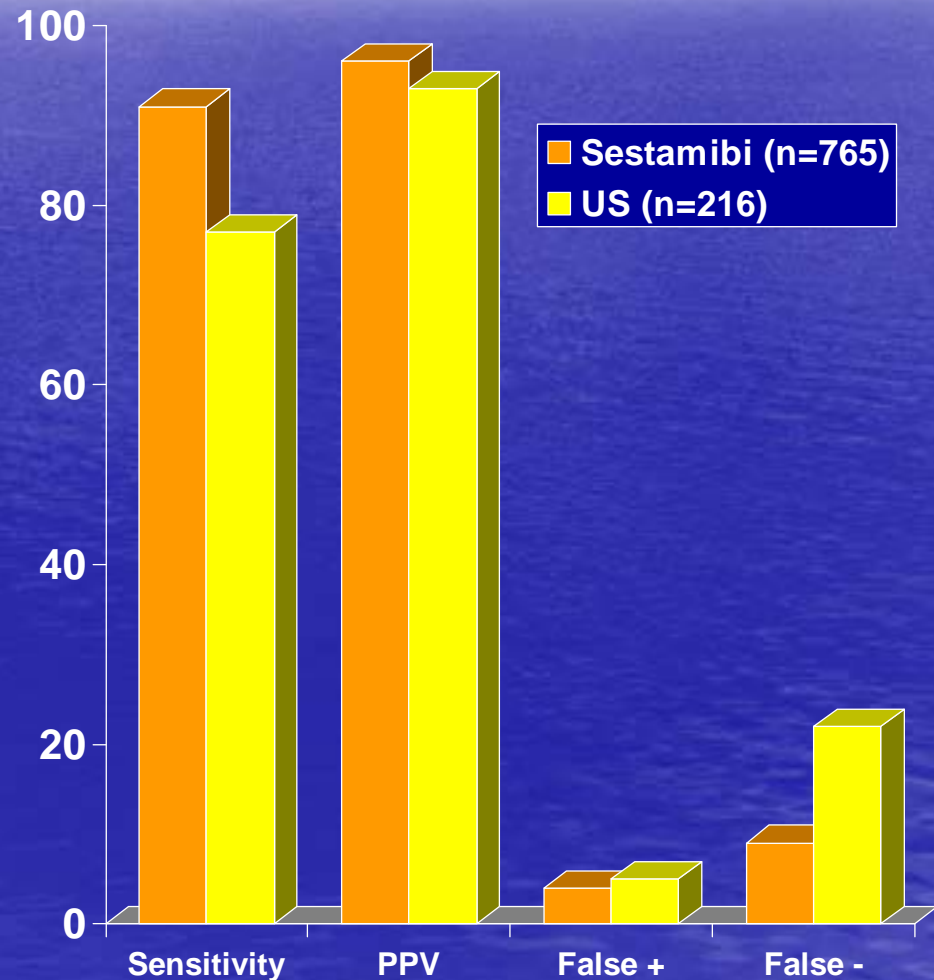
MIP * Includes reops (257 pts)

HPT: Localization

Overall

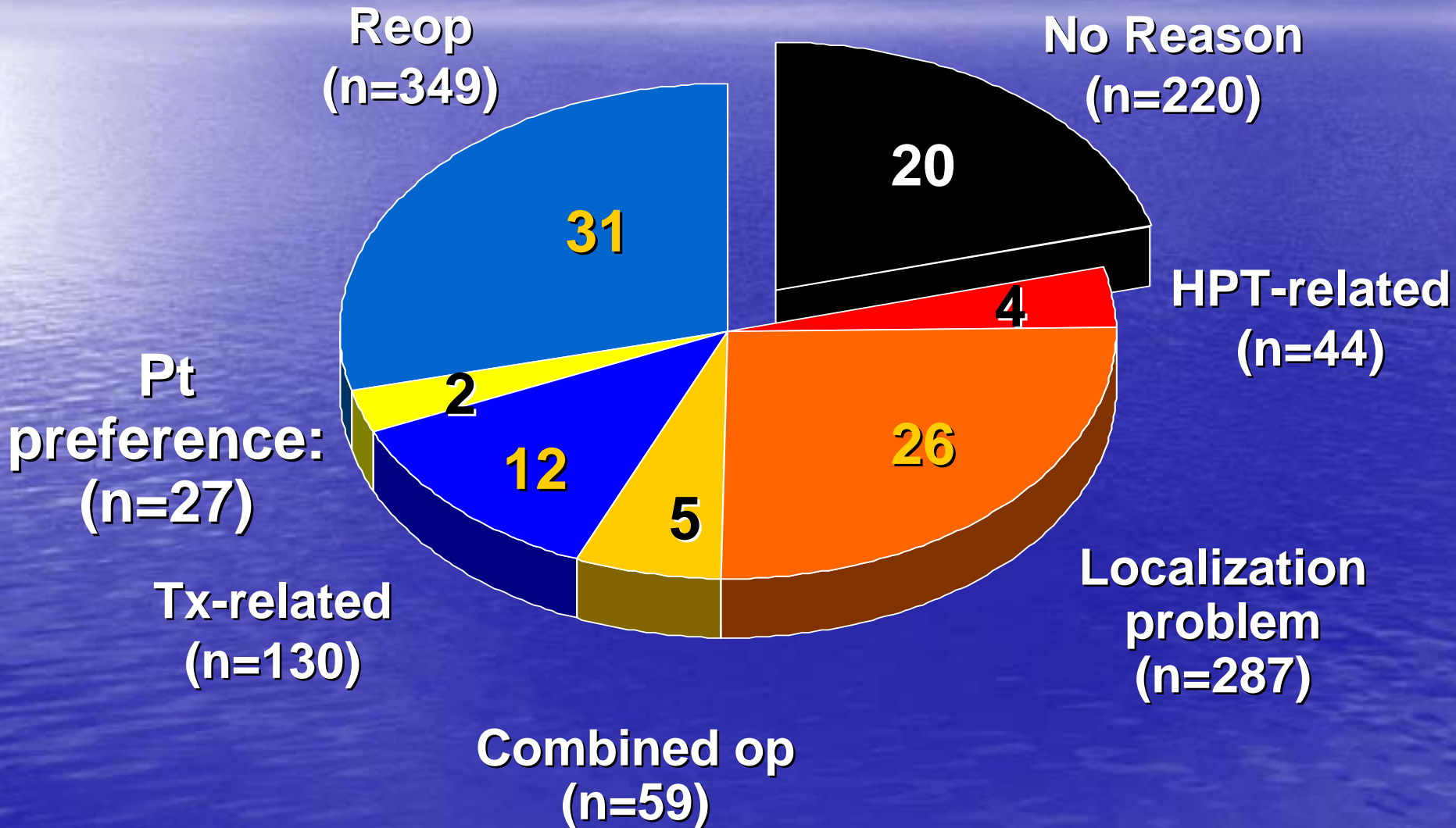


MAP Group



Reasons: Conventional Op

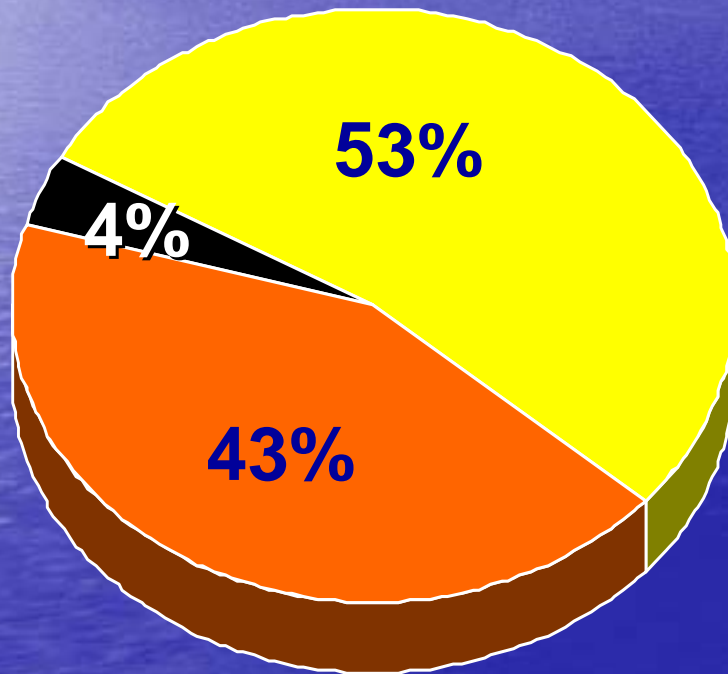
1116 pts (includes reops)



MIP: Length of Stay/Anesthesia

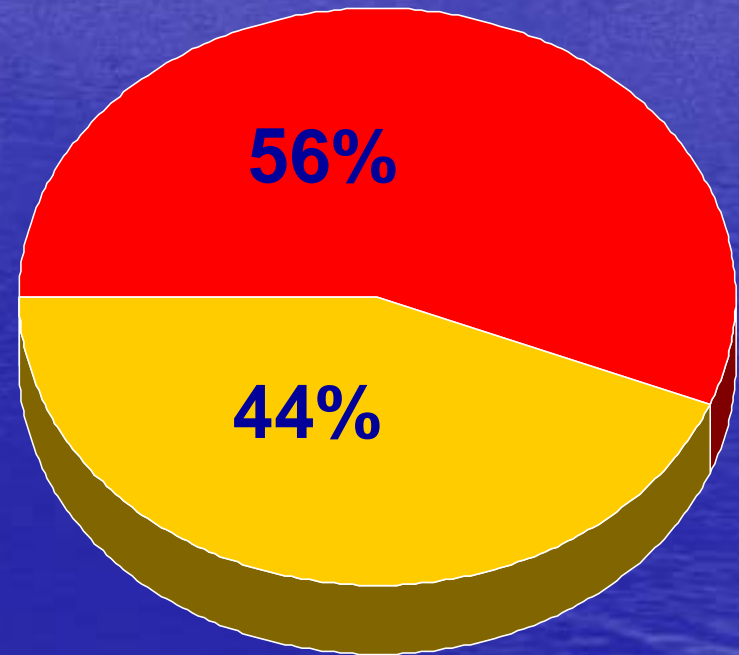
Outpatient

> 1 day



24°

General



MAC (local)

MIP: Methodology

- Influences
 - SPS: 765 cases (88%); Sensitivity 91%, PPV 96%, FP 4%, FN 9%
 - IOPTH: 1302 cases (63%); accuracy: 97%
 - 106 (8.9%) true negatives – most beneficial
 - Gamma-probe inaccurate in 32% of 93 cases

HPT: Success

Cure Rates (2052 patients)

- Conventional (exc reops) 96%
- MIP (exc reops) 98%
- Overall (inc reops) 97%
- MGD 95%

MIP: Assessment

- Advance
 - Estimate 60-70% eligible for image-guided MIP
 - Dependent on high-quality imaging and interpretation
 - IOPTH truly valuable in <10%, but quite reassuring in others
 - With the use of IOPTH, cure should be very little different from standard open procedure
 - γ - probe not valuable in our hands

MIP: Assessment-2

- Added Value
 - Small incision
 - Local anesthesia
 - for majority of patients
 - minimize pain, nausea, mental “fogginess”
 - outpatient
 - General anesthesia if pt still outpatient
 - Expense equivalent or increased

Modest step forward--not a quantum leap

Indications for Standard Exploration

- Negative preoperative imaging
- Concomitant thyroid pathology *
- Family history of endocrinopathy
- Family history of HPT *
- Imaging suggesting MGD *
- History of neck irradiation *
- Certain reoperations

*Relative contraindications for MIP

Parathyroid Incidentaloma

- Solitary---Remove
- MGD---Do Not Remove---Check for Vit. D deficiency and renal insufficiency

Parathyroid Incidentaloma

- **Thyroid Ultrasound Incidentaloma---**
Consider FNA for cytology, iPTH assay and Tg if not planning to operate on thyroid
--Check serum ionized calcium and iPTH
- Look for indications to operate



Verona - October 28, 2006



Asymptomatic Primary Hyperparathyroidism and Parathyroid Incidentaloma

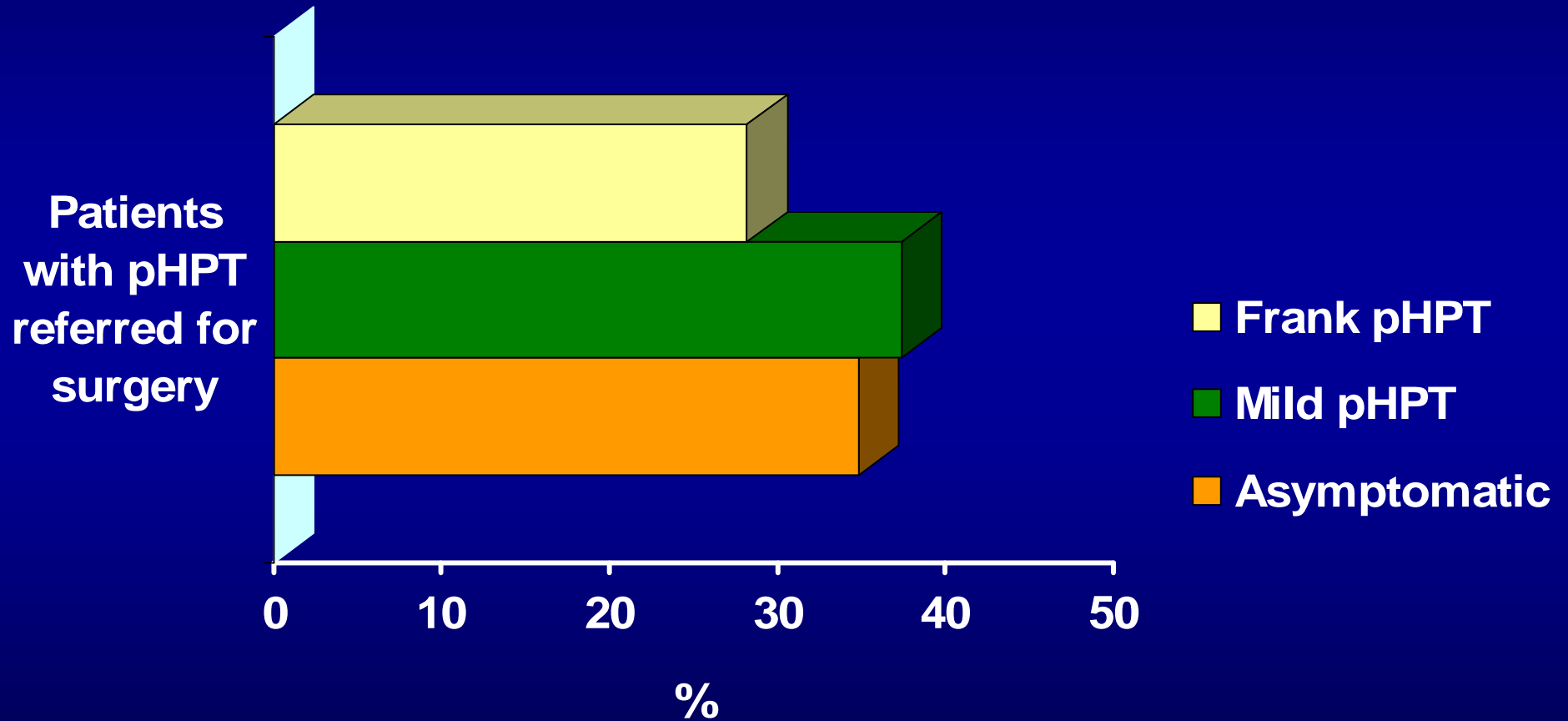
Andrea Frasoldati

Unità Operativa di Endocrinologia

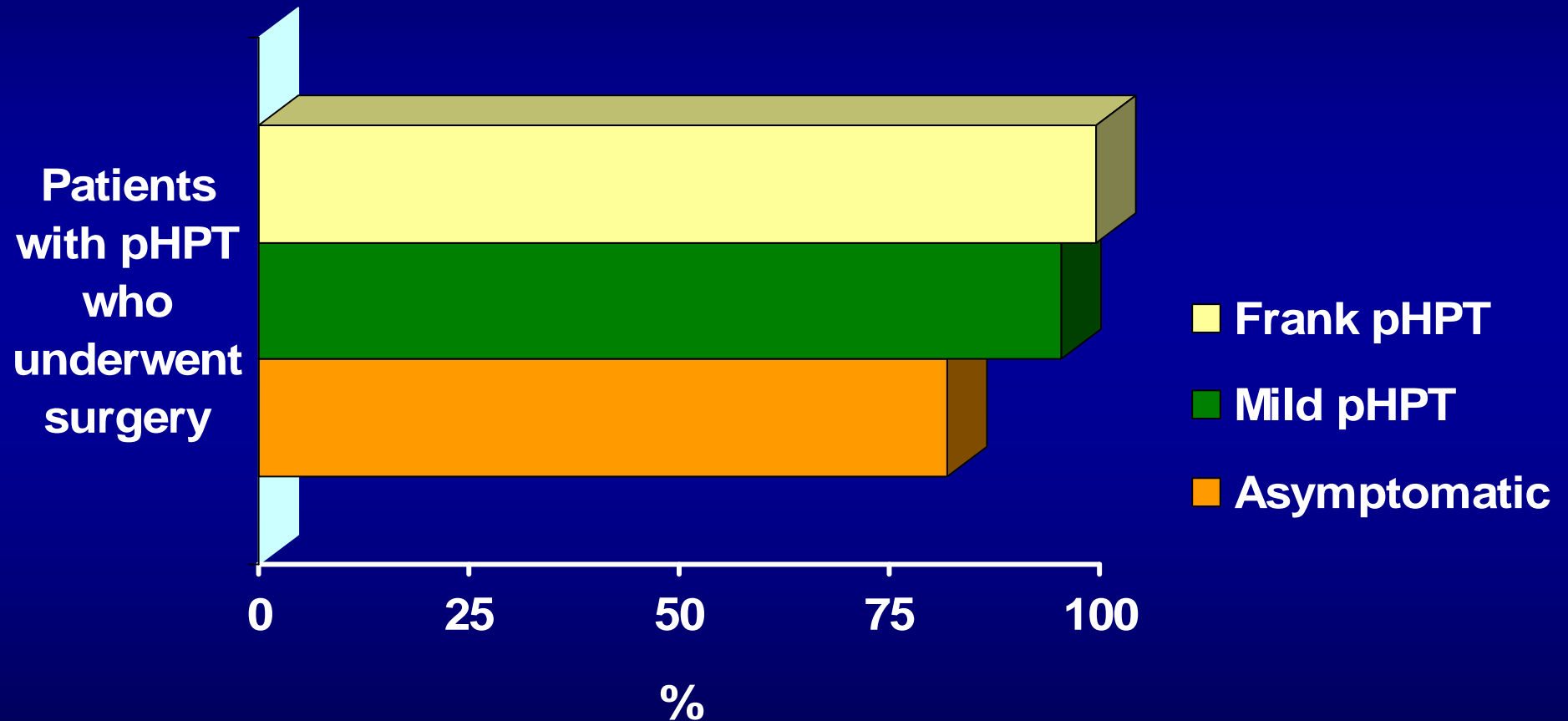
Arcispedale S. Maria Nuova Reggio Emilia

**Asymptomatic pHPT:
to treat or treat not?**

Profile of a clinical practice: Thresholds for surgery in pHPT



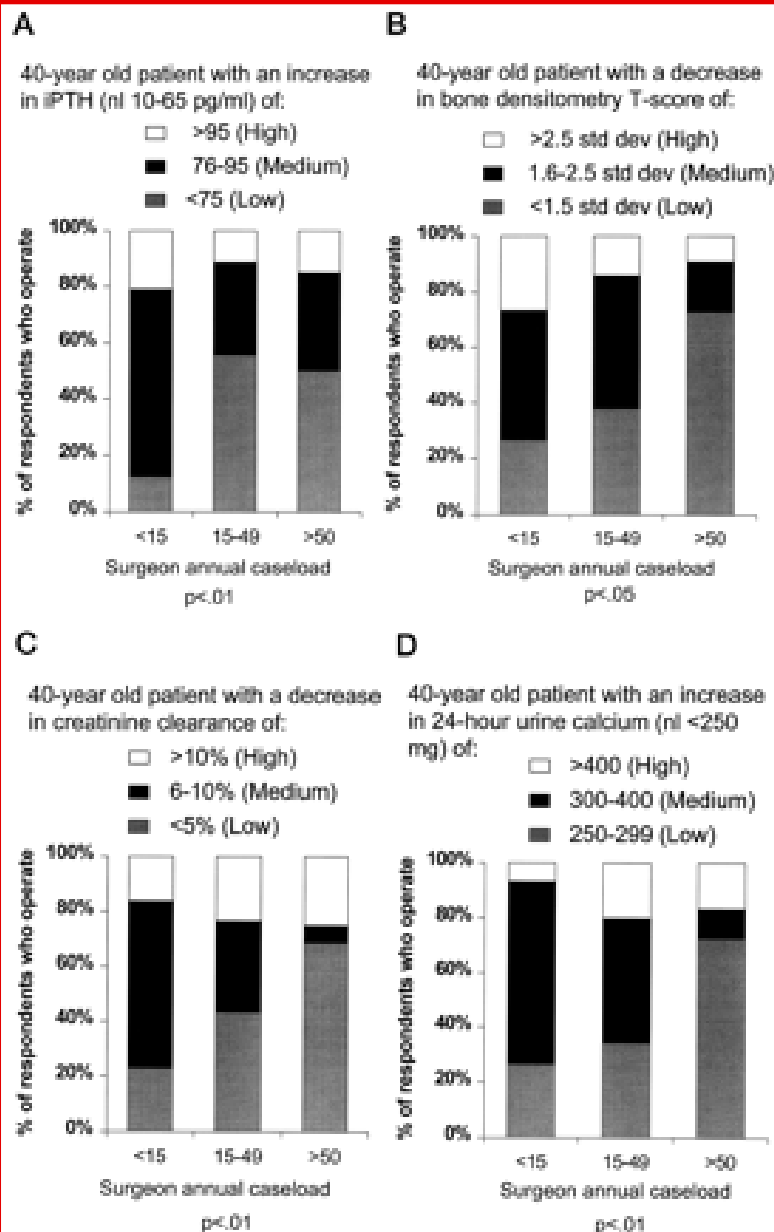
Profile of a clinical practice: Thresholds for surgery in pHPT



PROFILE OF A CLINICAL PRACTICE

Thresholds for Surgery and Surgical Outcomes for Patients with Primary Hyperparathyroidism: A National Survey of Endocrine Surgeons

JULIE ANN SOSA, NEIL R. POWE, MICHAEL A. LEVINE, ROBERT UDELSMAN,
AND MARTHA A. ZEIGER



High volume surgeons have significantly lower thresholds for surgery

Sosa JA et al., JCE&M, 1998 83:2658-2665

Analysis of cost/effectiveness in managing sporadic asymptomatic pHPT

	Cost (€)	QALY	Δ€	ΔQALY	Δ€/ΔQALY
Follow up/BNE	2538	15.7469			
BNE	3537	17.0329	999	1.2860	776
Follow-up/UNE	2563	15.7543			
UNE	3766	17.1181	1203	1.3638	882

Sejean et al., Eur J Endocrinol 2005, 153:915-927

What if we do not refer to surgery patients with asymptomatic pHPT?

- a. Do untreated patients have an increased mortality rate?
- b. Do asymptomatic patients progress to overt disease?
- c. Does surgery have a protective effect on pHPHtarget organs?

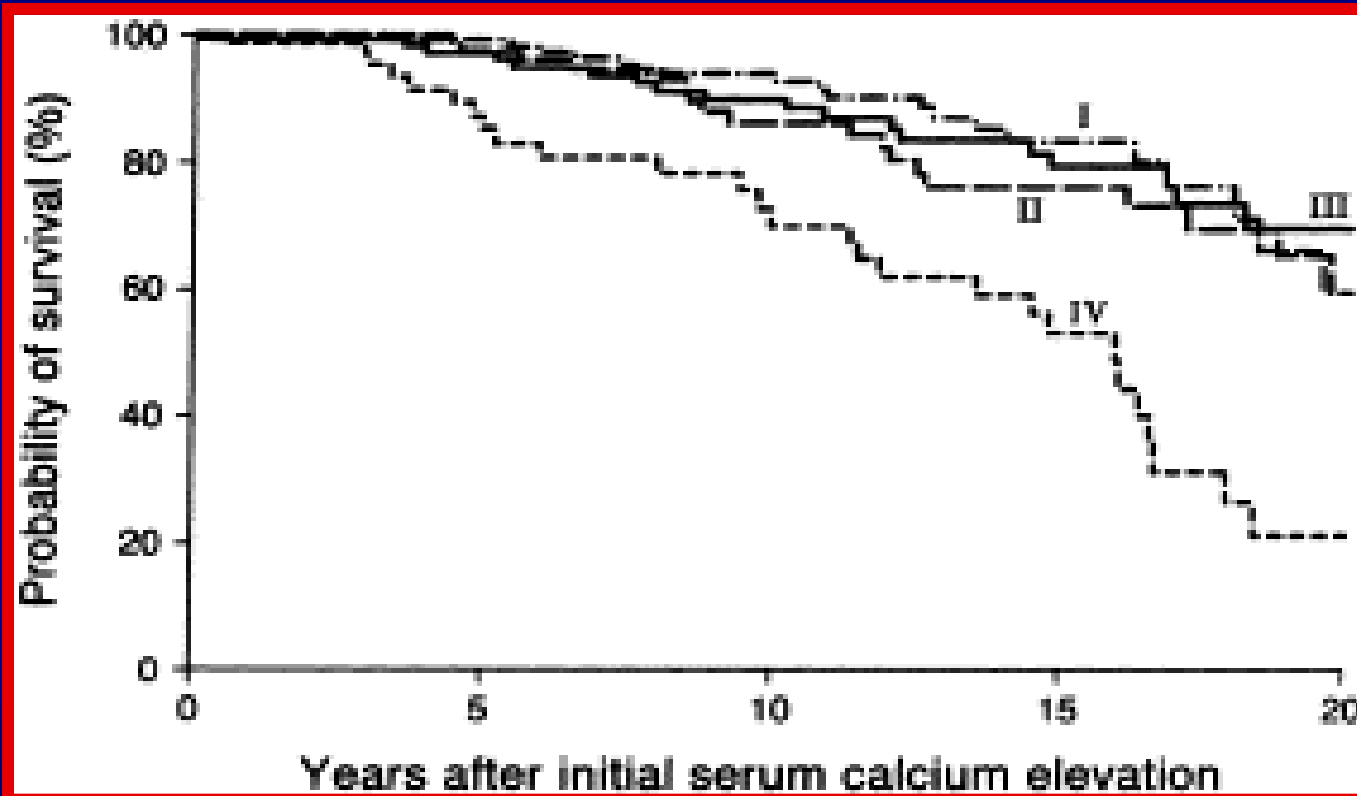
a. Do untreated pHPT patients have an increased mortality rate?

Relative Risk of death among patients with primary hyperparathyroidism

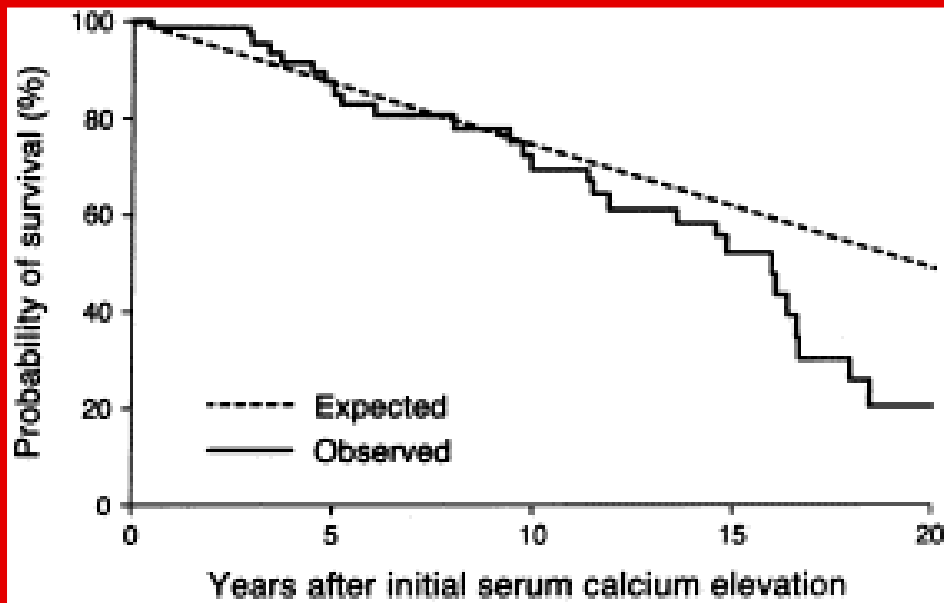
Causes of death	Relative Risk (95% confidence interval)
Cancer	0.58 (0.39-0.89)
Cardiovascular Disease	0.60 (0.45-0.79)
Respiratory Disease	0.97 (0.53-1.63)
Gastrointestinal Disease	0.88 (0.29-2.06)
Other Causes	1.00 (0.63-1.51)
All causes	0.67 (0.59-0.83)

Wermers et al., Am J Med 1998

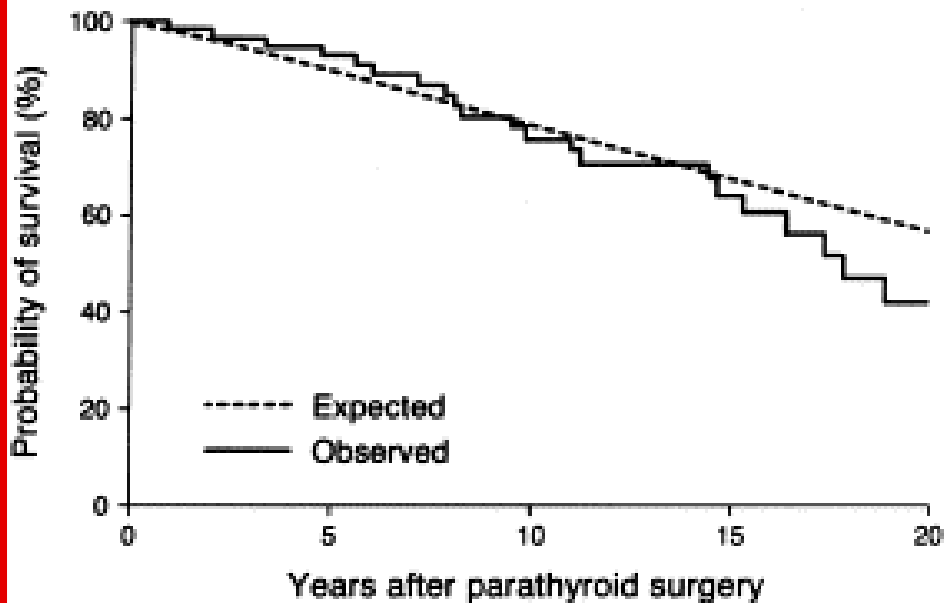
Survival as a function of serum calcium levels



- I = 10.2-10.5 mg/dl
- II = 10.6-10.7 mg/dl
- III = 10.8-11.1 mg/dl
- IV 11.2-16.0 mg/dl



(A)

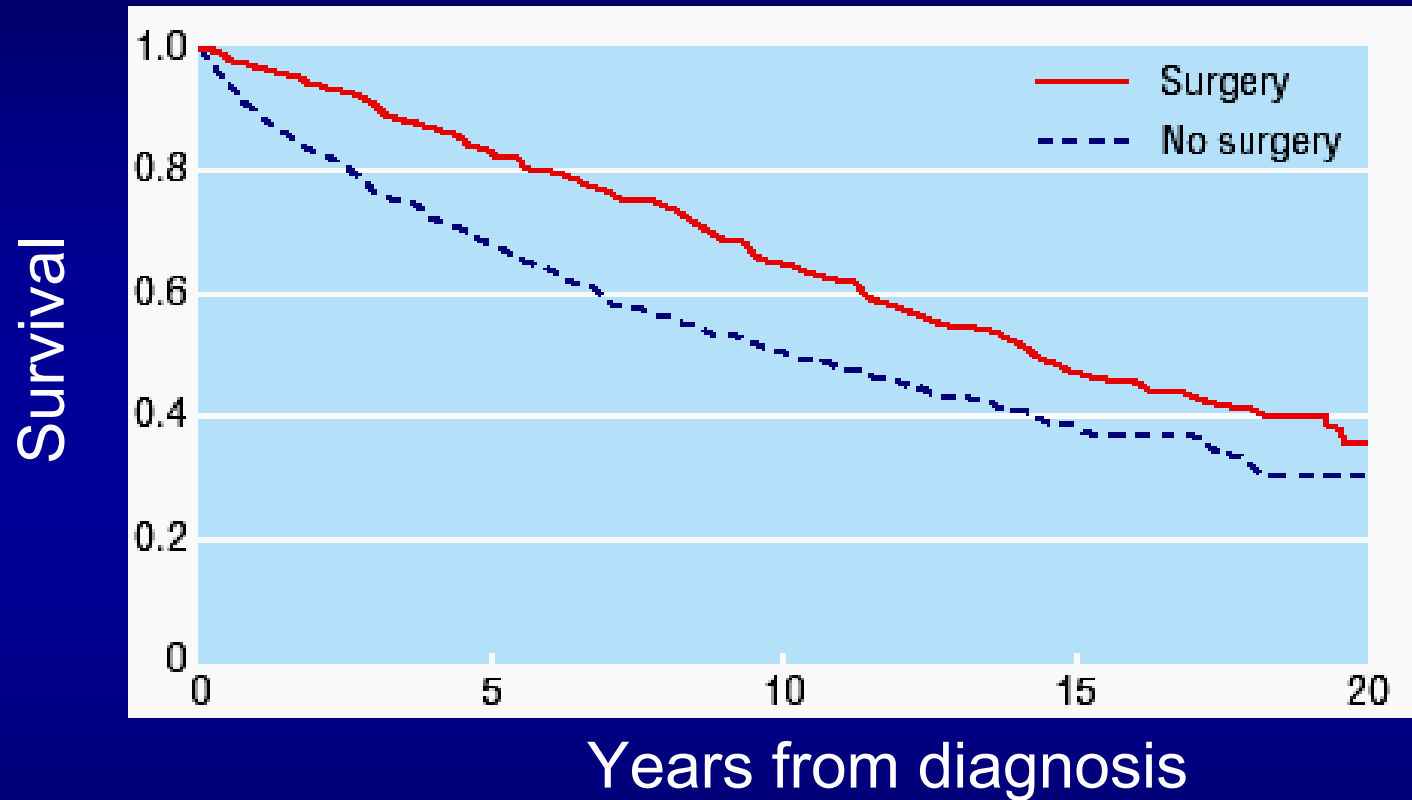


(B)

Survival among pts with highest serum calcium levels before (A) and following (B) parathyroid surgery

Wermers et al., Am J Med 1998

Survival in surgically and conservatively treated patients with primary HPT



**Death n. during follow-up: 591 (31%) surgically treated pts.
474 (37%) conservatively treated pts.**

Do untreated patients with mild/asymptomatic pHPT have an increased mortality rate?

No data indicating increased mortality in patients with mild/asymptomatic pHPT are available.

Survival may be affected by higher serum calcium levels.

b. Do asymptomatic patients progress to overt disease?

A 10-year prospective study of pHPT with or without parathyroid surgery.

- 121 patients with pHPT (asymptomatic = 101) followed-up for 10 years
- 61 (= 50%) underwent parathyroidectomy
- 60 (= 50%) not operated 52 asymptomatic



**No progression of disease in 38 (= 73%) patients
No kidney stones nor bone fractures**

Approximately one quarter of pts. did have some progression

Mild asymptomatic pHPT is not a risk factor for vertebral fractures.

174 consecutive patients (mean age, 62 years) with mild pHPT diagnosed in 1976-1985 not referred to surgery

The prevalence of vertebral fractures was 1.7%, i.e. not higher than in control subjects



The risk for vertebral fractures is not a reason to recommend surgical intervention in patients with asymptomatic pHPT.

Lack of biochemical progression or of accelerated bone loss in mild asymptomatic pHPT

n = 80 Patients with asymptomatic pHPT
Mean follow up = 46 months (1-11 yr)

- no biochemical change,
- no decline in forearm BD
- no increase in overall death rate



Short period of disease progression followed by disease stability? Data support the decision to withhold surgical intervention.

Do asymptomatic patients progress to overt disease?

In the few studies available, progression to overt disease takes place in a minority (20-25%) of subjects. In most patients, the disease is apparently stable.

c. Does surgery have a protective effect on pHPT target organs?

Follow-up study of bone mass in patients with mild asymptomatic hyperparathyroidism

48 women with asymptomatic HPT 26 operated on, 22 observed.
3 and 17 years follow-up

3 year follow-up BM ↑ in operated pts
unchanged in non operated pts.

17 year- follow BM \cong in both groups



Parathyroidectomy had an initial positive effect on bone mineralisation, but no long-term advantage

Elvius et al., Eur J Surgery 1995, 161:863-9.

Forearm bone density in pHPT: long-term follow-up with and without parathyroidectomy

108 patients who underwent successful surgery vs. 108 who remained unoperated

The Z-score was significantly reduced in both groups. In the unoperated patients BMD fell significantly but there was no change in Z-score, indicating that the rate of bone loss was the same as expected for normal ageing.



Successful parathyroid surgery may lead to abatement of the excess fracture risk, but the benefit to individual patients will depend mainly on their remaining life expectancy.

Does surgery have a protective effect on pHPT target organs?

Limited beneficial effects of surgery on bone densitometry are reported.

A favourable impact of surgery on non-classical target organs is controversial

Symptoms and associated conditions in patients with pHPT

Symptoms

Fatigue

Musculoskeletal aches/pains

Dyspepsia

Polydipsia

Constipation

Polyuria

Anorexia

Pruritus

Depression

Memory loss

Associated Conditions

Nephrolithiasis

Osteopenia

Weight loss

Gout

Pancreatitis

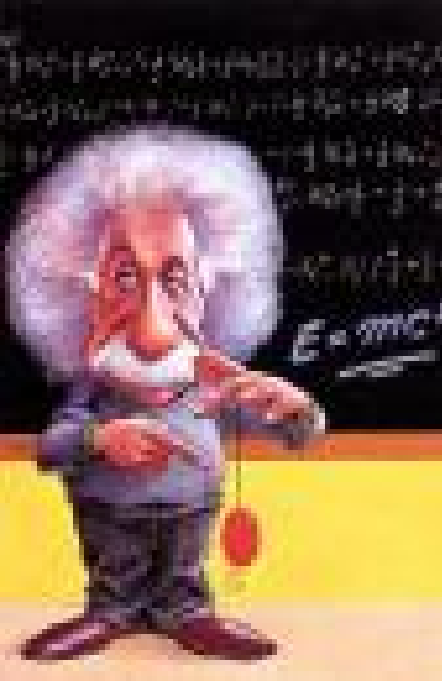
Bruising

Hypertension

Hematuria

Left ventricle mass indexes (LVMI) in patients with pHPT

Study	N pts	Calcium mg/dl	PTH pg/ml	pLVMI
Stefenelli	54	11.9	231±208	<0.001
Dalberg	44	11.1	82±	0.03
Piovesan	43	11.2	161 ± 73	<0.05
Almqvist	25	10.5	82 ± 34	<0.05
Dominiczak	23	10.9	5.8 (U/I)	0.03
Nilsson	30	10.5	77 ±24	0.06
Barletta	14	11.5	215 ±188	NS
Nuzzo	20	12.1	280 ±165	NS



Subclinical cognitive dysfunction in pHPT
(Brown et al., 1987)

Mnesic and learning functions improved after
parathyroidectomy (Numann et al., 1984)

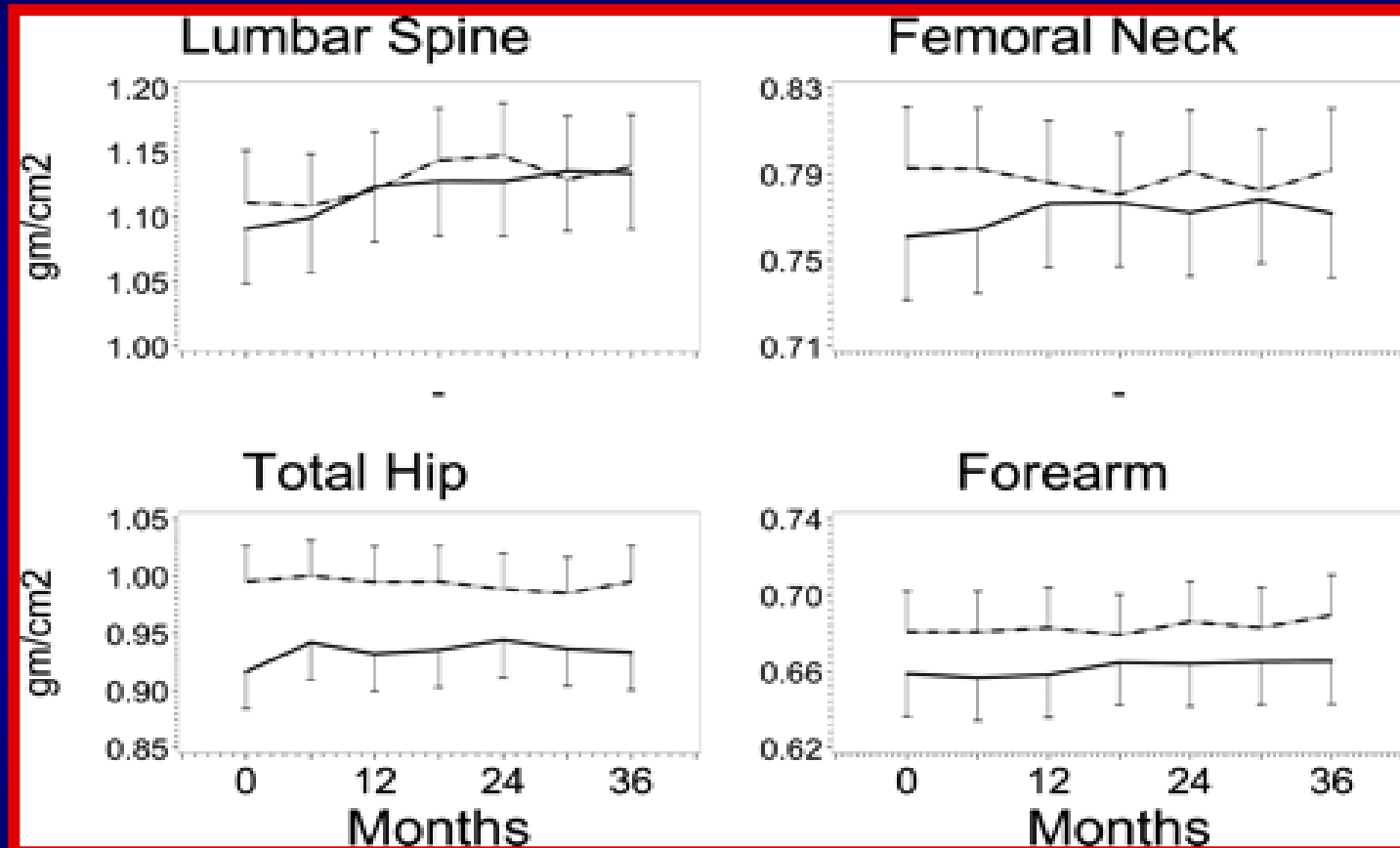
Sleep disturbances (Joborn et al, 2000)



Increased incidence of depression: beneficial
effects of parathyroidectomy (Clark et al., 1995;
Pasieka & Parsons, 1998; Quiros et al., 2003)

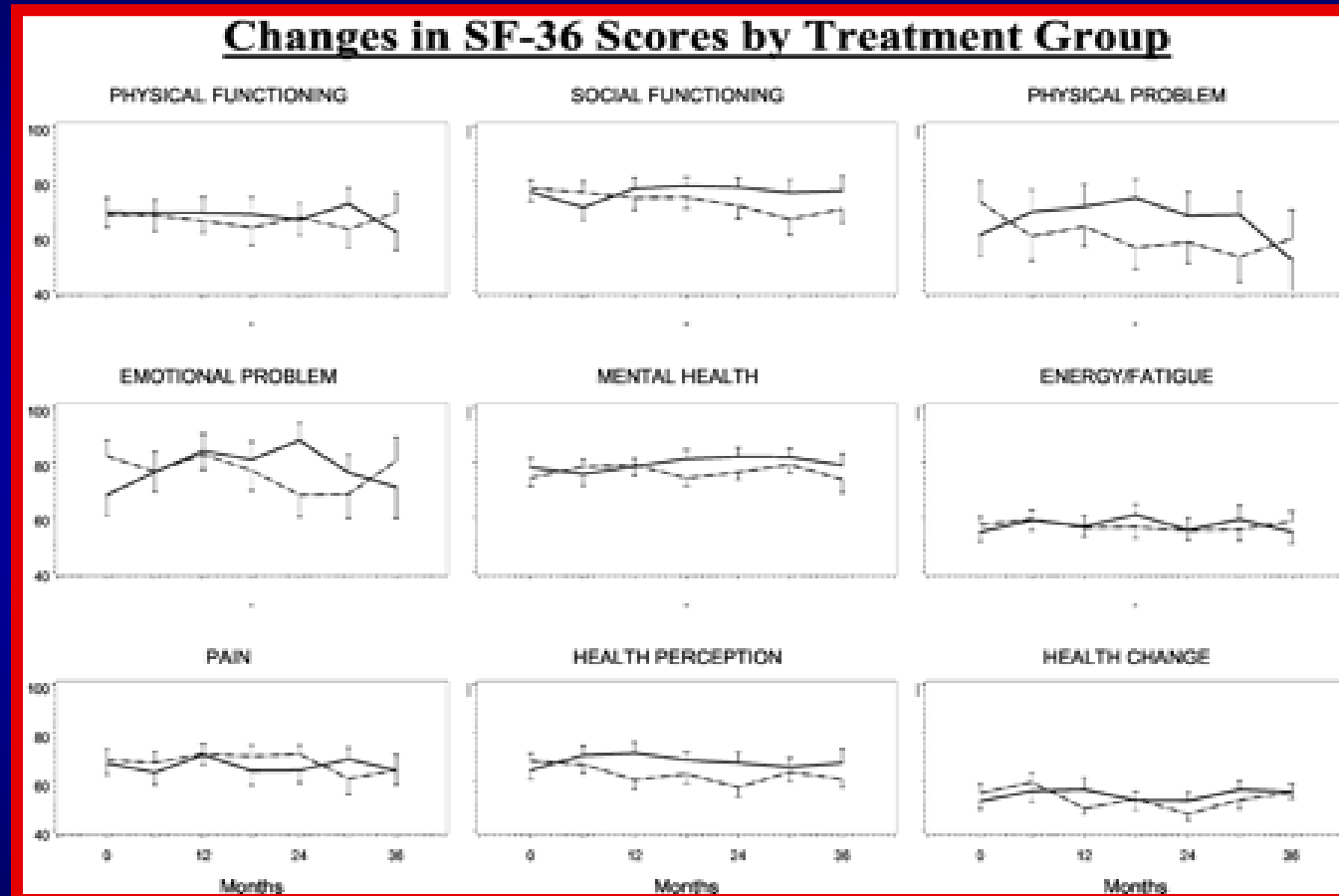
Increased psycho-social performance (SF-36)
with parathyroidectomy (Talpos et al., 2000)

Mild asymptomatic pHPT: changes in BMD



Parathyroidectomy : **solid line** No surgery: **dashed lines**.

Mild asymptomatic pHPT: Changes in SF-36 scores



Parathyroidectomy : **solid line** No surgery: **dashed lines**.
A higher score indicates better quality of life.

Limitations of the study

1. Problems in patients recruitment
2. Sample size too small and follow-up period too short (<3 yr) to assess other outcome variables such as nephrolithiasis, fractures, morbidity, and mortality.
3. Social and emotional benefits of surgery possibly due to a placebo effect



The ultimate balance of the risks and benefits of parathyroidectomy in patients with mild/asymptomatic pHPT can be determined only by a larger, longer-term, multicenter study

Considerations in favour of a “wait and see” attitude in mild/asymptomatic pHPT

- **Lack of consistent evidence of increased mortality rate in mild/asymptomatic pHPT**
- **Controversial evidence of increased morbidity with time**
- **In some instances, asymptomatic, non progressive pHPT may be secondary to acquired or genetically determined changes in calcium homeostasis**

***Asymptomatic pHPT: non surgical
treatment options***



Pharmacological tools for asymptomatic pHPT

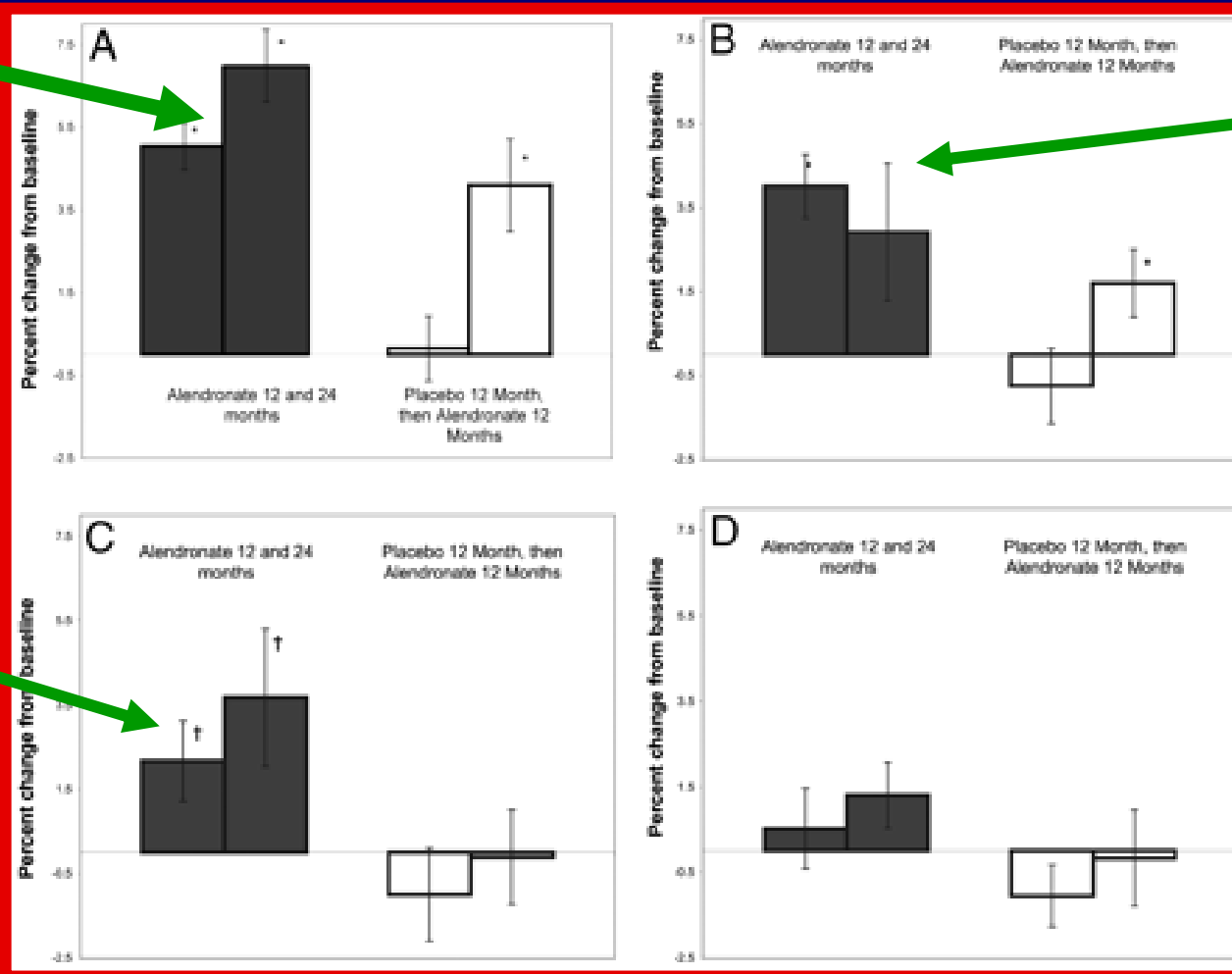
Biphosphonates

(Estrogens)

Calcimimetics

Effect of alendronate on lumbar spine (A), total hip (B), femoral neck (C), and one third distal radius (D) BMD.

+ 6.85%

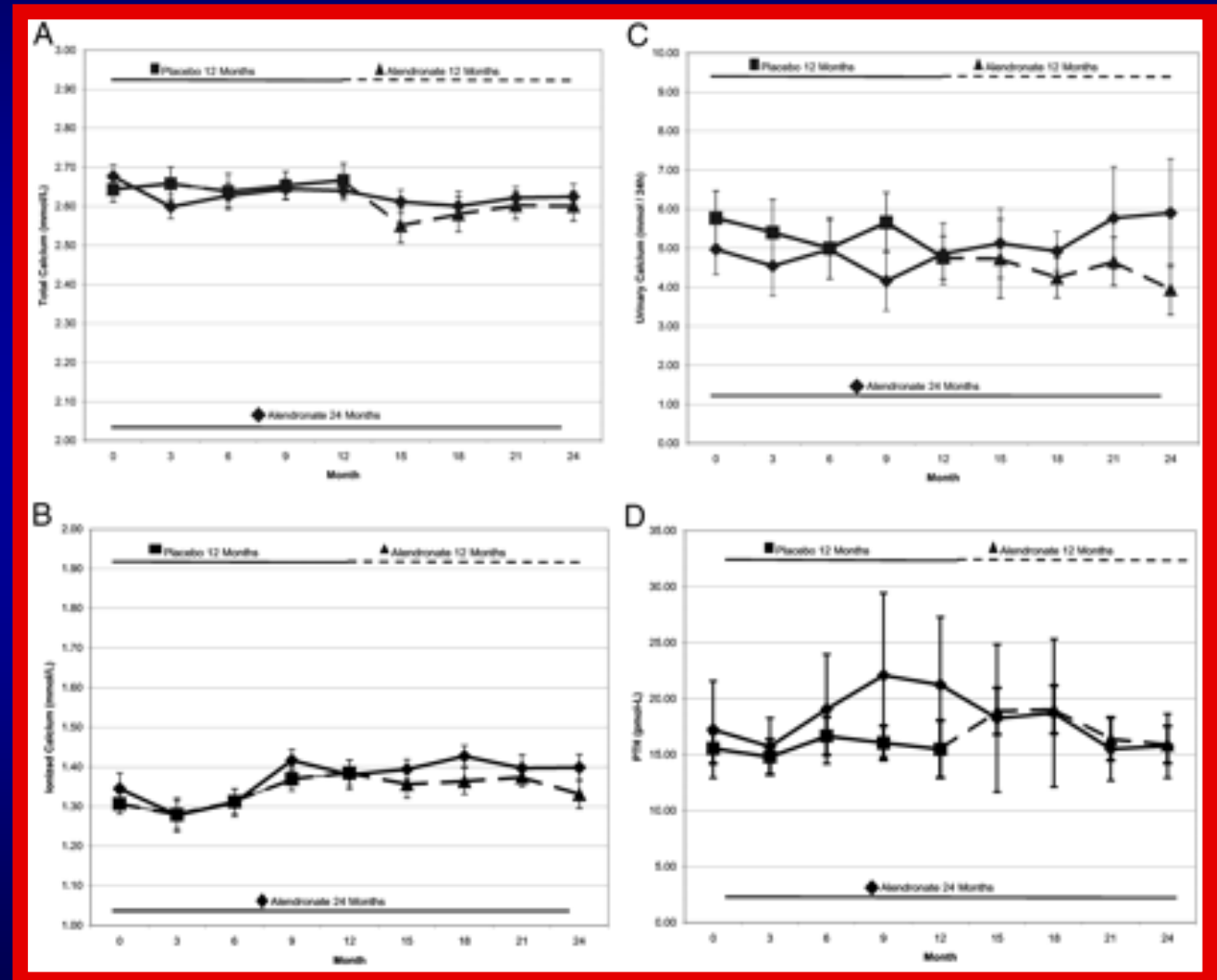


+ 4.1%

+ 3.67%

Effect of alendronate on total (A), ionized (B), and urinary calcium (C), and PTH (D).

no change



Alendronate in asymptomatic pHPT: A Double-Blind, Randomized, Placebo- Controlled Trial on 44 patients

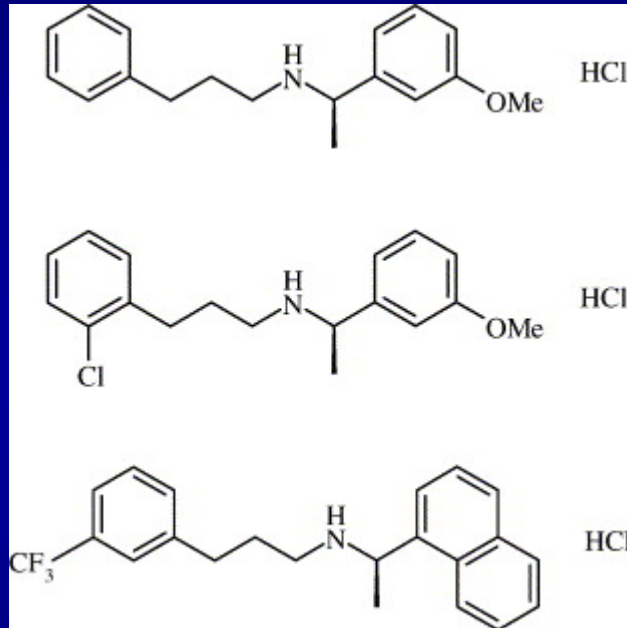
Alendronate is effective in increasing BM in pHPT.

Useful to those individuals with pHPT at risk for bone loss but not candidates for parathyroid surgery.

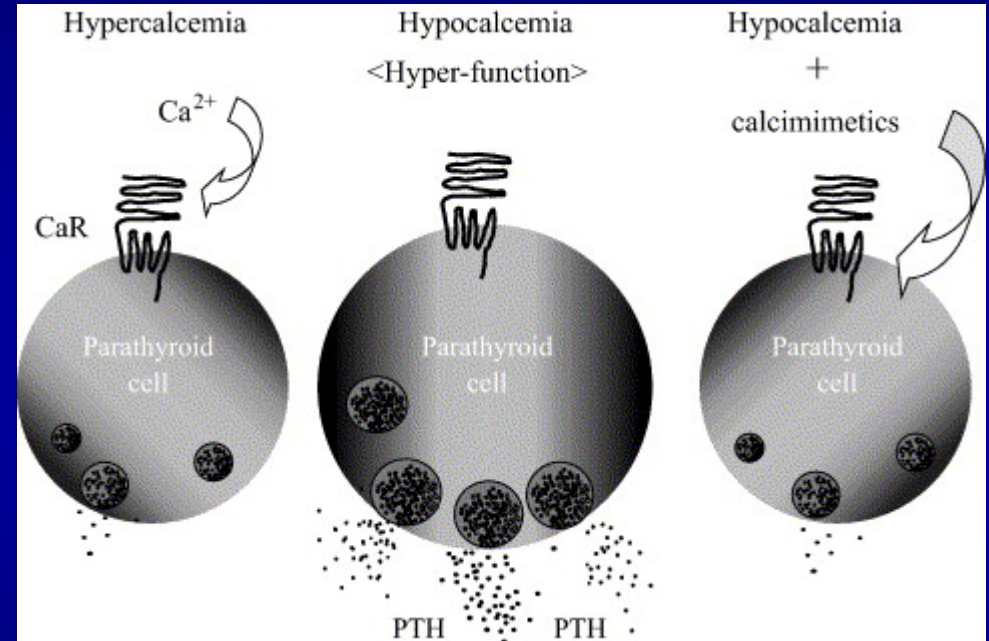
Useful in individuals who are candidates for surgery but either decline or for whom surgery is contraindicated.

Khan et al., JCE& M 2004, 89: 3319-3325

Calcimimetics: an innovative approach to controlling hyperparathyroidism



Chemical structure of the phenylalkylamine calcimimetic compounds



Action mode of calcimimetics.

Long-term (52 weeks) evaluation of cinacalcet in 78 patients with mild-to-moderate pHPT

Serum calcium ≤ 10.3 mg/dL, (and a decrease from baseline of ≥ 0.5 mg/dL) achieved in 73% of cinacalcet-treated patients (5% in controls).

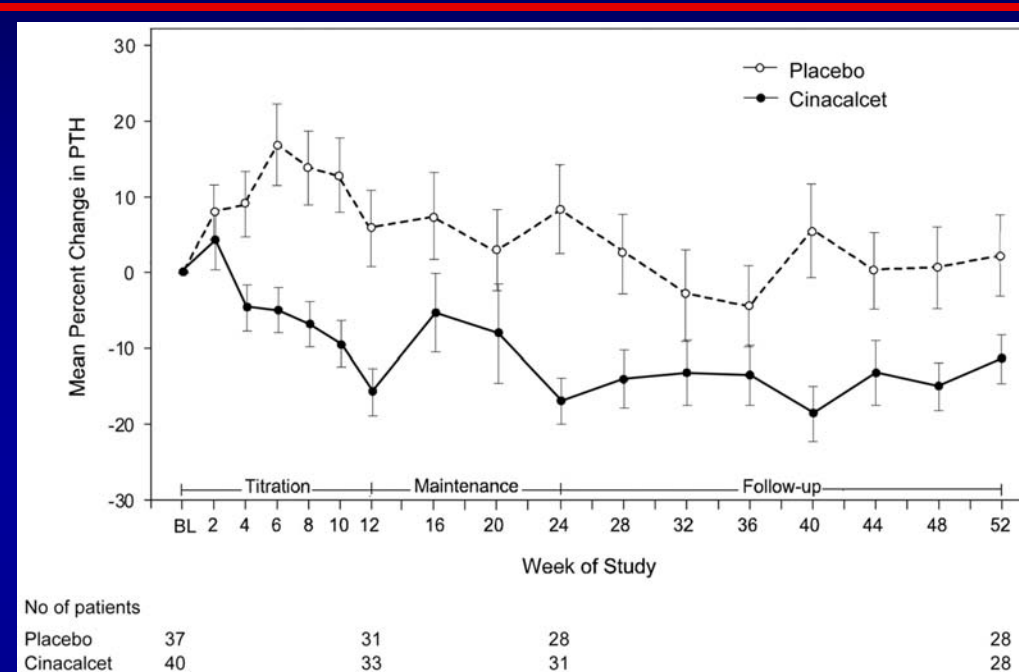
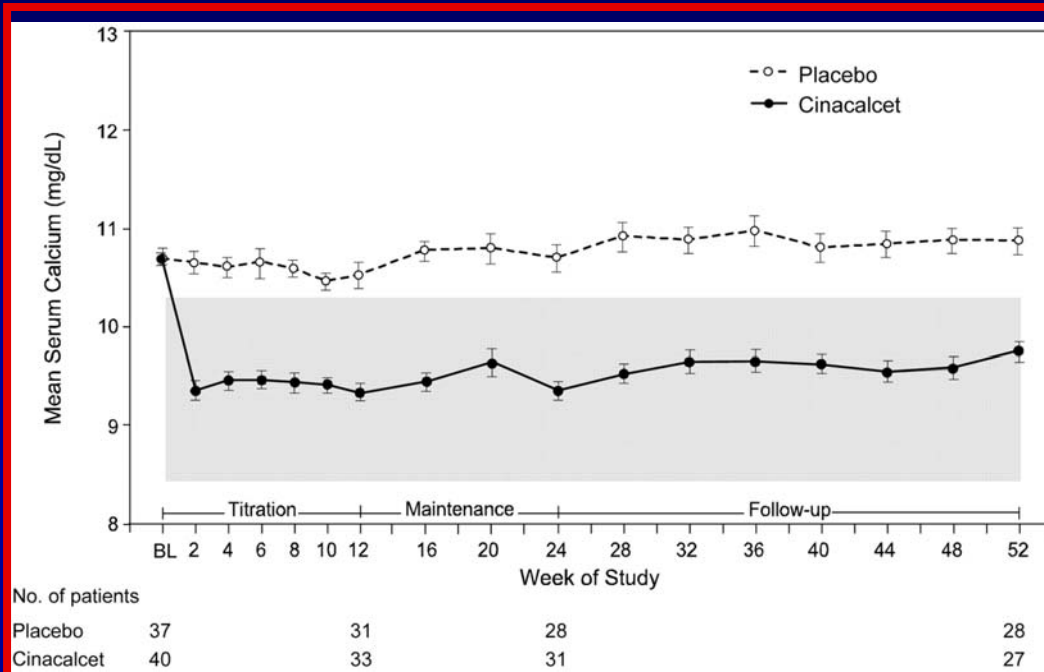
Mean plasma PTH levels were decreased by cinacalcet (from 105 ± 36 to 95 ± 34 pg/mL), while increased (from 120 ± 54 to 127 ± 53 pg/mL) in the control group.

Other Cinacalcet effects:

- \uparrow serum phosphorus levels
- \cong serum 1,25(OH)₂ D₃ levels and BMD
- \downarrow Urinary calcium excretion
- \uparrow markers of bone turnover

No major side effects (nausea 28%, headache 23%)

Effects of cinacalcet administration on PTH and calcium levels



BL, Baseline value. Data are presented as mean \pm SE.

Patients receiving cinacalcet showed a 7.6% reduction in plasma PTH ($P < 0.01$) and a significant reduction in serum calcium ($P < 0.001$) compared to the placebo group

Preoperative imaging in primary hyperparathyroidism

Parathyroid Imaging Sensitivity

	Scintiscan	US
Mazzeo, AJR 1996	62-82% ^o	85%
Gofrit, World J Surg 1997	n.d.	83%
Koslin, Larigoscope 1997	n.d.	84%
Isibashi, J Nucl Med 1998	83% ^o	78%
Hindie, J Nucl Med 1998	79-94%*	n.d.
Klinger, World J Surg 1998	82%*	75%
Gallowitsh, Invest Radiol 2000	87%*	78%
Chang, Am J Otorhyngol 2000	60% ^o	n.d.
Jones, Clinical Radiology 2001	83.7%*	n.d.
Castellani, J Nucl Med 2001	84% ^o	67%
Haber, Clin Endocrinol 2002	88%	77%

Cost of parathyroid gland imaging

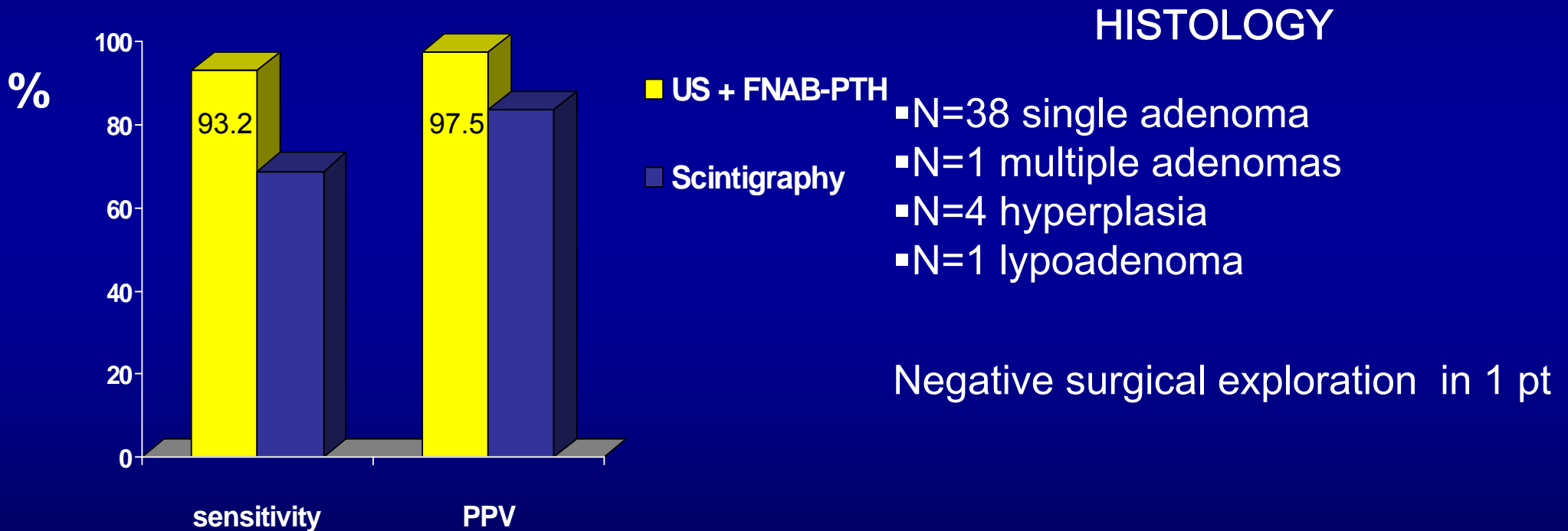
		% of physicians who use localization before primary operation	
Localization study	Cost (\$)	Referring physician	Surgeons
CT	270.7	8	3.4
MR	484.0	6.8	0
SestaMIBI	154.1	34.3	43.1
SestaMIBI + SPECT	287.9	15.9	25.9
TC-Thallium	100.4	8.2	0
US	79.1	26	27.6
Venous sampling	476.8	0.7	0

Ann Sosa et al., 1998

Localization imaging techniques

- ^{99}Tc sestamibi scanning and ultrasonography are currently considered the most effective first-line localizing techniques.
- CT, MRI and PET are usually used in a reserve role when first-line modalities fail
- The specific choice of preoperative imaging depends largely on availability, cost, radiologist's experience and surgeon's preference

Accuracy of PT localization in pHPT (patients n 45)



Laura P. age 52

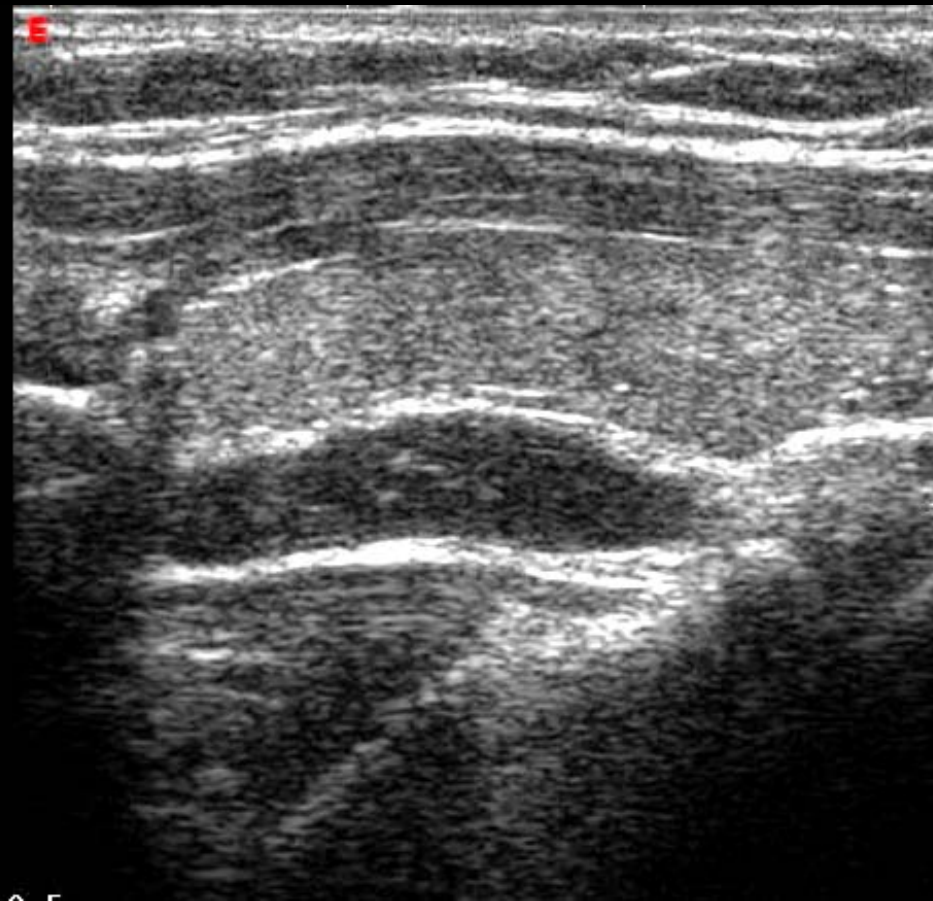
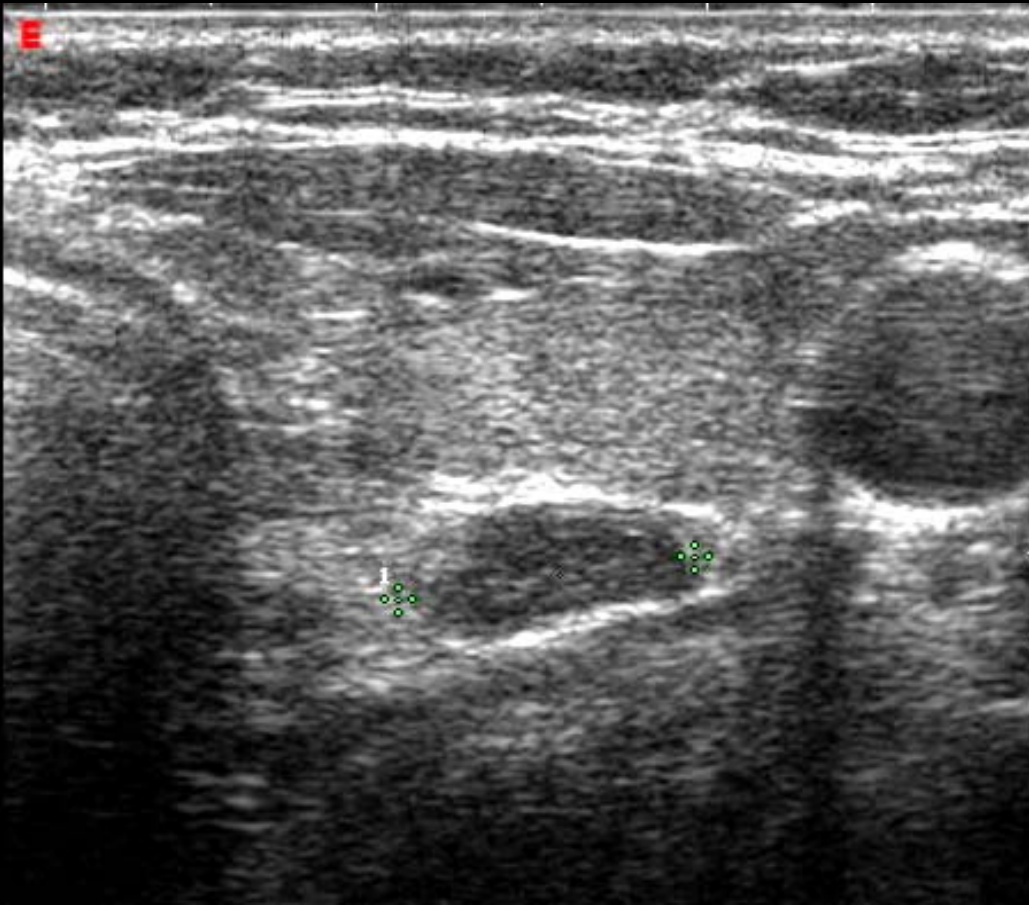
asymptomatic pHPT

Calcium 10.5 mg/dl

PTH 53 pg/ml

Superior parathyroid

US size 14 x 10 x 6 mm



Superior parathyroid

Zoia, age 51

asymptomatic, mild pHPT

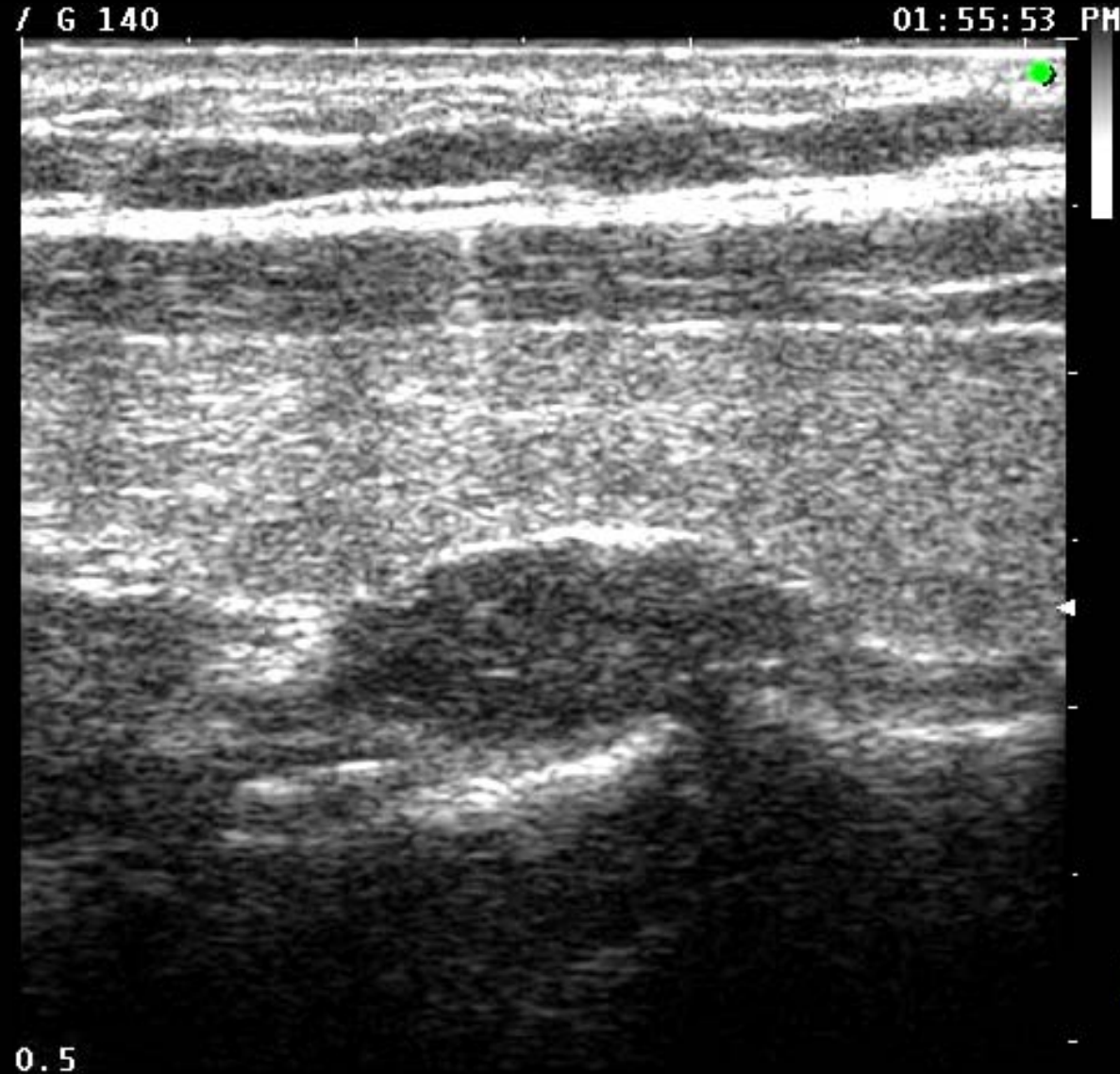
Calcium 9.6 mg/dl

PTH 97 pg/ml

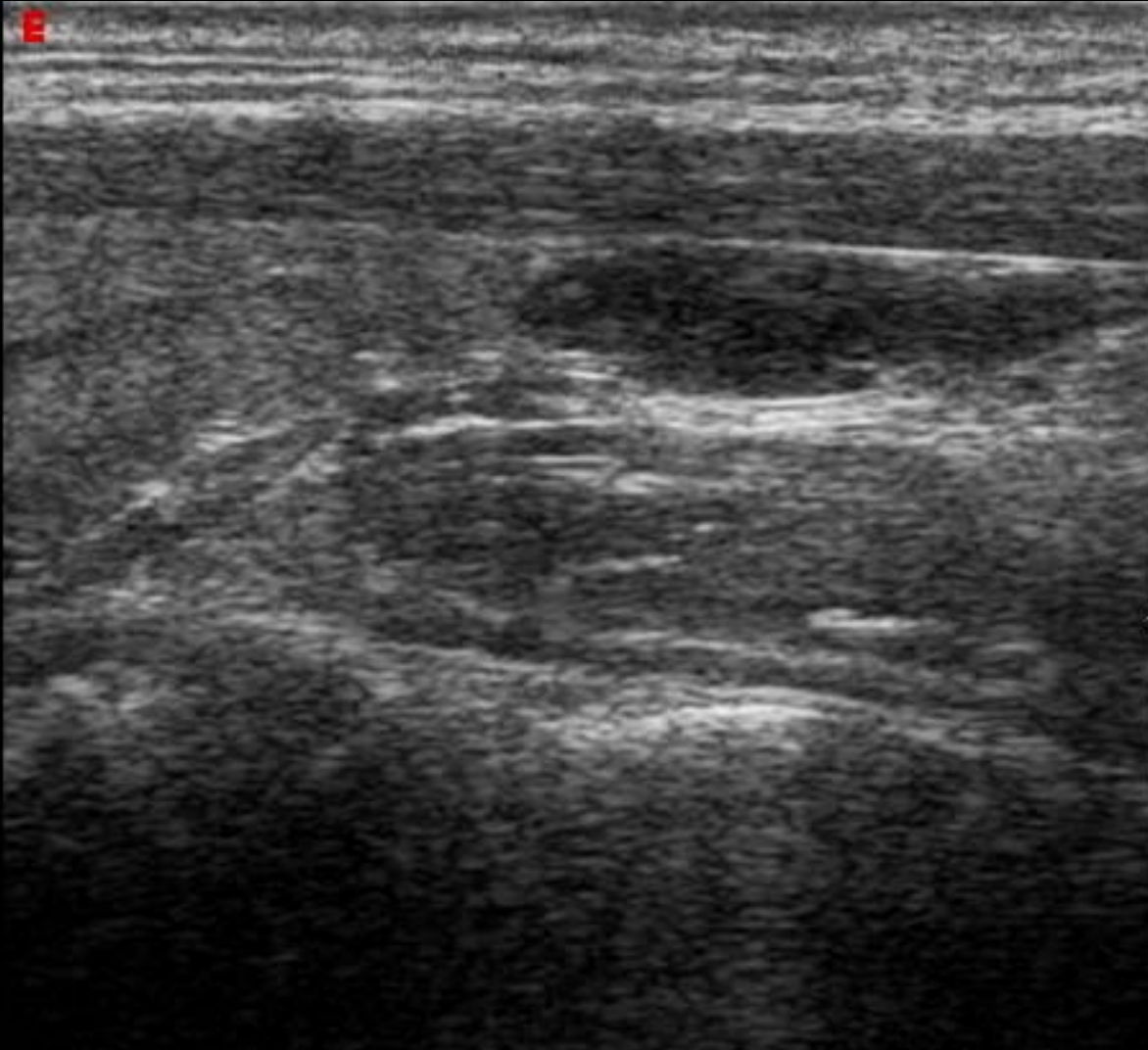
US size 15 x 11 x 9 mm

Excised

17 x 12 x 9 (1 gr weight)



Inferior parathyroid



Maria T, age 53

asymptomatic pHPT

calcium 11.0

PTH 72

US size 14 x 7 x 5 mm

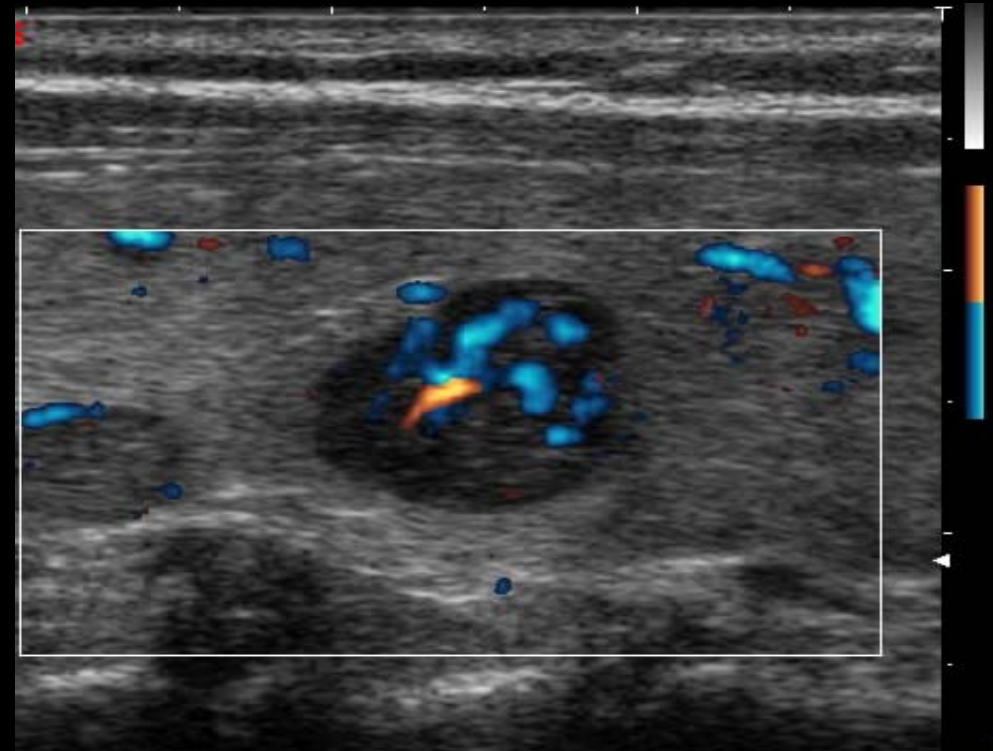
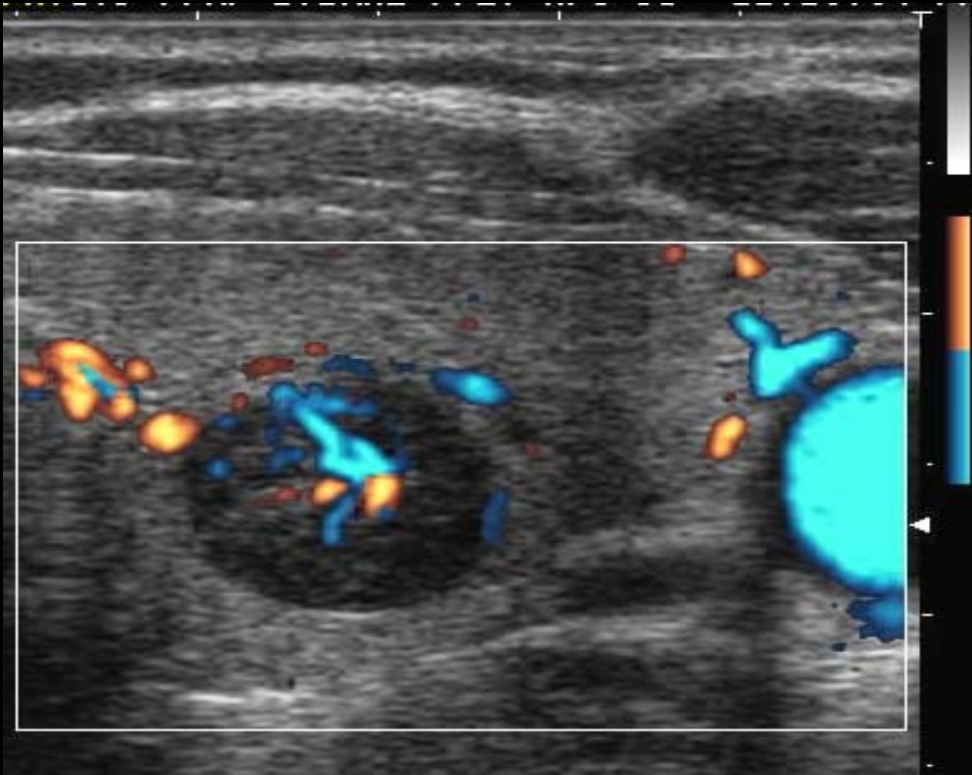
Superior parathyroid



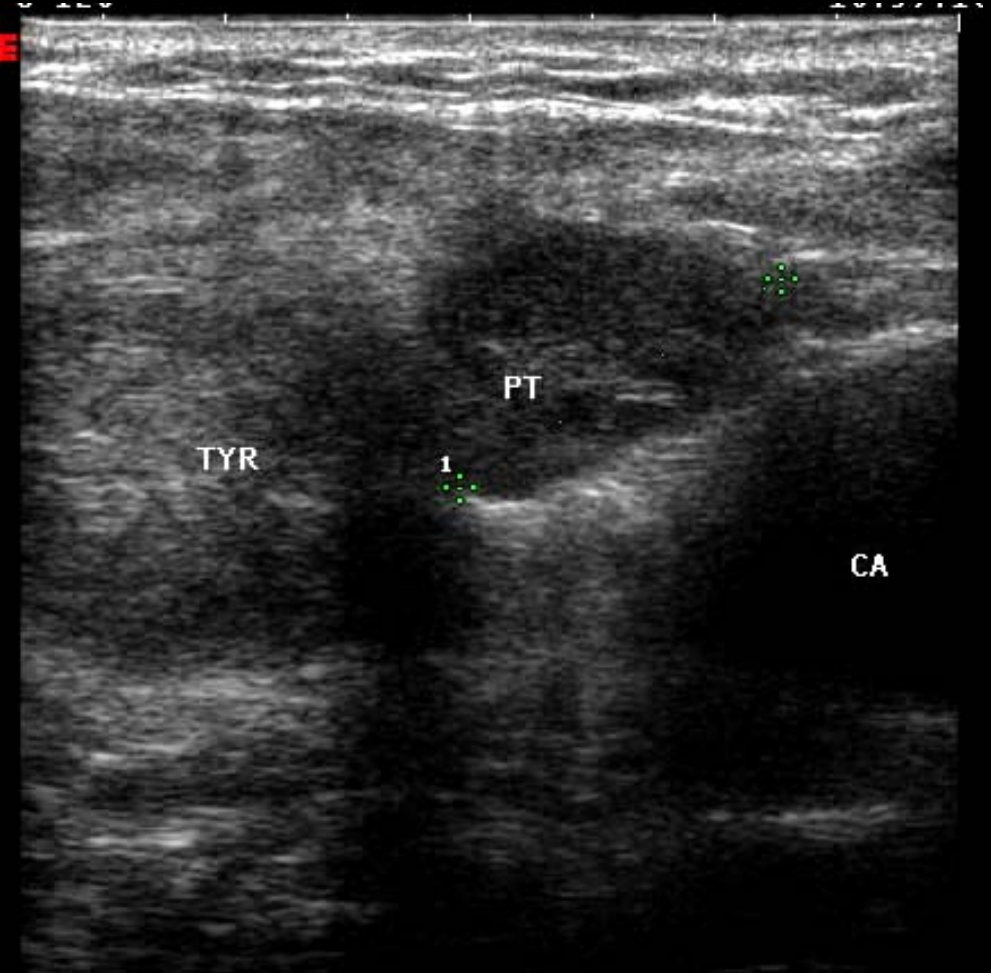
Rosanna, age 65, asymptomatic pHPT

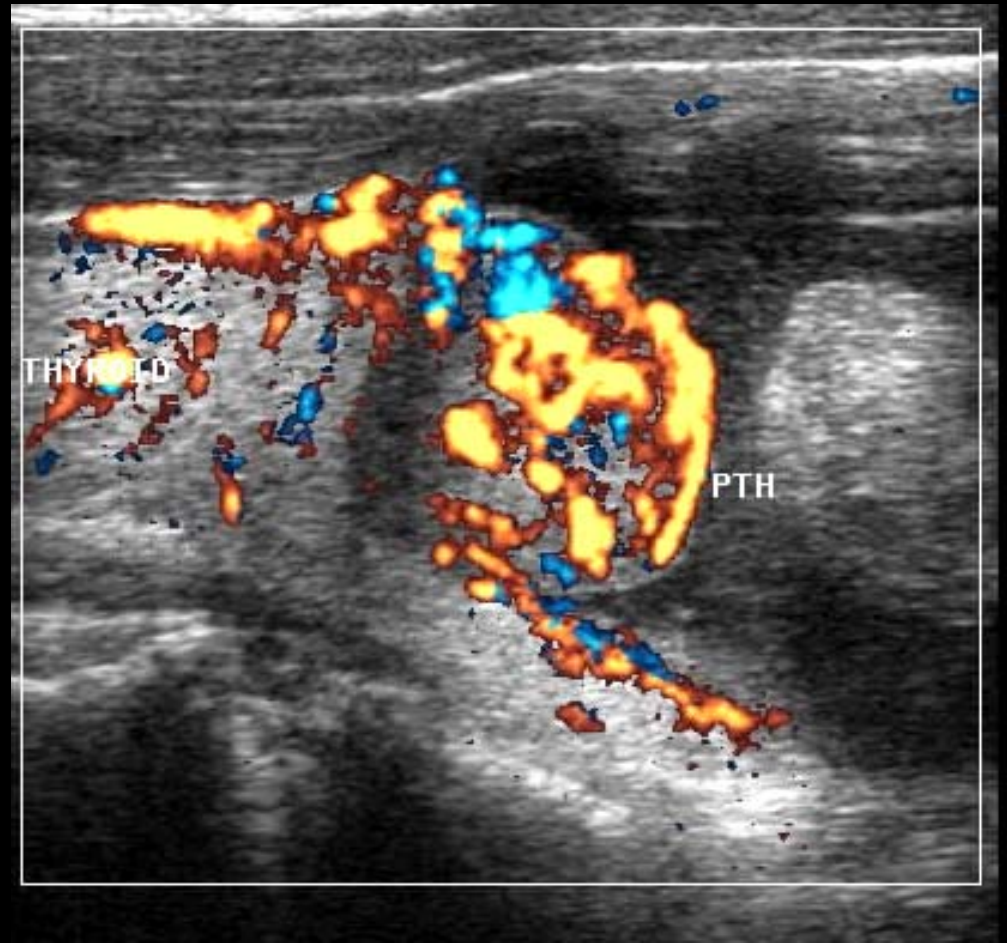
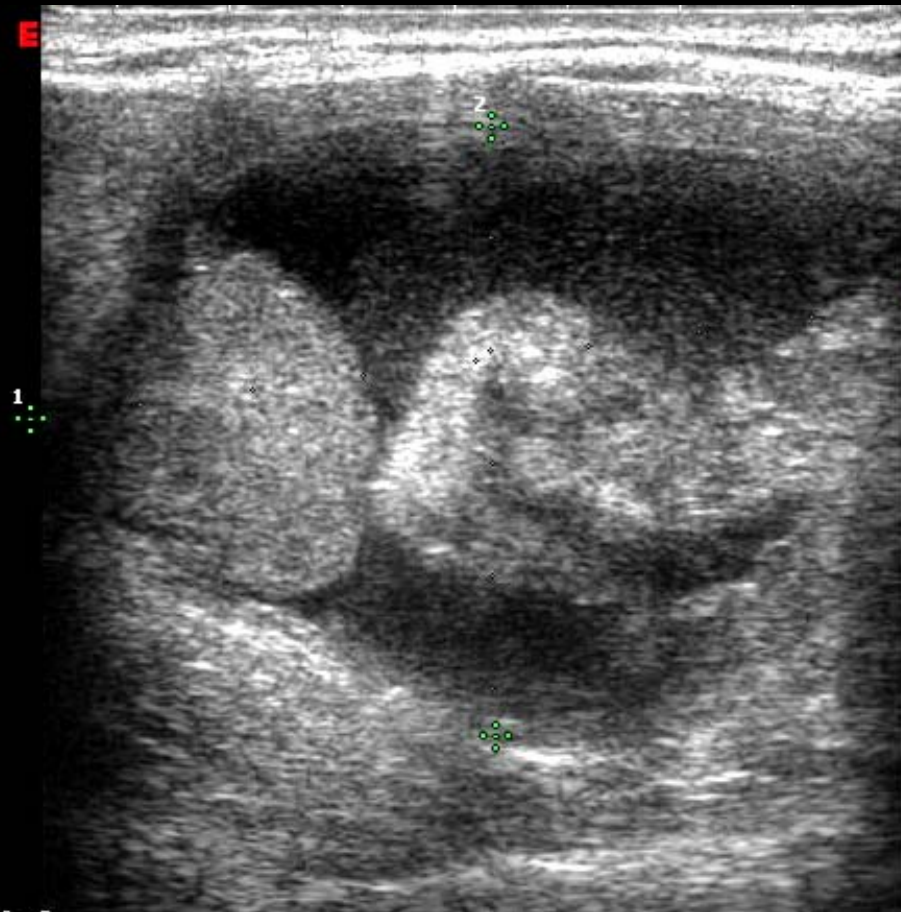
Calcium 9.5, PTH 95, uCa 305

Intrathyroidal parathyroid adenoma



Challenges in parathyroid US: Coexisting thyroid nodules

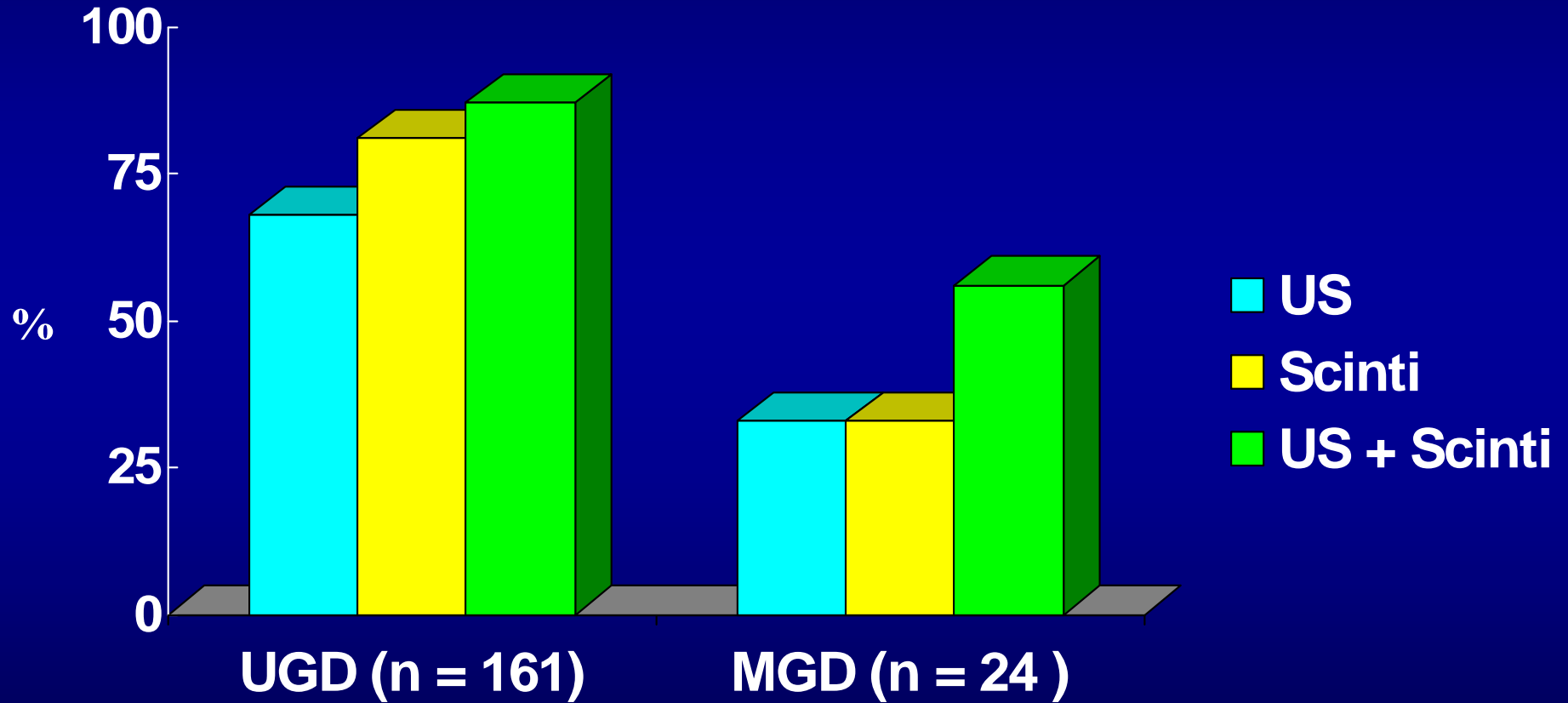




**Large “mixed” PT adenoma
complex vascular pattern**

Gianni, age 59
calcium 12.4 mg/dl
PTH 275 pg/ml

Sensitivity of imaging studies in pHPT



Ryan et al., Arch Surg, 2004

Sensitivity of Tc⁹⁹-sestamibi and high-resolution ultrasound

Diagnostic test	Sensitivity (%)
TC-Sestamibi	
Solitary adenoma	88.44
Multiple gland hyperplasia	44.46
Double adenoms	29.95
Carcinomas	33.0
High resolution Ultrasound	
Solitary adenoma	78.55
Multiple gland hyperplasia	34.86
Double adenoms	16.20
Carcinomas	100.00

Missing glands: the sonographer's perspective

- Small PT size (< 6 mm diameter)
- Multiglandular disease
- Ectopic location: mediastinum, retroclavicular, retrooesophageal, retrotracheal
- Atypical shape/structure
- Coexistence of nodular goiter
- Ultrasonographer lack of experience
- Inadequate US equipment

Factors which impact on scinti-scan localization of parathyroid adenomas

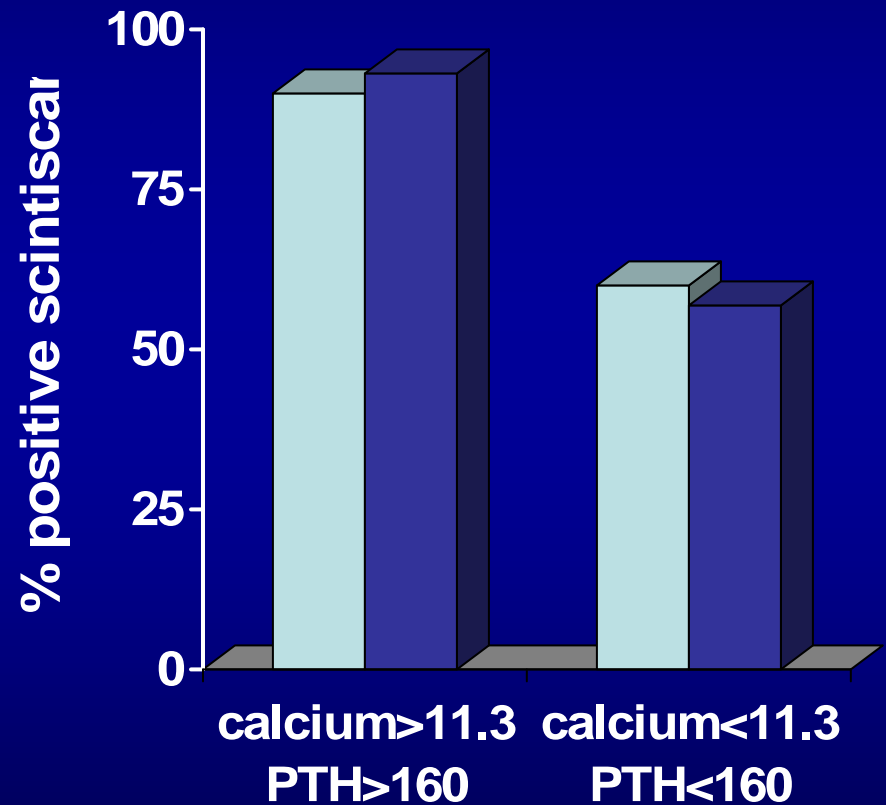
- Size
 - Location (Inferior vs. superior)
 - Multiglandular disease
 - Blood perfusion
 - Cell proliferation and metabolism
 - % oxyphil cells
 - PTH and calcium levels
- (P glycoprotein, MDR-related protein expression)

Impact of hypercalcemia and PTH on the sensitivity of preoperative sestamibi for pHPT

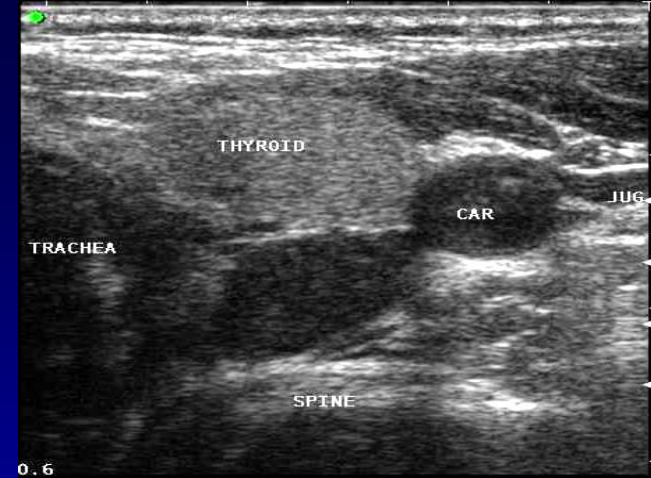
a retrospective review of 102 patients with pHPT and mild hypercalcemia

Lower Ca and PTH levels were correlated with reduced sensitivity of MIBI.

Increasing acceptance of surgery for pHPT with minimal hypercalcemia may make MIBI less attractive.



PT ultrasonography is operator-dependent.....



Ultrasound exams done at some radiology center or the radiology department of a hospital will also not show the tumor in most cases! ... not because the tumor isn't there... but because this test is highly dependant upon the skill of the person doing the test....Ultrasound scans done by endocrinologist or your endocrine surgeon in their office can be extremely helpful

Yet, Parathyroid Scintiscan is operator-dependent too...

Sestamibi scans are extremely variable depending on the techniques used. They require the highest degree of technician input. The use of special filters, patient placement, etc, are very important. Therefore, most scans done are not very good. About 30% of the scans are worthless, a other 30% are terrible or poor quality.....Sestamibi scanning is often not done correctly, and done for the wrong reasons, and interpreted wrong.

Be careful of your sestamibi scan. It can be extremely helpful if your sestamibi scan is positive, but if your scan is negative it doesn't mean much. It does not mean you don't have parathyroid disease if your scan is negative

FDG-PET in the localization of parathyroid adenoma and hyperplasia

	n. patients	Sensitivity	Specificity
Neumann, 1994	22 (4 MGD)	86.4%	-
Melon, 1995	9 (0 MGD)	22.2%	-
Neumann, 1996	21 (2 MGD)	86.0%	78%
Neumann, 1997*	20 (2 MGD)	61.9%	79%

* = recurrent pHPT

PET with (18) F-DOPA in the imaging of parathyroid adenoma in patients with pHPT

Eight patients with pHPT and histologically proven adenoma studied with PET prior to neck surgery

None showed any detectable uptake of (18) F-DOPA.
Ultrasonography detected 5/7 PA,
scintigraphy detected 3/7 PA.

CONCLUSION:

PET with (18) F-DOPA is not useful in the detection of PA in patients with primary hyperparathyroidism.

Parathyroid incidentaloma with normal calcium : how manage it ?

Parathyroid Incidentaloma: basic facts

- Parathyroid Incidentalomas (PI) may be occasionally (= 0.6%) detected during routine neck US examination
- ~30% of PI patients show asymptomatic hyperparathyroidism
- ~ 70% of PI patients do *not* have biochemical signs of HPT (**EUPARATHYROID - PI**)
- In EU-PI patients, HPT may eventually develop in 10% of patients

Parathyroid Incidentalomas: Biochemical Markers

	HPT-PI n=11	EU-PI n=24
Serum PTH (pg/ml)	148.9 ± 41.9*	42.0 ± 15.1
Serum Calcium (mg/dl)	10.9 ± 0.4*	9.6 ± 0.5
Serum Phosphate (mg/dl)	2.6 ± 0.4°	3.1 ± 0.5
Urinary Calcium (mg/day)	262.3 ± 151.9	202.4 ± 51.7
Serum alk. phosph. (U/l)	240.1 ± 55.8°	186.3 ± 58.5
Serum 25-OH Vit D (ng/ml)	18.13 ± 8.4	21.6 ± 9.6

Mean ± SD; * P<0.001; ° P<0.05

47 PI (0.63%)

Biochemical screening for pHPT

15 HPT-PI

32 EU-PI

11 surgery

4 HPT-PI

25 EU-PI

7 surgery

3 HPT-PI

Euthyroid PI (~ 70.0%)

US/FNA signs

Pure PT Cysts

Solid/Mixed PI

**US follow-up
(every 12-18 months)**

**PEI
(in case of volume
increase and/or
symptoms)**

**Biochemical follow-up
(every 12-18 months)**

Bone densitometry