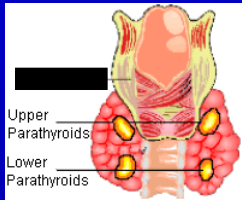


1. Donna di 52 anni con Iperparatiroidismo Primario Ipercalcemico (Calcio=11.8 Mg/Dl, PTH=98 Pg/Ml, Vit. D=34 Ng/Dl) da Adenoma Paratiroideo Destro. Da tempo lamentava facile affaticabilità, astenia, sonnolenza, scarsa capacità di concentrazione, perdita di memoria, tendenza al pianto ingiustificato. Quale delle seguenti affermazioni è corretta?

- A. I disturbi neurocognitivi sono parte delle manifestazioni cliniche dell'iperparatiroidismo primario e rappresentano di per sé indicazione all'intervento chirurgico
- B. I disturbi neuromuscolari (astenia, affaticabilità) sono correlabili all'iperparatiroidismo primario e correlano con i livelli di calcio
- C. La presenza di disturbi cognitivi costituisce sempre un'indicazione alla ricerca di un iperparatiroidismo primario
- D. I disturbi neurocognitivi sono parte delle manifestazioni cliniche dell'iperparatiroidismo primario e non sempre migliorano dopo asportazione chirurgica dell'adenoma

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



Primary hyperparathyroidism (PHPT) is a disease characterized by hypercalcemia attributable to autonomous overproduction of parathyroid hormone (PTH). Although some patients with PHPT may have normal serum calcium concentrations, most have hypercalcemia.

Endocr Pract. 2005;11(1)

Epidemiology

PHPT can occur at any age; however, it is most commonly seen in the postmenopausal female population

Pallan S et al, BMJ. 2012 Mar 19;344

PHPT is present in about 1% of the adult population. The incidence of the disease increases to 2% or higher after age 55 years and is 2 to 3 times more common in women than in men

Endocr Pract. 2005;11(1)

Bollerslev J et al. Eur J Endocrinol. 2011;165:851



Causes of primary hyperparathyroidism

Pathological conditions related to familial/isolated PHPT*

Single adenomas (85%)

Hyperplasia and multiple adenomas (15%)

Carcinomas (0.5%)

Clinical conditions associated to familial PHPT*

MEN** type 1 and 2

Hyperparathyroidism-jaw tumor syndrome

Familial isolated hyperparathyroidism

* Primary hyperparathyroidism; ** Multiple endocrine neoplasia.

Bandeira F et al . Arq Bras Endocrinol Metab. 2013;57

Clinical Manifestations

The clinical features of PHPT are mainly due to the direct and indirect effects of excess PTH on the skeleton, kidneys, and intestine and normally include

- bone resorption of calcium and phosphorus
- enhanced intestinal absorption of calcium
- renal tubular reabsorption of calcium
 - hypercalciuria

If patients are symptomatic, common related findings may include a history of renal calculi, bone pain, pathologic fractures, bone shaft tumors, proximal muscle weakness (especially of the lower extremities), or nonspecific symptoms such as depression, lethargy, and vague aches and pains



Nontraditional Manifestations of Primary Hyperparathyroidism

“In the mild form of PHPT seen commonly today, many patients report nonspecific symptoms, including **weakness, easy fatigability, depression, intellectual weariness, memory loss, decreased concentration, loss of initiative, anxiety, irritability, and sleep disturbance**

However, the 2008 Workshop on Asymptomatic PHPT did not add psychiatric and cognitive symptoms to the list of criteria for parathyroidectomy

Walker MD et al . Jour Clin Densit. 2013; 16: 40



Presentation, Management, and Outcomes of Hyperparathyroidism in Octogenarians and Nonagenarians

TABLE 2 Prevalence of comorbidities

	≥80 years of age	<80 years of age	<i>p</i> value
<i>N</i>	154 (8.4 %)	1671 (91.6 %)	
Hypertension	122 (79 %)	855 (51 %)	<.01
Coronary artery disease	49 (32 %)	193 (12 %)	<.01
Diabetes mellitus	27 (18 %)	232 (14 %)	NS
Congestive heart failure	21 (14 %)	52 (3 %)	<.01
Chronic obstructive pulmonary disease	18 (12 %)	138 (8 %)	NS
Cerebral vascular disease	17 (11 %)	35 (2 %)	<.01
Psychiatric disorder	15 (10 %)	306 (18 %)	.01

Data are expressed as number (%)

Oltmann SC et al., Ann Surg Oncol . 2013

psychiatric symptoms
had been attributed to senile depression



Muscle Function Is Impaired in Patients With "Asymptomatic" Primary Hyperparathyroidism

Muscle and balance tests: postural stability, muscle strength, and function in all patients/matched controls and asymptomatic patients/matched controls

Test	All PHPT	Matched controls	<i>p</i>	Asymptomatic PHPT	Matched controls	<i>p</i>
Balance results (m²/s)						
Normal standing eyes open	5.1 (3.5–7.5)	4.5 (2.9–6.4)	0.06	5.5 (3.1–7.3)	3.5 (2.3–5.4)	0.05
Normal standing eyes closed	12.6 (9.4–22.3)	6.7 (3.6–12.7)	<0.001	9.7 (5.8–13.6)	4.1 (3.3–9.5)	0.04
Semitandem standing	29.0 (19.8–39.2)	22.8 (16.2–34.7)	0.17	20.4 (12–40)	17.0 (14–25)	0.97
Tandem standing	58.3 (42.4–77.1)	40.3 (27.6–73.3)	0.08	41.0 (27–78)	34.0 (22–40)	0.26
Physical tests (s)						
All: time to walk	7 (6–8)	7 (6–8)	0.16	7 (6–8)	7 (6–8)	0.75
All: repeated chair stands	25 (19–28)	20 (17–23)	0.002	24 (18–27)	21 (19–22)	0.16
Isometric muscle strength						
Hand	290 (221–358)	332 (269–387)	0.07	360 (258–440)	387 (312–426)	0.64
Elbow flex	167 (147–230)	199 (174–236)	0.03	231 (166–303)	249 (191–266)	0.21
Elbow ext	112 (95–153)	140 (118–175)	<0.001	141 (101–153)	170 (122–181)	0.11
Knee ext60	319 (229–373)	410 (332–503)	<0.001	370 (278–412)	515 (377–578)	0.02
Knee ext90	320 (249–392)	358 (289–466)	0.02	381 (279–459)	504 (338–591)	0.07
Knee flex60	136 (90–173)	180 (144–236)	<0.001	159 (110–204)	230 (159–296)	0.03
Knee flex90	128 (92–176)	169 (130–209)	<0.001	158 (120–204)	217 (136–253)	0.06

Results are given as the number of patients or the median and 25–75 percentiles

Rolighed L et al. World J Surg 2013

What Symptom Improvement Can Be Expected After Operation for Primary Hyperparathyroidism?

Does parathyroidectomy improve symptoms if present?

Objective detection of neuromuscular symptoms uses a wide range of formal strength or sensory measurements to confirm subjective patient complaints or objectively identify subclinical deficits.

These formal tests are not widely available or utilized in typical pHPT patient assessment which helps to explain the limitations of most studies to date, i.e., small sample size, decreased generalizability, and lack of factors identified that can predict which patients are most likely to benefit with respect to neuromuscular symptomatology after PTx

“Overall, it does appear that the majority of studies to date demonstrate either **subjective or objective improvement in neuromuscular symptoms with PTx,** even in those considered asymptomatic or mildly symptomatic. Further studies on how to identify and quantify symptoms and predict who may benefit will be beneficial”

Caron NR et al, World J Surg. 2009 ;33:11



Neurocognitive Dysfunction

The prevalence of these abnormalities is not well defined due to the lack of rigorous evaluation of these symptoms in most studies, a small number of studies, and wide variation in the instruments used to assess the psycho-cognitive manifestations

Bilezikian JP et al . J Clin Endocrinol Metab. 2009;94:335

Bandeira F et al . Arq Bras Endocrinol Metab. 2013;57

Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: Patient description and effects on the SF-36 health survey

Talpos GB et al Surgery 2000;128:1013

Neurocognitive Dysfunction



Improved function is seen after parathyroidectomy when compared with patients who did not undergo operation

Randomized Controlled Clinical Trial of Surgery Versus No Surgery in Patients with Mild Asymptomatic Primary Hyperparathyroidism

Rao DSet al.J Clin Endocrinol Metab 2004;89: 5415

... measurable benefits of surgery on BMD, quality of life, and psychological function can be demonstrated.

Medical Observation, Compared with Parathyroidectomy, for Asymptomatic Primary Hyperparathyroidism: A Prospective, Randomized Trial

Jens Bollerslev J et al J Clin Endocrinol Metab 2007 92: 1687

No benefit of operative treatment, compared with medical observation, was found on these measures so far.

Surgery or Surveillance for Mild Asymptomatic Primary Hyperparathyroidism: A Prospective, Randomized Clinical Trial

Ambrogini E et al J Clin Endocrinol Metab 2007;92: 3114

In patients with mild asymptomatic PHPT, successful PTx is followed by an improvement in BMD and quality of life.



Presentation of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

Question 2. Can Neurocognitive Dysfunction be Detected in Asymptomatic PHPT? What is the Evidence for a Causal Relationship?

Consensus response

"Although patients with mild PHPT clearly have neuropsychological complaints, available data remain incomplete on their precise nature and their reversibility with surgery. However, there are some data supporting a modest beneficial effect of parathyroidectomy on quality of life and psychological functioning. Further efforts to define neuropsychological and cognitive deficits that are specific to PHPT are needed"

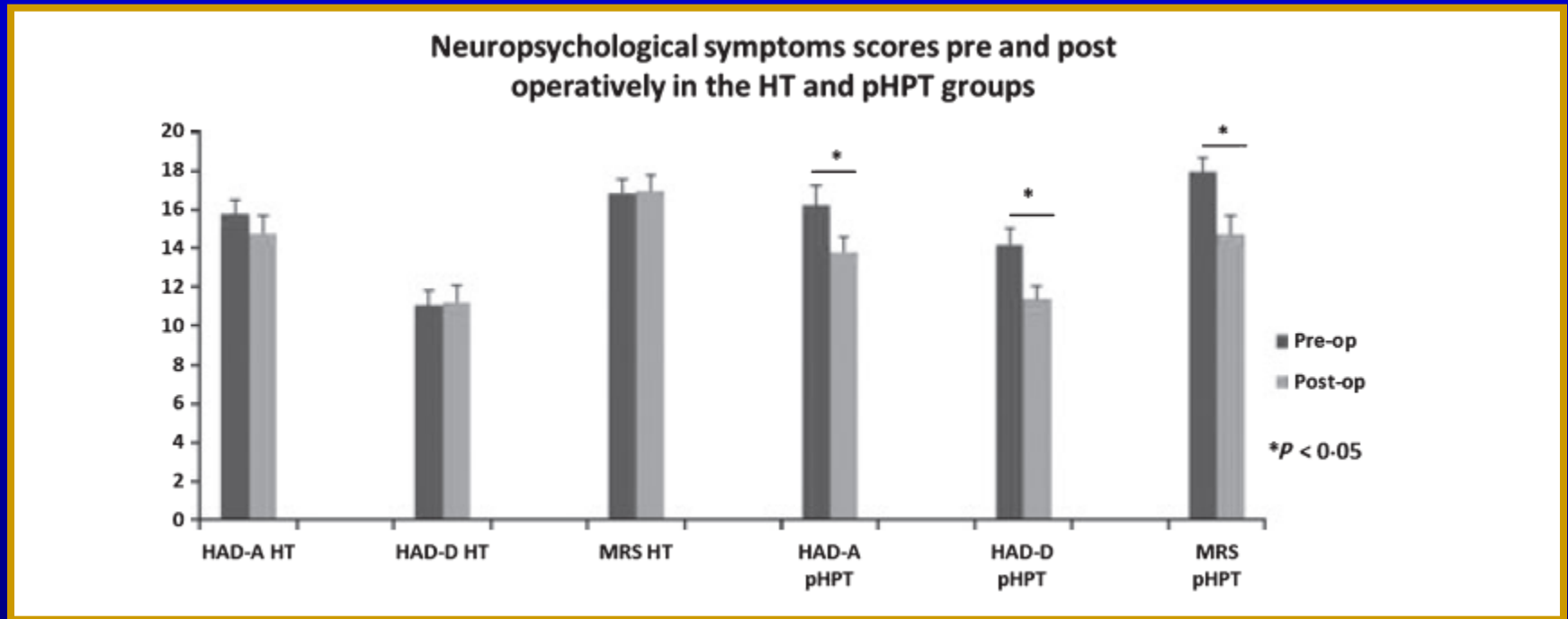
Silverberg SJ et al, J Clin Endocrinol Metab. 2009 ;94:351

Indications for surgery in asymptomatic primary hyperparathyroidism treatment

- 1 – Serum calcium > 1 mg/dL above ULN*
- 2 – Creatinine clearance < 60 mL/min/1.73 m²
- 3 – T-score < -2.5 at the lumbar spine, hip and/or distal radius or previous fragility fracture
- 4 – Age < 50 years
- 5 – Patients whose medical monitoring is not possible

Bilezikian JP et al . J Clin Endocrinol Metab. 2009;94:335
Bandeira F et al . Arq Bras Endocrinol Metab. 2013;57

The effect of parathyroidectomy on neuropsychological symptoms and biochemical parameters in patients with asymptomatic primary hyperparathyroidism



Conclusions Asymptomatic pHPT is associated with neuropsychological symptoms that improve after parathyroidectomy.

Kahal H et al Clinical Endocrinology.2012; 76:196

Neuropsychological Features in Primary Hyperparathyroidism: A Prospective Study

Subjects were female, at least 45 yr old, menopausal for at least 1 yr

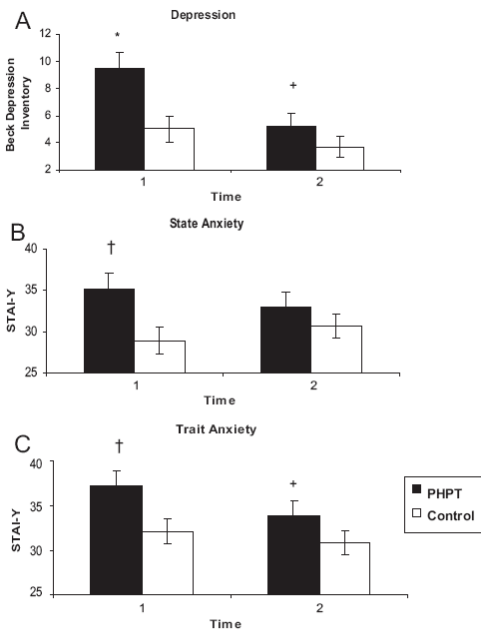


FIG. 1. A, Depression measured by BDI. B and C, State and trait anxiety as measured by STAI-Y. Higher scores indicate more symptoms. Scores are adjusted for age, IQ, and education. *, $P < 0.01$ compared with control group; †, $P < 0.05$ compared with control group; +, $P < 0.01$ compared with baseline. The test used to determine significance is the linear mixed model for repeated measures. Error bars represent 1 SEM.

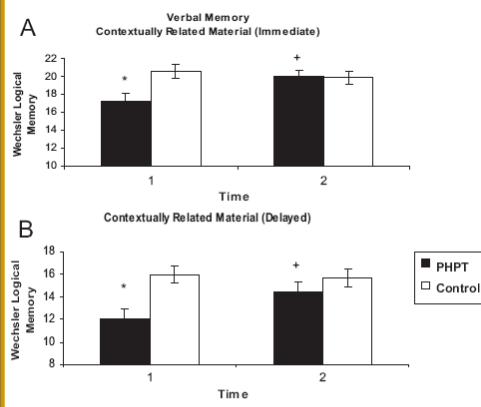


FIG. 2. Memory for contextually related material (short story) at immediate (A) and delayed intervals (B). Higher scores indicate memory for more story elements. Scores are adjusted for age, IQ, education, anxiety, and depression. *, $P \leq 0.01$ compared with control group; +, $P < 0.01$ compared with baseline. The test used to determine significance is the linear mixed model for repeated measures. Error bars represent 1 SEM.

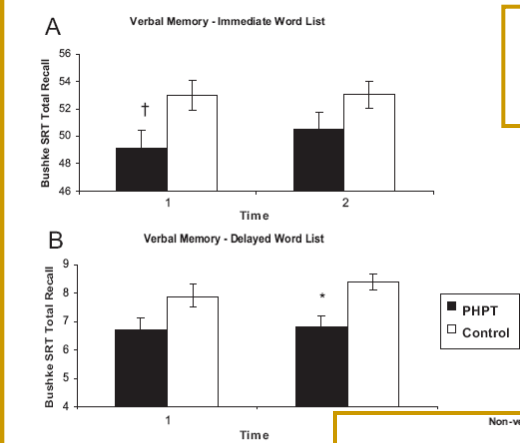


FIG. 3. Memory for a word list at immediate (A) and delayed intervals (B). Higher scores indicate memory for more words. Scores are adjusted for age, IQ, education, anxiety, and depression. †, $P \leq 0.05$ compared with control group; *, $P < 0.01$ compared with control group. P value vs. control at baseline for delayed recall. The test used to determine significance is the linear mixed model for repeated measures. Error bars represent 1 SEM.

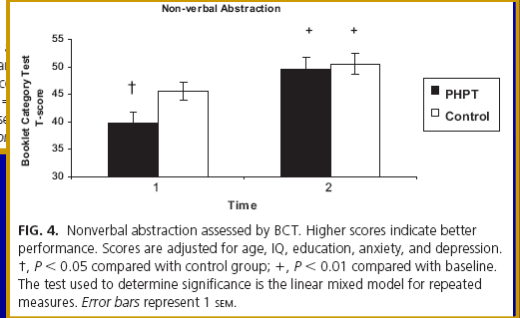


FIG. 4. Nonverbal abstraction assessed by BCT. Higher scores indicate better performance. Scores are adjusted for age, IQ, education, anxiety, and depression. †, $P < 0.05$ compared with control group; +, $P < 0.01$ compared with baseline. The test used to determine significance is the linear mixed model for repeated measures. Error bars represent 1 SEM.

We conclude that mild PHPT in postmenopausal women is associated with weaker performance in the cognitive domains of verbal memory and nonverbal abstraction.

This is independent of anxiety and depressive symptoms, which are also more common in PHPT than in a control population

Parathyroidectomy leads to improvement in some of the psychiatric and cognitive deficits

Walker MD et al J Clin Endocrinol Metab 2009;94: 1951

4. Donna di 48 anni, con cicli mestruali regolari, fumatrice. recente riscontro di iperparatiroidismo primario asintomatico (PTH=112 pg/ml, ca=11.7 mg/Dl, p=2.7 mg/dl, vitamina d=31 ng/ml).
Quale quadro ti aspetteresti alla dexa?

- A. L'iperparatiroidismo è asintomatico per cui mi aspetto valori di BMD comparabili con quelli di una donna con gli stessi fattori di rischio e senza iperparatiroidismo
- B. Valori di BMD ugualmente ridotti in tutti i siti (lombare, femorale, radiale)
- C. Maggiore compromissione dell'osso trabecolare con valori di BMD ridotti maggiormente a livello del sito lombare
- D. Maggiore compromissione dell'osso corticale con valori di BMD ridotti maggiormente a livello dei siti femorali e radiale



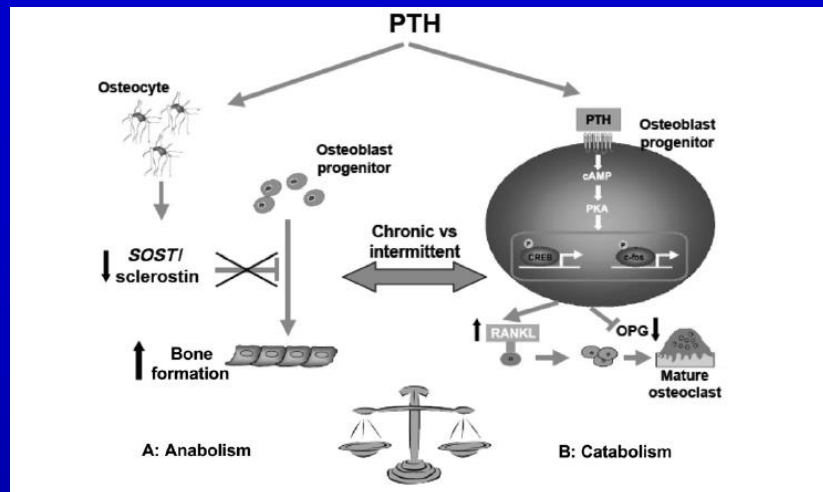
SMOKING → risk factor for osteoporosis and osteoporotic fractures

- ↑ production of 2-hydroxyoestrogens with short biological half-life and low oestrogenic activity
- ↑ SHBG leading to lower concentrations of biologically active oestrogens
- ↓ Calcium absorption in smokers vs nonsmokers
- ↓ 25-OHD and 1,25(OH)₂D plasma levels
- ↓ plasma PTH ?

The adverse effects of smoking on the skeleton could partly be due to significant changes in the PTH-vitamin D system seen among smokers.

However, at present it is unknown to what extent these alterations are effective in patients with PHPT

Primary hyperparathyroidism and the skeleton



PHPT is characterized by an increased activation frequency of bone multicellular units (BMUs), resulting in an increased bone remodeling space

In cancellous bone the activation frequency of BMUs and the number of osteoblasts and osteoclasts are increased, but the resorption depth is shallowed and the bone formation period is longer

This can explain the relative preservation of trabecular bone often observed in mild PHPT

In the cortical compartment cortical porosity and endocortical bone resorption are enhanced, thus leading to cortical bone loss"



Primary hyperparathyroidism and the skeleton

245 consecutive Caucasian patients
aged 19-91 yrs (median 63, 87% females)

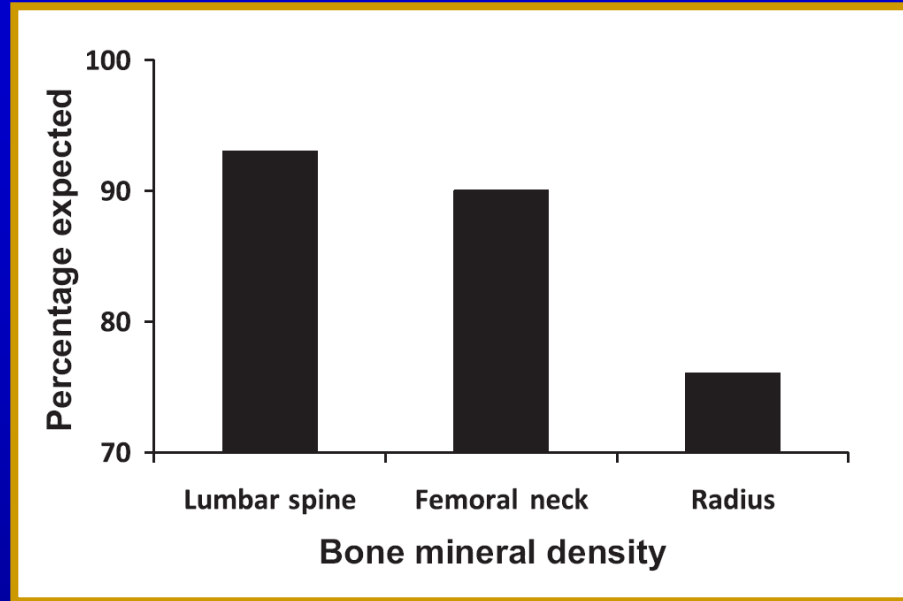
Regional BMD in 245 Danish Caucasian patients with primary hyperparathyroidism.
Osteopenia and osteoporosis is defined according to WHO guidelines

	Femoral neck N = 238	Lumbar spine N = 235	Forearm N = 208
BMD, g/cm ² , median (range)	0.68 (0.31-1.27)	0.90 (0.45-1.52)	0.45 (0.18-0.74)
BMD, Z-score, median (range)	-0.52 (-3.81 to 4.29)*	0.10 (-3.36 to 5.14)	-0.99 (-4.59 to 3.04)*
Subnormal BMD:			
BMD, Z-score < -2, %	7	6	20
Osteopenia:			
BMD, -2.5 < T-score < -1.0, %	42	21	31
Osteoporosis:			
BMD, T score < -2.5, %	39	40	44

Z-score: deviation (in SD) from mean of normal sex- and age-matched controls. T-score: deviation (in SD) from mean of young adult sex matched controls.
*P < 0.001 vs. 0.

BMD is reduced in the femoral neck and the forearm, but not in the lumbar spine
This result was not changed by excluding patients with fractures in the lumbar region or radiological signs of spondylarthrititis

Pattern of BMD in patients with primary hyperparathyroidism



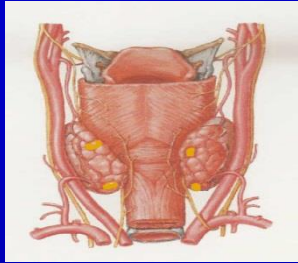
BMD is lowest at skeletal sites with the highest proportion of cortical bone.

This is strikingly different than in postmenopausal osteoporosis, when BMD is typically lowest at skeletal sites with the highest proportion of trabecular bone

This pattern is not universally observed because some patients with PHPT may have bone loss from other diseases, including postmenopausal estrogen deficiency, as well



There is a robust correlation between BMD and fracture risk in women and men without PHPT



In patients with long-standing symptomatic PHPT, overt skeletal disease, including low BMD and fractures, is common

Much less is known of the relationship between BMD and fracture risk with PHPT that is mild and asymptomatic

“Despite the preferential involvement of cortical bone in PHPT, an increased rate of vertebral fractures has been reported in most studies, some of which also included patients with asymptomatic PHPT”

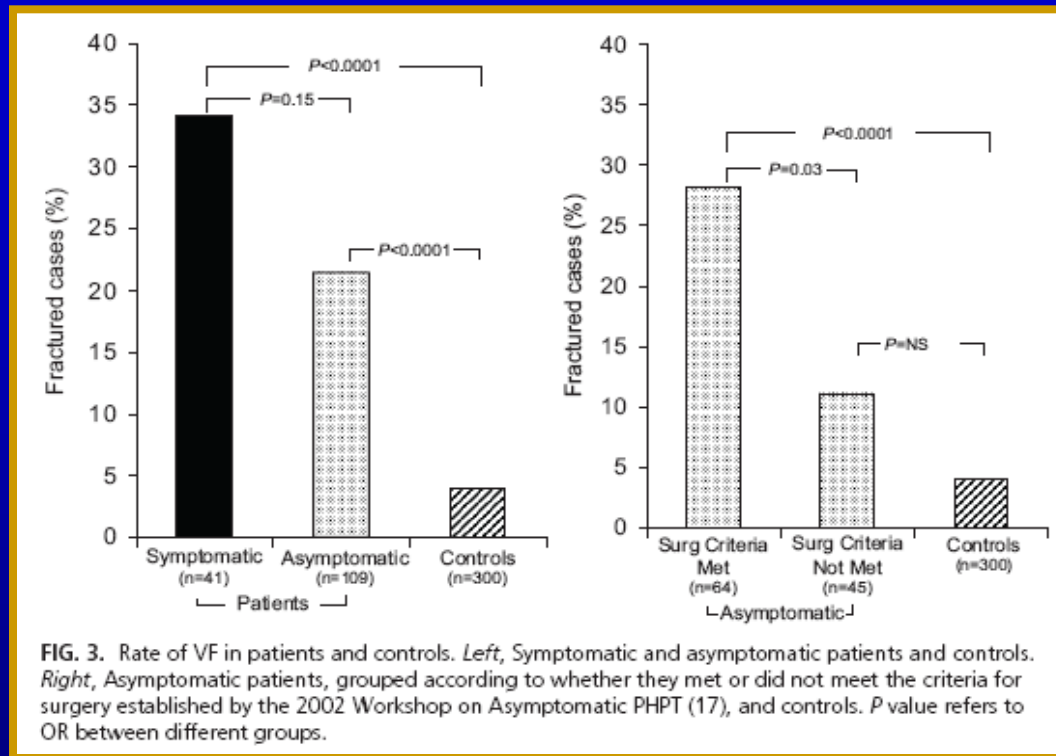
Vignali E et al. J Clin Endocrinol Metab. 2009;94:2306

Lewiecki EM & Miller PD. J Clin Dens. 2013;16: 28

Morphometric Vertebral Fractures in Postmenopausal Women with Primary Hyperparathyroidism

This series mostly included patients with asymptomatic PHPT (72.7%) and therefore generally reflects the current most common presentation of the disease

Vertebral fractures were evaluated using the Genant semiquantitative method



Vertebral Fracture rate is increased in postmenopausal women with PHPT compared to controls, independently of whether they are classified as symptomatic or asymptomatic



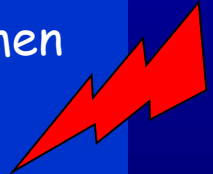
The risk of fractures in postmenopausal women with primary hyperparathyroidism

	Healthy women (C)	Mild PHPT patients (M)	Non-mild PHPT patients (NM)
<i>n</i>	89	25	73
vFr	<i>n</i> =8 (9%)	<i>n</i> =11* (44%)	<i>n</i> =35* (47%)
Non-vFr	<i>n</i> =17 (19.1%)	0	<i>n</i> =13 (17.8%)

vFr, vertebral fractures; *n*, number of controls and patients with fractures; in brackets percentage of controls and patients with fractures. **P*<0.001 vs controls by χ^2 -analysis.

The risk of vertebral fractures is higher in postmenopausal women with PHPT, independently of the severity of the disease, even if BMD appears well preserved in mild patients

Other factors, such as bone quality, seem to be relevant in determining fracture risk



AACE/AAES Task Force on Primary Hyperparathyroidism

DIAGNOSIS

Losses of BMD from PHPT are more pronounced in the forearm (cortical bone) than in the spine (trabecular bone) and hip (mixed cortical and trabecular bone) but may occur at all skeletal sites

Although forearm losses of BMD may be more commonly associated with PHPT, the benefit from surgical treatment is more notable for the hip and spine because of the morbidity and mortality associated with fracture

Patients with PHPT should undergo DEXA scanning of these 3 sites for reliable documentation of their BMD status as a criterion for recommending parathyroidectomy



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

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

^a Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.

^b Some physicians still regard 24-h urinary calcium excretion >400 mg as an indication for surgery.

^c Lumbar spine, total hip, femoral neck, or 33% radius (1/3 site). This recommendation is made recognizing that other skeletal features may contribute to fracture risk in PHPT and that the validity of this cut-point for any site vis-à-vis fracture risk prediction has not been established in PHPT.

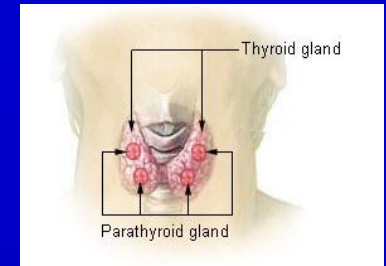
^d Consistent with the position established by the International Society for Clinical Densitometry, the use of Z-scores instead of T-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 yr.

5. Donna di 25 anni, con tireopatia autoimmune ed ipotiroidismo primario e riscontro incidentale di iperparatiroidismo primario (calcio= 12.5 mg/Dl, fosforo= 3.1 mg/dl, paratormone=88.6 pg/ml, vitamina d= 32 ng/ml). All'ecografia del collo tiroide di volume ridotto pari a 5 ml, sotto il polo inferiore del lobo sinistro formazione ipoecogena di 7x9x14 mm, sotto il polo inferiore del lobo destro formazione ipoecogena di 5x6x12 mm compatibili con paratiroidi ingrandite.

Quale trattamento sceglieresti e quando?

- A. Paratiroidectomia inferiore destra e sinistra appena possibile
- B. Il tipo di intervento chirurgico ed il timing devono essere pianificati dopo aver eseguito l'analisi genetica
- C. E' importante cercare una sindrome genetica perchè nell'ambito di una MEN1 sarebbe più corretto un atteggiamento iniziale di follow up
- D. Paratiroidectomia inferiore destra e sinistra previa verifica di catecolamine e metanefrine urinarie

Primary Hyperparathyroidism



Solitary parathyroid adenomas → 85% to 90% of cases
Multiple hyperfunctioning parathyroid glands → 10% to 15% of case
(hyperplasia and multiple adenomas)

Sporadic 90-95%

Solitary parathyroid adenomas → 75% to 85% of cases
Multiple hyperfunctioning parathyroid glands
2 glands → 2-12% of case
3 glands → <1-2% of case
4 or more glands → < 1-15% of case

Hereditary 5-10%

Multiple gland disease is the most common finding in individuals with familial hyperparathyroidism syndromes

Parathyroid carcinoma → 0.7% of all cases

Inherited Causes of Primary Hyperparathyroidism

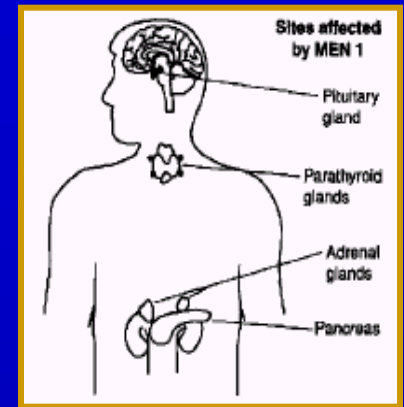
Syndrome	Gene (Map Locus)	Parathyroid Pathology	Other Manifestation
MEN 1 (OMIM131100)	MEN1 (11q13)	Hyperplasia (90%)	Adenomas of the pituitary, pancreas, carcinoid tumors of bronchus and thymus, facial angiofibromas, collagenomas, multiple lipomas
MEN 2A (OMIM 171400)	RET (10q11.2)	Hyperplasia (20%-30%)	Medullary thyroid carcinoma and C-cell hyperplasia, pheochromocytoma
MEN 4 (OMIM 610755)	CDKN1B (12p13.1-p12)	Parathyroid tumors	Adenomas of the pituitary pheochromocytoma pancreas tumors and thyroid tumors
Familial hypocalciuric hypercalcemia (FHH) (OMIM 145980)	CaSR heterozygous state (3q13.3-q21)	Primary parathyroid hyperplasia due to insensitivity to calcium levels	
Neonatal Severe Primary Hyperparathyroidism (NSHPT) (OMIM 145980)	CaSR homozygous state (3q13.3-q21)	Primary parathyroid hyperplasia due to insensitivity to calcium levels	
Autosomal Dominant Moderate Hyperparathyroidism (ADMH) (OMIM 601199)	CaSR (3q21-1)	Hyperplasia o adenomas	
Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT) (OMIM 145001)	HRPT2 (1q25-q32)	Adenomas (cystic) and carcinoma	Multiple jaw fibromas (30%) kidney lesions including cystis, hamartomas, carcinoma, Wilms tumor
Familial Isolated Hyperparathyroidism (FIHPT) (OMIM 14500)	Associated MEN1, CaSR and HRPT2 (11q13- 3q13.3-q21, and 1q25-q32)	Multiglandular (chief cell) hyperplasia	



MEN 1

Definition

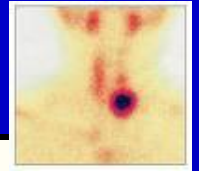
MEN 1 is an autosomal dominant disorder characterized by
parathyroid adenomas
entero-pancreatic endocrine tumors
and
pituitary tumors



Expression of MEN1 with estimated penetrance (in parentheses) at age 40 yr

Endocrine features	Nonendocrine features
Parathyroid adenoma (90%)	Lipomas (30%)
Entero-pancreatic tumor	Facial angiofibromas (85%)
Gastrinoma (40%)@	Collagenomas (70%)
Insulinoma (10%)	
NF^α including pancreatic polypeptide (20% ^b)	Rare, maybe innate, endocrine or nonendocrine features
Other: glucagonoma , VIPoma , somatostatinoma , etc. (2%)	
Foregut carcinoid	
Thymic carcinoid NF (2%)	Pheochromocytoma (<1%)
Bronchial carcinoid NF (2%)	Ependymoma (1%)
Gastric enterochromaffin-like tumor NF (10%)	
Anterior pituitary tumor	
Prolactinoma (20%)	
Other: GH + PRL, GH, NF (each 5%)	
ACTH (2%), TSH (rare)	
Adrenal cortex NF (25%)	

Hyperparathyroidism and MEN 1



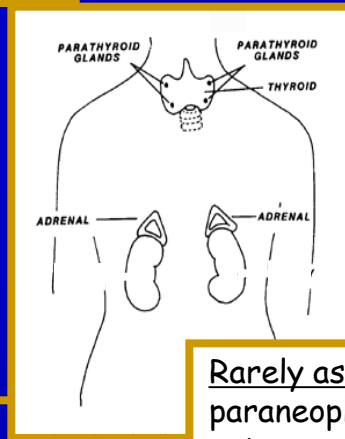
	Familial MEN1	Sporadic
Ratio M/F	=	F>M (2-fold)
Decade of life	2° -3° decade	4° -6° decade
Gland involvement	Multiple	Single adenoma (80 – 85%)
Recurrence rate	High (50 % at 12 yrs)	Low (5 % at 10 yrs)

Approximately 1-2 % of all cases of primary hyperparathyroidism are due to MEN1

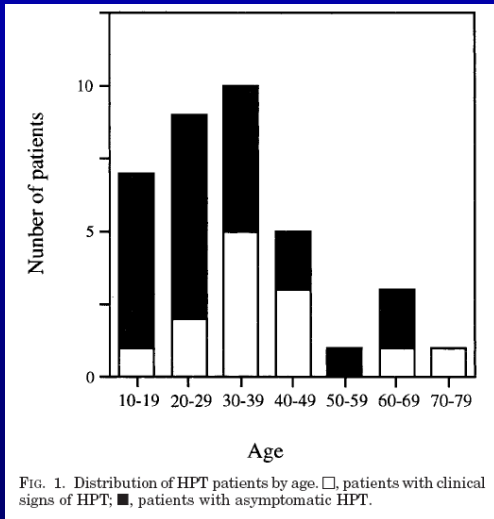
MEN 2A

Definition

MEN2A is an autosomal dominant disorder characterized by medullary thyroid cancer, unilateral or bilateral pheochromocytoma, and primary parathyroid hyperplasia.



Rarely associated with paraneoplastic syndromes, cutaneous lichen amyloidosis, excessive ACTH, and Hirschsprung's disease.



31 patients synchronous with MTC or pheochromocytoma

3 patients first presentation of the MEN 2 syndrome

Schuffenecker I et al J Clin Endocrinol Metab 1998;83: 487

Brandi ML et al. J Clin Endocrinol Metab, 2001, 86:5658

Falchetti A et al. Best Pract & Res Clin Rheumatol 2008; 22:149

EFE 2013



Age-related neoplastic risk profiles in multiple endocrine neoplasia type 2A caused by germline RET Cys634Trp (TGC>TGG) mutation

age-related penetrance profiles

	MTC	PHEO	HPT
30 years	52%	20%	3%
50 years	83%	67%	21%

92 carriers from 20 unrelated families worldwide

Milos I et al .Endocr Relat Cancer. 2008 Sep 15. [Epub ahead of print]

Inherited Causes of Primary Hyperparathyroidism

Syndrome	Parathyroid Pathology	Treatment
MEN 1 (OMIM131100)	Hyperplasia (90%)	Subtotal parathyroidectomy (SPTX)or total parathyroidectomy (TPTX) and autologous parathyroid tissue graft plus transcervical thymectomy
MEN 2A (OMIM 171400)	Hyperplasia (20%-30%)	Resection of the visibly enlarged parathyroid gland(s), SPTX, or TPTX with forearm autograft
MEN 4 (OMIM 610755)	Parathyroid tumors	SPTX or TPTX and autologous parathyroid tissue graft
Familial hypocalciuri hypercalcemia (FHH) (OMIM 145980)	Primary parathyroid hyperplasia due to insensitivity to calcium levels	Not benefit from surgery SPTX in subjects with symptomatic PHPT, even if it is associated with a high incidence of persistent hypercalcaemia
Neonatal Severe Primary Hyperparathyroidism (NSHPT) (OMIM 145980)	Primary parathyroid hyperplasia due to insensitivity to calcium levels	TPTX in the first months of life
Autosomal Dominant Moderate Hyperparathyroidism (ADMH)	Hyperplasia o adenomas	SPTX or TPTX
Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT)	Adenomas (cystic) and carcinoma	Uniglandular disease adenomectomy Multiglandular disease SPTX orTPTX and autologous reimplantation Carcinoma <i>en bloc</i> resection of primary tumor
Familial Isolated Hyperparathyroidism (FIHPT)	Multiglandular (chief cell) hyperplasia	Uniglandular disease adenomectomy Multiglandular disease SPTX



Hyperparathyroidism and MEN 1

TREATMENT

Treatment of choice → **SURGERY**
subtotal parathyroidectomy (SPTX) or
total parathyroidectomy (TPTX) and
autologous parathyroid tissue graft plus transcervical thymectomy

Criteria for the decision about timing for parathyroid surgery:

- severity of PHPT symptoms
- concentration of circulating PTH and calcium
- presence of MEN1-associated endocrinopathies, especially ZES
- patient age

Surgery is recommended in young asymptomatic patients
in whom the serum calcium values are
more than 1 mg/dl over the upper-normal limit and
whose bone mineral density values are lower than -2.5 T-score



Primary hyperparathyroidism in multiple endocrine neoplasia type 1: when to perform surgery?

Early parathyroidectomy predisposes the patient to an earlier recurrence of hyperparathyroidism and the possibility of progressively challenging reoperations



Late surgical interventions are easier because of the glands' more visible enlargement, but hypercalcemic complications increase

Giusti F et al. Clinics.2012;67:141

The timing of surgery requires careful consideration

- surgical experience
- availability for longterm
- regular serum calcium monitoring
- accessibility of calcitriol (or vitamin D analogs)
- patient preference

Thakker RV et al. J Clin Endocrinol Metab, 2012, 97:2990



Hyperparathyroidism and MEN 2A



TREATMENT

Surgery

subtotal parathyroidectomy (surgical ablation of three parathyroid glands and part of the fourth gland)

or

total parathyroidectomy (all four parathyroid glands and thymic tissue)



Pheochromocytoma should be excluded before parathyroidectomy

Falchetti A et al .Best Practice & Research Clinical Rheumatology.2008; 22:149

Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

Question 3. Have sequence tests for the *CASR* gene, MEN-related genes, and other genes become suitable for routine evaluation of some forms of PHPT?

Conclusions

DNA sequence testing for mutations of *CASR*, *MEN1*, and *HRPT2* genes can provide clinically useful information, particularly in known or suspected cases of familial hyperparathyroidism. These studies are not recommended on a routine basis. Mutations in the *RET* gene are of particular value in the management of medullary thyroid carcinoma in MEN2A.



Primary Hyperparathyroidism in clinical practice

Use of genetic tests

We recommend searching for mutation in MEN1 to confirm clinical diagnosis (even in atypical cases) and to identify carriers (in the first decade)

We suggest searching for mutation in HRPT2 in familial form of PTPT not due to MEN1 mutation or in presence of parathyroid carcinoma

We suggest searching for mutation of Ca RS gene in patients with biochemical finding suggestive for FHH or when screening of the familial form of PHPT is inconclusive and also in newborns with severe hypercalcemia

MEN 1

Genetic diagnosis

Who to test?

- index case → meets clinical criteria for MEN1
- w/o MEN1 criteria but suspicious/atypical MEN1
 - 2 or more MEN1-related tumors
 - multiple parathyroid tumors before age 30
 - true recurrent hyperparathyroidism
 - gastrinoma or multiple islet cell tumors at any age
 - familial isolated hyperparathyroidism

- family member with known familial *MEN1* mutation → asymptomatic relative
- relative expressing familial MEN



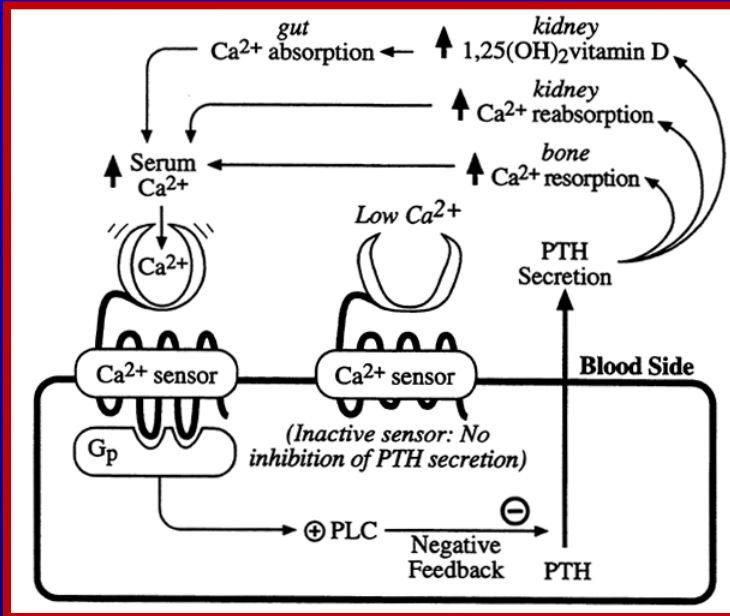
7. Donna di 53 anni con iperparatiroidismo primario (pth=270 pg/ml, calcio=11.64 mg/Dl) e deficit di vitamina d (vitamina d=15.1 ng/ml).
Consigliaresti la supplementazione con vitamina d?

- A. No, peggiorerebbe l'ipercalcemia
- B. Sì, con colecalciferolo monitorando i livelli di calcio e di calciuria
- C. Sì, con calcitriolo monitorando i livelli di calcio e di calciuria
- D. Sì, allo stesso modo di chi è normocalcemico

VITAMINA D e PARATORMONE

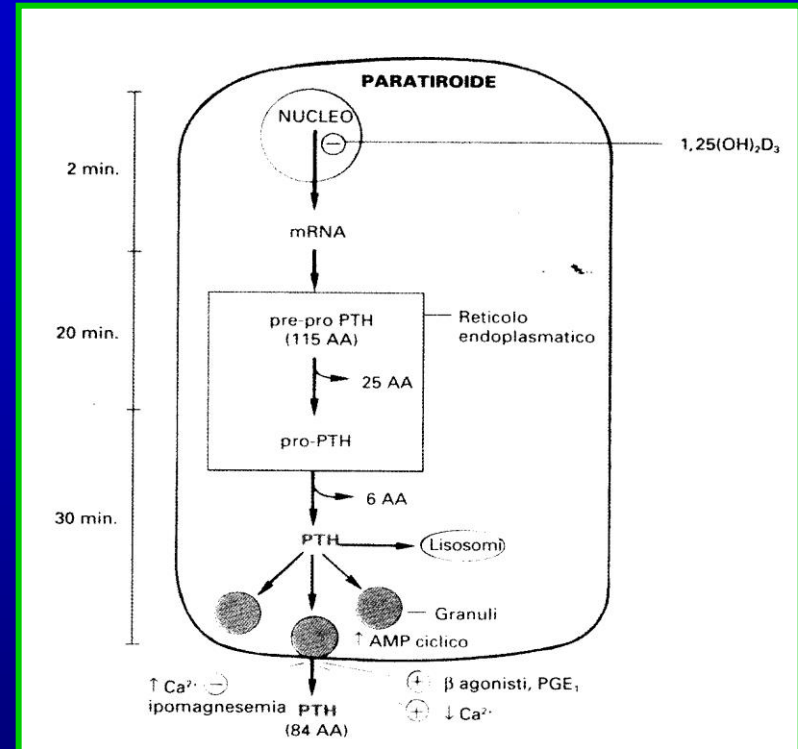
Effetti diretti → VDR

Effetti indiretti → Calcemia



La sintesi del PTH è controllata dalle concentrazioni di Ca⁺⁺ nei fluidi extracellulari

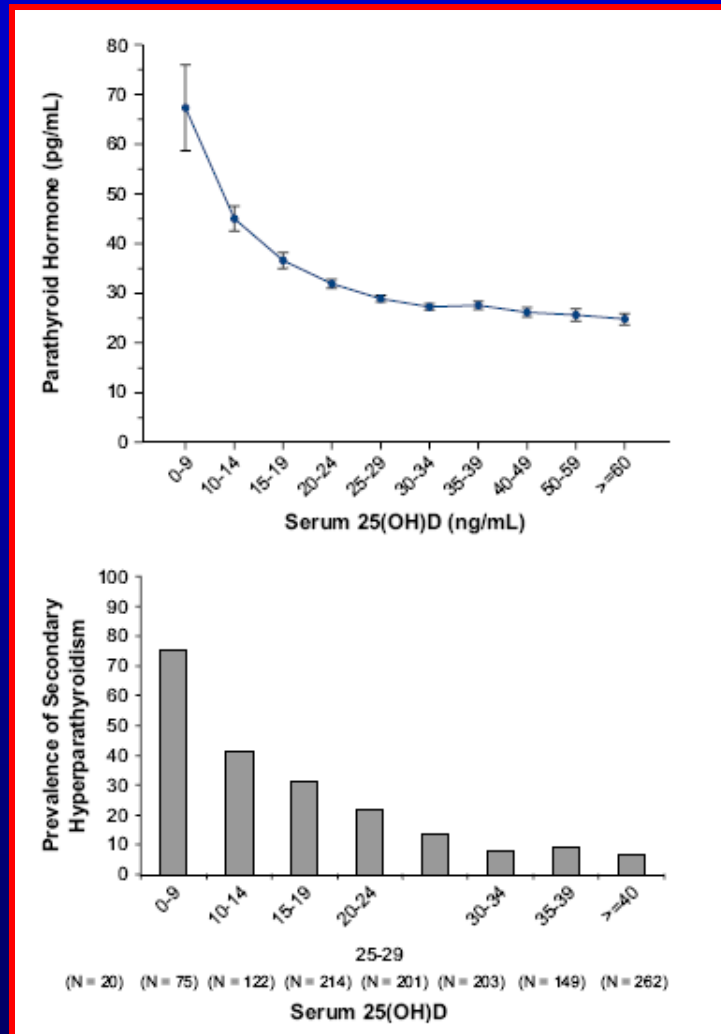
↓ Ca → ↑ PTH



A livello delle cellule paratiroidee reprime l'espressione del gene del PTH
aumenta l'espressione del gene codificante VDR
regola in senso stimolatorio l'espressione di CaSR



VITAMINA D e PARATORMONE

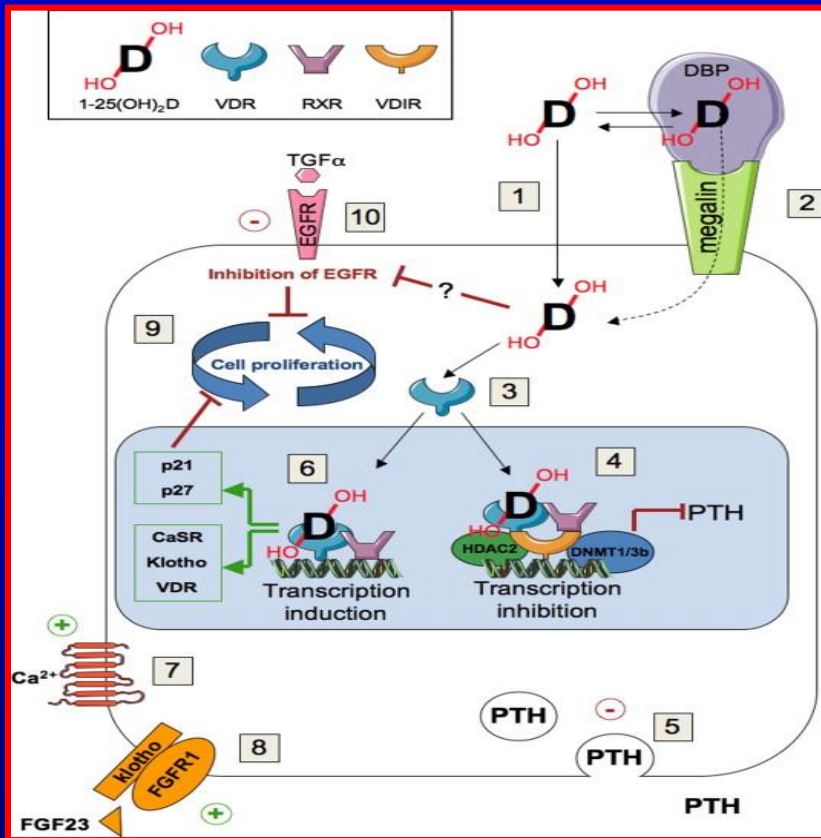


Holick MF. Ann Epidemiol 2009;19:73-78.



VITAMINA D e PARATORMONE

Effetti diretti



A livello delle cellule paratiroidi ha azione anti-proliferativa

meccanismo verosimilmente VDR-indipendente che coinvolge il pathway EGFR/TGFα

VITAMINA D ed IPERPARATIROIDISMO

**IL DEFICIT di VITAMINA D
è più frequente nei pazienti con
IPERPARATIROIDISMO PRIMARIO
che nella popolazione generale con ampia variabilità
geografica di
PREVALENZA, SEVERITA' e PRESENTAZIONE
CLINICA**

Vitamin D status in primary hyperparathyroidism: a Southern European perspective

Baseline characteristics of 113 patients with primary hyperparathyroidism (pHPT) compared with 113 age- and sex-matched healthy blood donor controls

	pHPT (<i>n</i> = 113)	Controls (<i>n</i> = 113)	<i>P</i>
Age (years)	52.9 ± 8.5	51.7 ± 7.7	NS [†]
Sex (M/F)	35/78	35/78	NS [†]
BMI (kg/m ²)	25.59 ± 4.90	25.05 ± 3.50	NS
S-Calcium (mM)	2.78 ± 0.33	2.36 ± 0.87	<0.00001
Ionized calcium (mM)	1.45 ± 0.18	1.21 ± 0.046	<0.00001
PTH (ng/l)*	141 (105–234)	39.1 (29.5–50.2)	<0.00001
25OHD (ng/ml)	29.8 ± 19.1	42.5 ± 21.9	<0.00001
(nm)	74.4 ± 47.7	106.8 ± 54.7	<0.00001
VDD (%)	38 (33.6%)	12 (10.6%)	<0.0001
Severe VDD (%)	10 (8.8%)	2 (1.8%)	<0.034

*Median (interquartile range).
†These lack of difference is expected due to the stratification criteria.
PTH, parathyroid hormone; VDD, Vitamin D deficiency



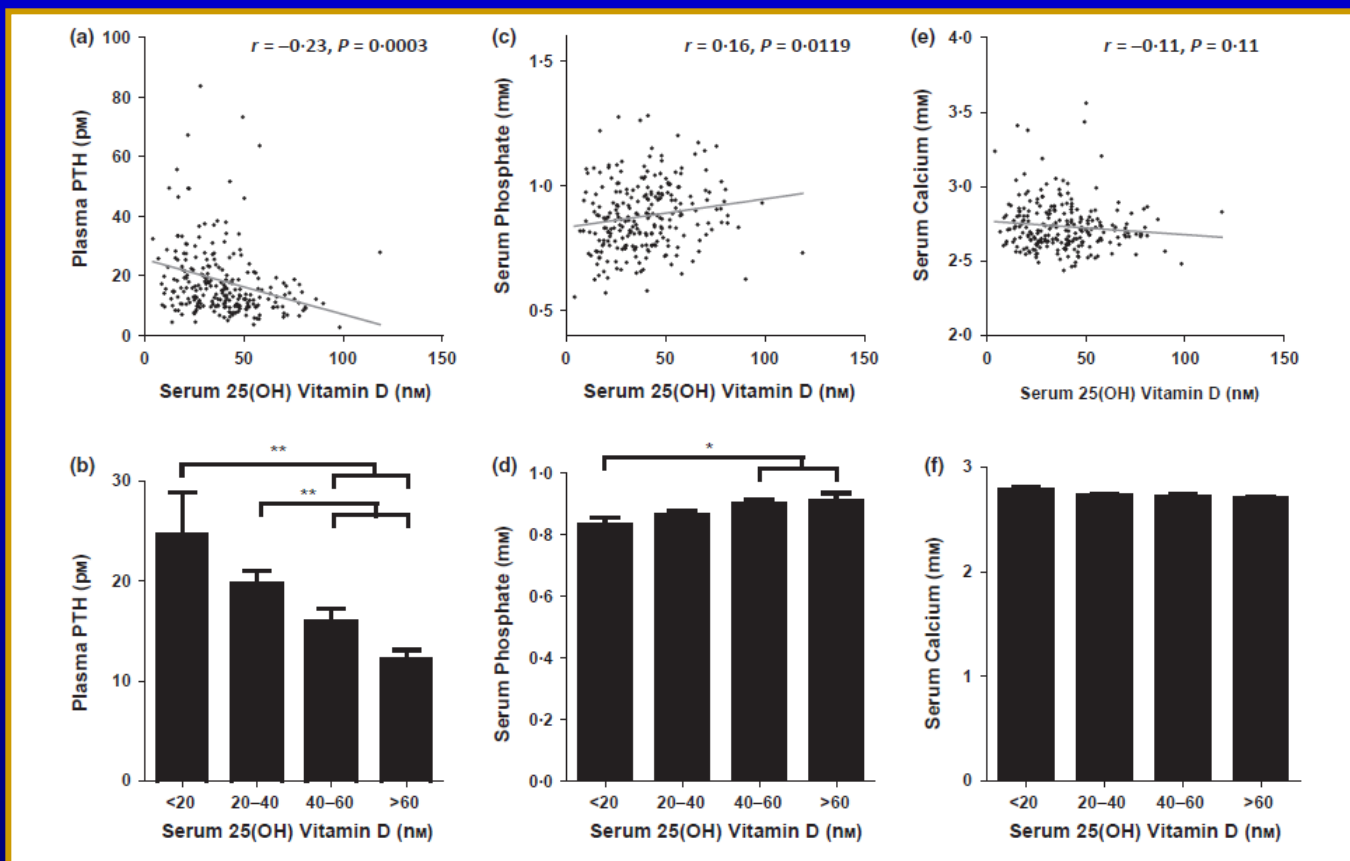
Vitamin D status in primary hyperparathyroidism: a Southern European perspective

Clinical, biochemical and skeletal characteristics in the series of 206 primary hyperparathyroidism patients subdivided according to levels of 25OHD

	Plasma 25OHD		P
	<20 ng/ml (n = 75)	≥ 20 ng/ml (n = 131)	
25OHD (ng/ml)	12.2 ± 4.4	41.0 ± 20.4	<0.0000001
Bone disease (%)	20 (26.7%)	17 (13%)	0.0226
Stone disease (%)	37 (49.3%)	55 (42%)	NS
Age (years)	60.8 ± 14.1	59.4 ± 13.4	NS
BMI (kg/m ²)	25.5 ± 6.1	25.2 ± 4.6	NS
PTH (ng/l)	280.5 ± 249.4	175.9 ± 154.4	<0.0004
S-Calcium (mM)	2.82 ± 0.37	2.75 ± 0.25	0.046
Ionized calcium (mM)	1.49 ± 0.19	1.42 ± 0.15	0.023
S-Phosphate (mM)	0.80 ± 0.16	0.87 ± 0.18	0.009
S-Creatinine (μM)	70.7 ± 16.8	77.8 ± 23.9	<0.04
Alkaline phosphatase (U/l)	124.1 ± 72.7	94.3 ± 36.4	<0.0003
Bone alkaline phosphatase (U/l)	29.4 ± 23.9	19.9 ± 13.7	<0.0006
Osteocalcin (ng/ml)	67.2 ± 69.2	45.8 ± 29.2	<0.003
Urinary cross-links (nmMcr/ml)	15.9 ± 17.5	9.6 ± 5.9	<0.022
Femoral BMD (g/cm ²)	0.69 ± 0.14	0.76 ± 0.19	<0.017
Femoral T-score	-2.28 ± 1.2	-1.85 ± 1.26	<0.025
Lumbar BMD (g/cm ²)	0.77 ± 0.17	0.84 ± 0.17	<0.005
Lumbar T-score	-2.79 ± 1.36	-2.36 ± 1.42	<0.045
Forearm BMD (g/cm ²)	0.38 ± 0.11	0.44 ± 0.13	<0.001
Forearm T-score	-2.85 ± 1.68	-1.94 ± 1.58	<0.00045

BMD, bone mineral density; PTH, parathyroid hormone.

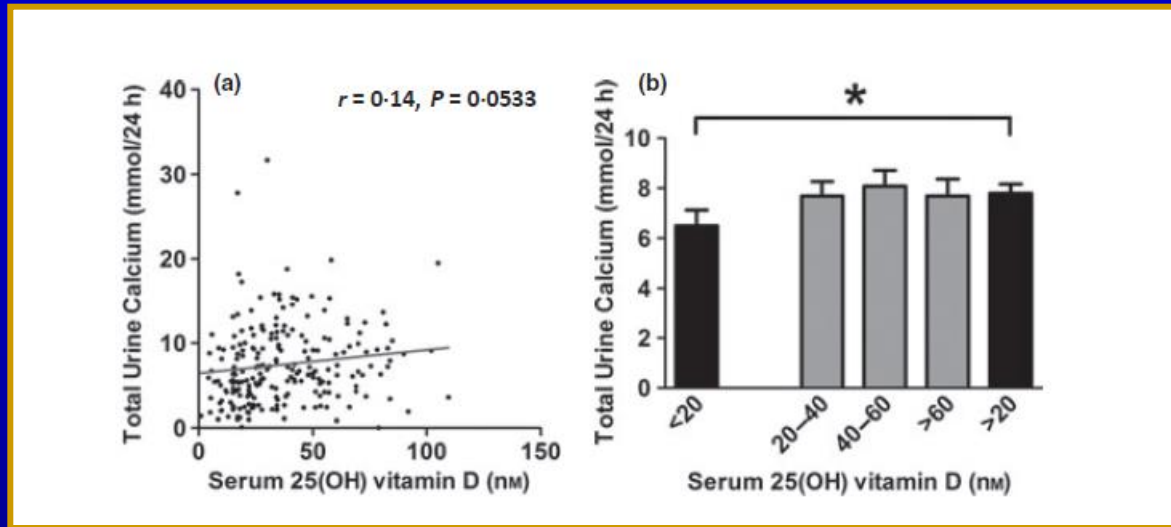
Associations of serum 25-hydroxyvitamin D with circulating PTH, phosphate and calcium in patients with primary hyperparathyroidism



Relationships between the mean circulating levels of circulating 25-OH vitamin D, parathyroid hormone (PTH), phosphate and calcium during the entire pretreatment period in each patient with primary hyperparathyroidism.



Associations of serum 25-hydroxyvitamin D with circulating PTH, phosphate and calcium in patients with primary hyperparathyroidism



Relationships between measurements of circulating 25-OH vitamin D and total urinary calcium excretion in each patient with primary hyperparathyroidism (PHP)

Multifactorial Risk Profile for Bone Fractures in Primary Hyperparathyroidism

Table 3. Final logistic regression model showing determinants of bone fracture in the 5-year-period prior to pHPT surgery.

Variable	β -Coefficient	SE (β)	<i>p</i> -value
Constant	-1.3922	1.0536	
Histopathology (adenoma/hyperplasia)	1.8614	1.3493	0.17
Intact s-PTH	0.1010	0.0516	< 0.05
s-25(OH)D ₃	-0.0610	0.0232	< 0.01
s-ICTP	0.1211	0.0659	0.07

Table 5. Final logistic regression model showing determinants of bone fracture in the 10-year-period prior to pHPT surgery.

Variable	β -Coefficient	SE (β)	<i>p</i> -value
Constant	-0.9169	0.9922	
Intact s-PTH	0.0621	0.0459	0.18
s-25(OH)D ₃	-0.0420	0.0183	< 0.05
s-ICTP	0.0841	0.0573	0.14

In PHPT, serum levels of 25-hydroxyvitamin D 3 and PTH were independently associated with a history of bone fractures



IPERPARATIROIDISMO PRIMARIO → DEFICIT di VITAMINA D

Possibili cause

- Deplezione dei depositi di 25 (OH) D per maggiore conversione in 1-25 (OH) D (↑ PTH)
- Riduzione della conversione a livello cutaneo del 7-deidrocoleterolo in pre-vitamina D (↑ Calcemia e ↑ PTH)
- Aumento dell'inattivazione epatica di 25 (OH) D (↑ calcitriolo)
- Ridotta assunzione di cibi ricchi di vit D e di supplementi di vit D
- Ridotta esposizione alla luce UV per riduzione delle attività all'aria aperta
- Ridotta biodisponibilità per aumentato peso corporeo

Bollerslev J et al. Eur J Endocrinol. 2011;165:851,
Nutri R et al. J Endocrin Invest. 2011; 34:45



DEFICIT di VITAMINA D ED IPERPARATIROIDISMO PRIMARIO

Supplementazione Vitamina D

- Diagnosi differenziale tra PHPT e SHPT
- Riduzione del rischio postoperatorio di ipocalcemia
- Effetti a lungo termine su rischio di frattura, funzione muscolare e rischio cardiovascolare



- Ipercalcemia
- Ipercalciuria
- Compromissione funzione renale
- Litiasi renale

VITAMINA D ed IPERPARATIROIDISMO

Current evidence for recommendation of surgery, medical treatment and vitamin D repletion in mild primary hyperparathyroidism

Statement	Design	Level of evidence
PHPT is associated with vitamin D insufficiency/deficiency	Clinical decision rule	2b
→ Vitamin D supplementation increases diagnostic separation between PHPT and SHPT	Case series	4
→ Vitamin D treatment lowers preoperative PTH levels	1 Case series 3 Cohort studies	4 2b
→ Vitamin D treatment lowers bone turnover (inconsistent results)	3 Low-quality cohort studies	4
→ High vitamin D status decreases risk of postoperative hypocalcaemia and SHPT	1 Case series	4



IPERPARATIROIDISMO PRIMARIO NORMOCALCEMICO

It is important to rule out causes for an elevated parathyroid hormone level apart from primary hyperparathyroidism

The most common cause of secondary elevations in parathyroid hormone is vitamin D deficiency

If the cause of the elevated PTH level is low vitamin D, repletion with vitamin D would be associated with normalization of the PTH level

It should be noted, however, that occasionally when vitamin D deficiency is corrected, a normocalcemic patient becomes hypercalcemic and thus their presentation becomes that of traditional hypercalcemic primary hyperparathyroidism. In that instance, the normocalcemia was due to the Vitamin D deficiency



VITAMINA D ed IPERPARATIROIDISMO

Supplementazione Vitamina D → Iperparatiroidismo primario

Ipocalcemia Postchirurgica

	<i>Asymptomatic (n = 108)</i>	<i>Symptomatic (n = 73)</i>	<i>P value†</i>
Preoperative calcium levels (mg/dL)	11.1 ± 0.6	11.0 ± 0.7	.53
Preoperative iPTH levels (pg/mL)‡	141.6 ± 77.9	152.8 ± 67.9	.15
Preoperative 25[OH]D levels (ng/mL)‡¶	28.7 ± 22.2	20.1 ± 16.4	.004
Adenoma weight (mg)‡#	1,052.4 ± 1,436.1	1,258.2 ± 1,677.8	.49
Percent intraoperative change in iPTH from baseline to 10 minutes**§	72.0 ± 20.1	73.1 ± 15.0	.87
Postoperative calcium levels (mg/dL) ^a	9.4 ± 0.5	9.3 ± 0.8	.20
Postoperative iPTH levels (pg/mL)‡ ^b	57.9 ± 33.4	56.5 ± 38.9	.58

Il deficit di 25 OH vitamina D è un fattore di rischio per i sintomi di ipocalcemia postchirurgica e iperparatiroidismo secondario dopo paratiroidectomia minimamente invasiva

Stewart ZA et al. Surgery 2005;138:1018

Studies addressing the effects of vitamin D supplementation in subjects with primary hyperparathyroidism

Study	No.	Inclusion criteria	Supplementation regimen	Outcomes
Kantorovich et al (2000) ¹⁸	5	25-OHD <25 nmol/L	1000 mg elemental calcium daily and 50 000 units vitamin D ₂ twice weekly for 5 weeks	No significant change in serum calcium Hypercalciuria in three subjects
Grey et al (2005) ¹³	21	Serum calcium <3.0 mmol/L 25-OHD <50 nmol/L	50 000 units vitamin D ₃ weekly for 4 weeks then monthly for 12 months	No significant change in serum calcium Hypercalciuria in three subjects at 6 months, persisting in two at 12 months: no consequent urolithiasis recorded 25% decrease in PTH
Grubbs et al (2008) ²⁰	112	25-OHD <75 nmol/L	Vitamin D ₂ , median dose 400 000 units (range 24 000–1 500 000 units) over 3–210 days (median 28 days)	No significant change in serum calcium
Tucci (2009) ²¹	56	Serum calcium 2.63–3.0 mmol/L 25-OHD <60 nmol/L	50 000 units vitamin D ₂ weekly for 8 weeks, then maintenance doses ranging from 800 units daily to 100 000 units monthly. Final measures after 34 weeks of supplementation	No significant change in serum calcium or urine calcium excretion
Isidro and Ruano (2009) ²²	27	25-OHD <50 nmol/L	480–960 units 25-OHD daily for 12 months	No significant change in serum calcium Significant increase in mean urinary calcium excretion
Velayoudom-Cephise et al (2011) ²³	22	25-OHD <75 nmol/L	800–1200 units vitamin D ₂ daily for 3–6 months then 100 000 units vitamin D ₃ monthly Final measures after 6 months of supplementation	Significant decrease in serum calcium Nonsignificant increase in mean urinary calcium excretion 49% decrease in mean PTH

25-OHD = 25-hydroxyvitamin D; vitamin D₂ = ergocalciferol; vitamin D₃ = cholecalciferol



Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

Question 5: Should we measure 25-OHD in all patients with suspected PHPT? How should the different reference ranges for different assays be interpreted? What represents the threshold for overtreatment?

Conclusions

Vitamin D deficiency is common in patients with PHPT, and measurement of serum 25-OHD levels is recommended routinely. Vitamin D deficiency should be treated before making any medical or surgical management decisions. It is recommended that serum 25-OHD be maintained above 50 nmol/liter.

Standardization of the clinical laboratory measurement of serum 25-OHD assays is needed. It is also recommended that further research be conducted to determine the optimal vitamin D levels for individuals with PHPT, including randomized clinical trial data with vitamin D supplementation.



Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

Recommendation

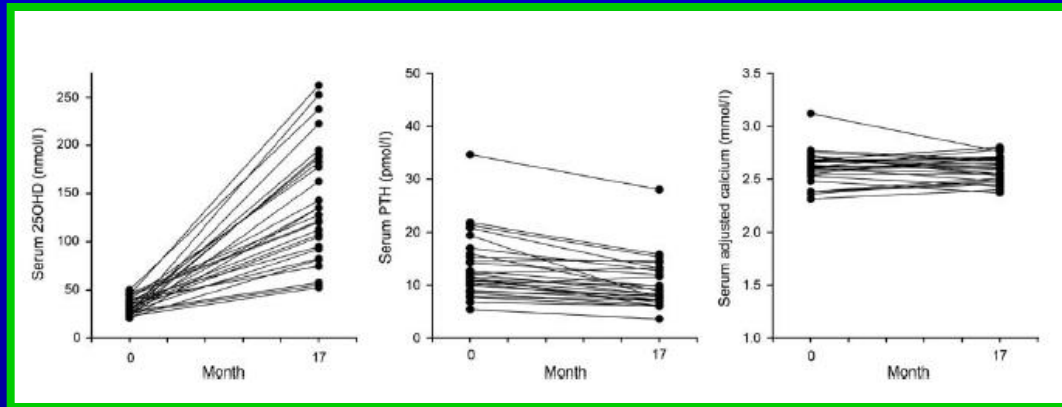
3.7 For patients with primary hyperparathyroidism and vitamin D deficiency, we suggest treatment with vitamin D as needed. Serum calcium levels should be monitored (2|⊕⊕⊕⊕)

3.7 Evidence

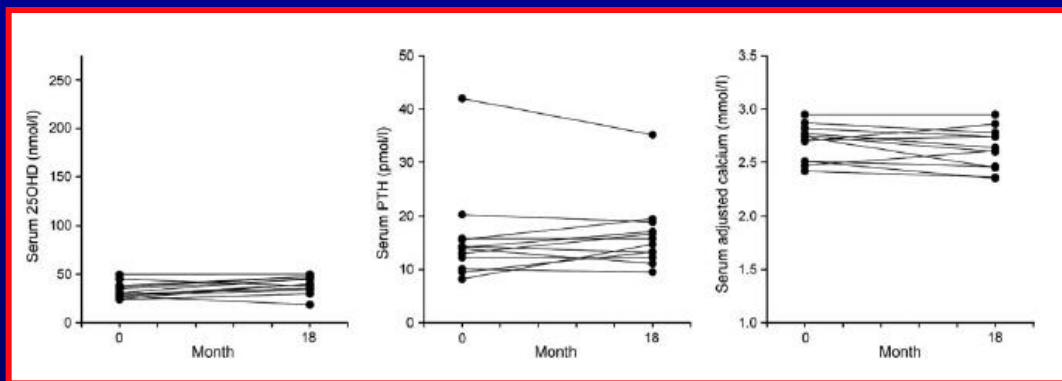
Patients with primary hyperparathyroidism and hypercalcemia are often vitamin D deficient. It is important to correct their vitamin D deficiency and maintain sufficiency. Most patients will not increase their serum calcium level, and serum PTH may even decrease. Their serum calcium should be monitored.

Prolonged treatment with vitamin D in postmenopausal women with primary hyperparathyroidism

Changes in 25OHD, PTH and adjCa levels in postmenopausal women with pHPT and coexistent hypovitaminosis D



treated with vitamin D with in various preparations



not treated with vitamin D

9. Donna di 80 anni, con cardiopatia ischemica, bpcO, malattia di parkinson ed osteoporosi, affetta da iperparatiroidismo primario ipercalcemico (calcio=12.3 mg/Dl, PTH=198 pg/ml) da verosimile adenoma paratiroideo destro. Consiglierebbe?

- A. Date le comorbidità e l'età della paziente (che rendono controindicato l'intervento chirurgico), e' indicato stretto follow up
- B. Terapia medica con cinacalcet perchè il problema più rilevante è abbassare la calcemia
- C. Terapia medica con bisfosfonati perchè il problema più rilevante è prevenire il rischio di frattura di femore
- D. Una opzione ragionevole potrebbe essere associare la terapia con cinacalcet e bisfosfonati

Management of primary hyperparathyroidism

Medical Therapy

Pharmacological treatment can be indicated for patients with:

- contraindications to surgical treatment
- surgical failure
- no current criteria for surgical treatment

At this time, there are insufficient long-term data to recommend as an alternative to surgery any of the four classes of potential medical approaches:

bisphosphonates

estrogen

selective estrogen receptor modulators (SERMs)

calcimimetic

Management of primary hyperparathyroidism

The decision to employ a pharmacological approach depends on
goal of treatment
↓ serum calcium levels
and/or
↑ BMD

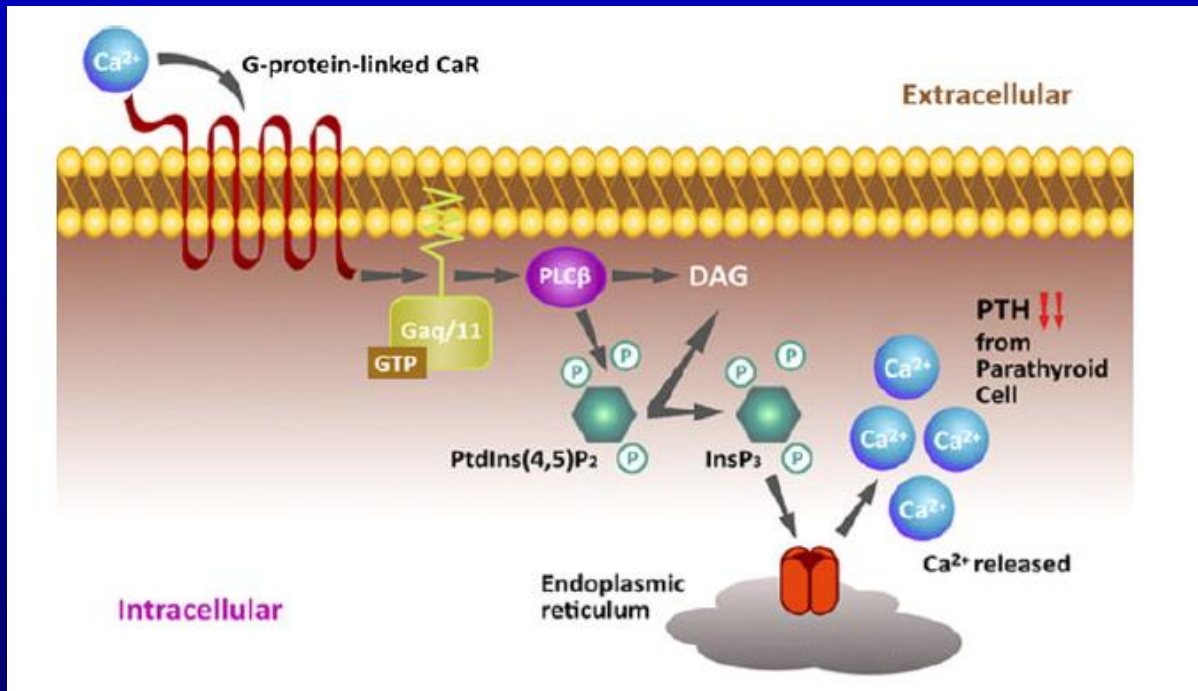
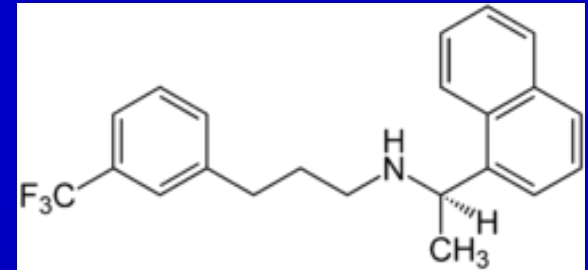
Medical treatment and the effects on bone

Treatment	BMD ¹	BTM ²	Serum calcium	Serum PTH ³	Level of evidence
Cinacalcet hydrochloride	No change	Increases	Decreases to normal often	Decreases slightly	1B
Conjugated estrogen + medroxyprogesterone	Increases	Decreases	No change	No change	1B
Raloxifene	NA ⁴	Decreases	Decreases	Decreases	1B
Alendronate	Increases	Decreases	No change	No change	1B

¹BMD: bone mineral density; ²BTM: bone turnover markers; ³PTH: parathyroid hormone; ⁴NA: not available.

Cinacalcet

Calcimimetics act at the calcium sensing receptor to reduce synthesis and secretion of PTH with consequent lowering of serum calcium



Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study

Cinacalcet is currently indicated for:

- treatment of secondary HPT in patients with chronic kidney disease on dialysis
- treatment of hypercalcemia in patients with parathyroid carcinoma
- reduction of hypercalcemia in patients with PHPT for whom parathyroidectomy is indicated on the basis of calcium levels but in whom surgery is clinically inappropriate or is contraindicated

Cinacalcet as alternative treatment for primary hyperparathyroidism: achievements and prospects

Short-term indication

Interim solution before surgery

Long-term indications

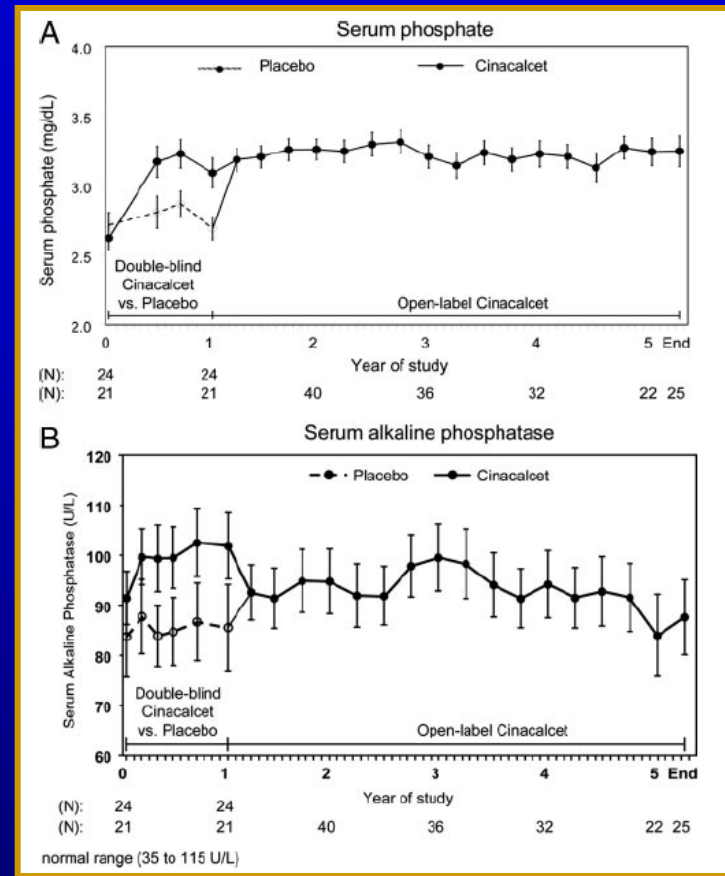
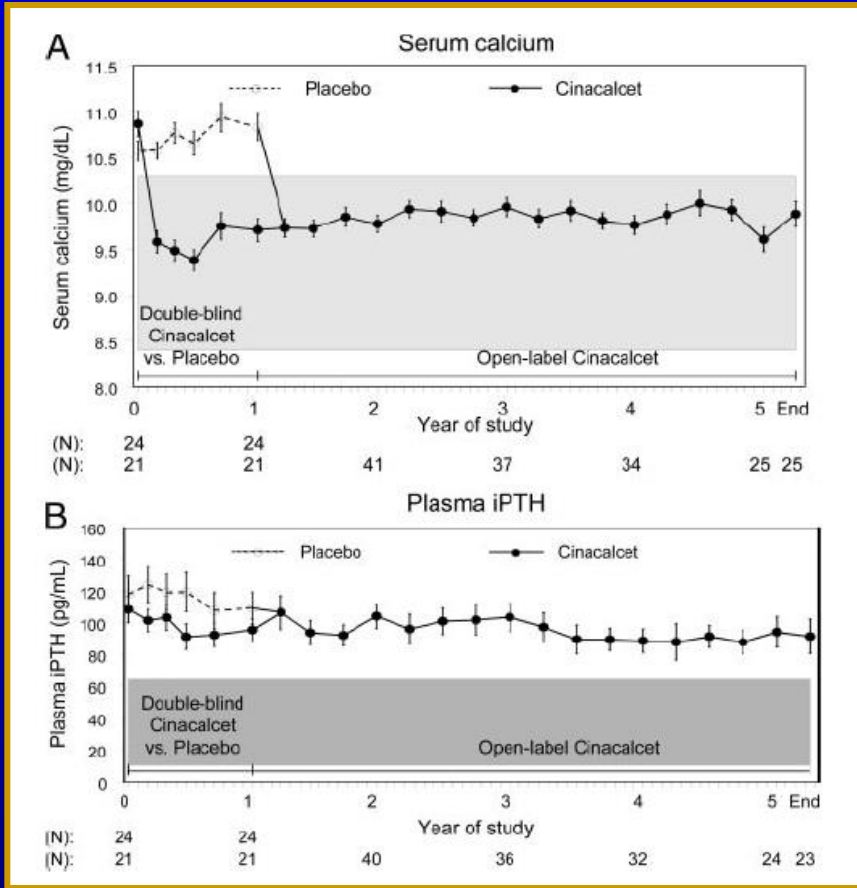
Intractable pHPT

Patients with pHPT whom surgery is inappropriate

Inoperable thyroid carcinoma

MEN1 associated hyperparathyroidism

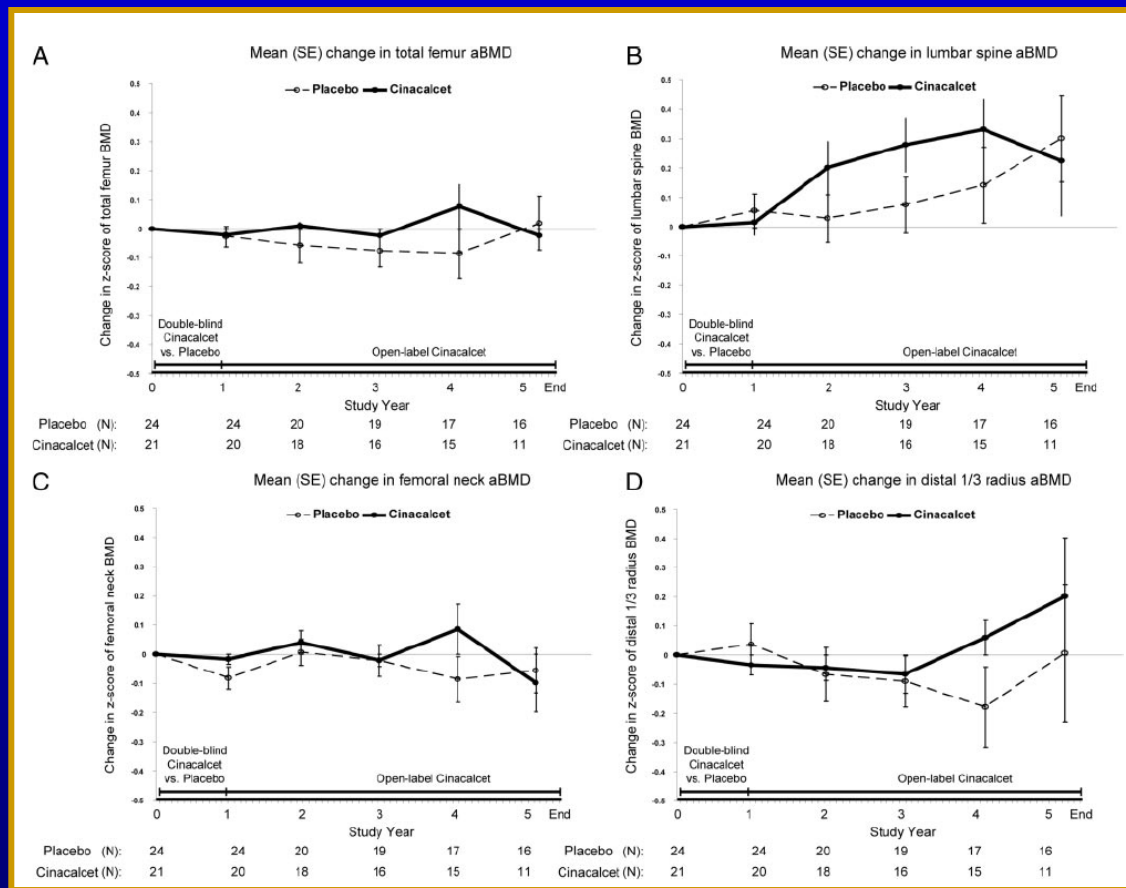
Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study



Cinacalcet treatment improved biochemical measures of PHPT including reducing serum calcium and PTH and increasing serum phosphate with slight increases in alkaline phosphatase



Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study



Analysis of Z-scores showed no improvements in BMD at the spine, wrist, femoral neck, and total femur and a nonsignificant trend to increased Z-scores at the lumbar spine



Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study

AE rate over the course of the parent trial and the open-label extension (no significant differences)

	Placebo (n = 24)	Cinacalcet
AE during initial 52-wk placebo-controlled trial (%)		
Headache	38	10
Arthralgia	25	14
Myalgia	25	24
Nausea	17	29
AE during the 4.5-yr, open-label extension study (%)		
Arthralgia		38
Myalgia		27
Diarrhea		22
Upper respiratory infection		20
Nausea		20

For the cinacalcet values, n = 21 for the initial trial and 45 for the extension study.



Medical Management of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

Bisphosphonate

Alendronate decreases bone turnover and increases BMD at the lumbar spine and proximal femur in PHPT

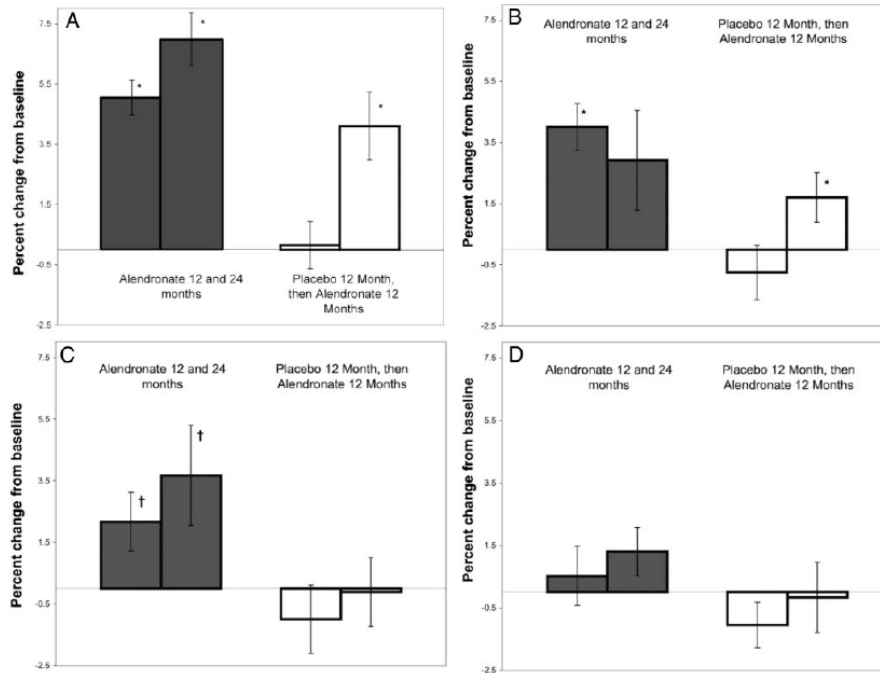
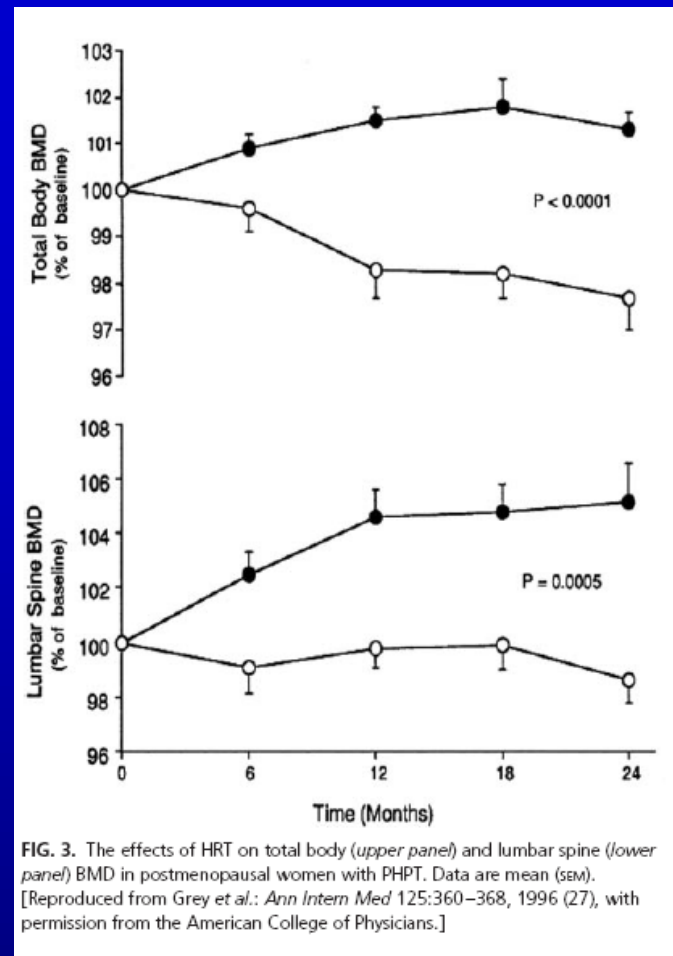


FIG. 1. Effects of alendronate on lumbar spine (A), total hip (B), femoral neck (C), and one third distal radius (D) BMD. *, Significantly higher than baseline ($P < 0.001$); †, Significantly higher than baseline ($P < .05$). [Reproduced with permission from Khan et al.: *J Clin Endocrinol Metab* 89:3319–3325, 2004 (23).]

Bisphosphonate therapy in PHPT may lead to improvement in bone strength, there are no direct data to confirm this effect, and fracture outcomes have not been evaluated

Hormon replacement therapy

In postmenopausal women with PHPT, a 2-yr randomized, placebo-controlled trial demonstrated beneficial effects on BMD at multiple sites throughout the skeleton in the estrogen-treated women, with between-group differences at the end of the study similar to those reported in eucalcemic women treated with HRT



Bisphosphonates and HRT are treatment options for those individuals with PHPT for whom skeletal protection is the primary reason for intervention. Of the two agents, bisphosphonates are clearly preferred, because of the adverse nonskeletal effects of long-term HRT

Cinacalcet hydrochloride in combination with alendronate normalizes hypercalcemia and improves bone mineral density in patients with primary hyperparathyroidism

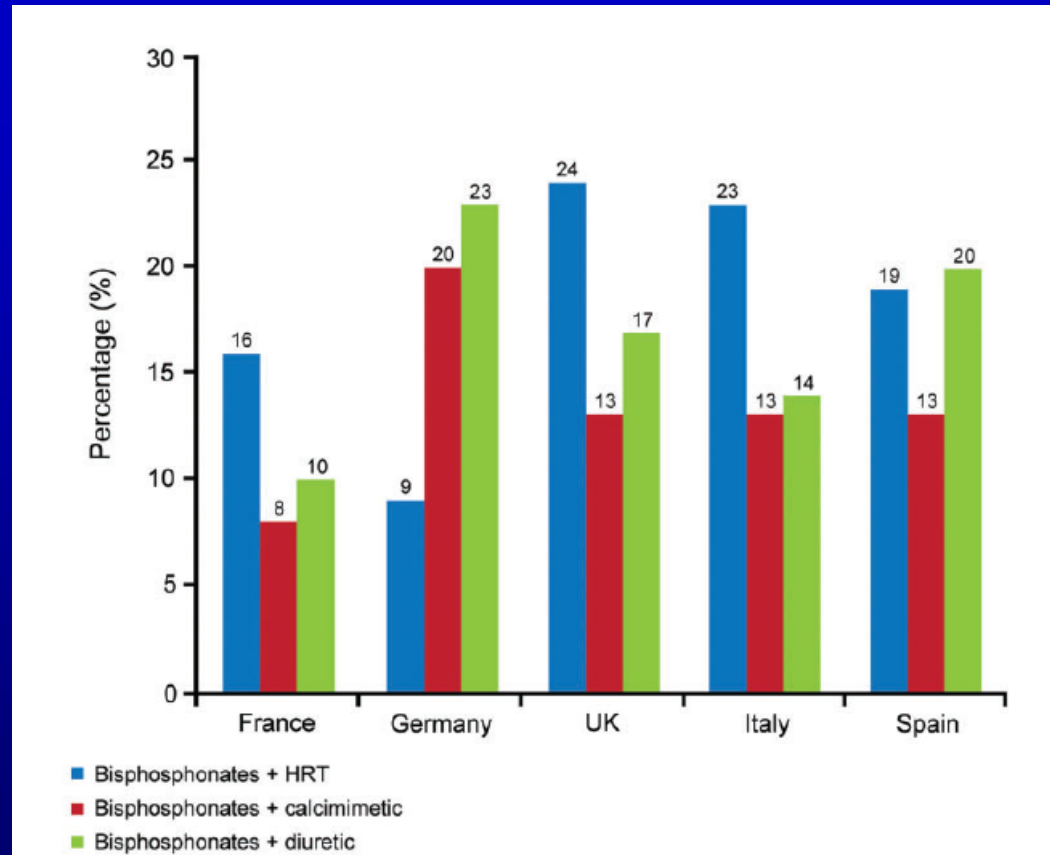
% change of biochemistry and bone mineral density from baseline to month 12 according to treatment subgroup

	Cinacalcet + alendronate <i>n</i> = 10	Cinacalcet <i>n</i> = 13
Serum calcium (mg/dl)	-14 ± 1.4	-12 ± 1.3
Serum PTH (pg/ml)	-29 ± 8.4	-25 ± 5.9
Bone alkaline phosphatase (U/L)	-41 ± 9.5 ^a	-16 ± 4.8
Serum 25OH-Vitamin D (ng/ml)	+18 ± 4.8	+17 ± 4.0
24-h urine calcium (mg/die)	-29 ± 8.7	-25 ± 7.7
24-h urine calcium to creatinine ratio	-23 ± 7.6	-18 ± 5.5
Lumbar spine (<i>T</i> -score)	+9.6 ± 1.4 ^b	+1.3 ± 0.9
Total femur (<i>T</i> -score)	+3.9 ± 1.0 ^a	+1.1 ± 0.8

- The biochemical abnormalities are rapidly improved by cinacalcet, resulting in normocalcemia and decrease of serum PTH and urinary calcium concentrations
 - These results are stably maintained during a 24 month follow-up
- Cinacalcet is equally effective on calcium and PTH serum abnormalities either when used in monotherapy or in combination with alendronate
- BMD is unchanged in patients receiving cinacalcet in monotherapy and improved in those receiving a combined therapy with cinacalcet and alendronate



In the present survey, bisphosphonates were the most widely used treatments for PHPT and when used in combination were generally combined with HRT, diuretics or cinacalcet



DONNA DI 41 ANNI, CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 11.8 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 2.4 MG/DL, V.N.:2.5-5.1) ED IPERPTH (220 PG/ML; V.N.:15-90).

IN UNA IPOTETICA SCALETTA SEQUENZIALE QUALE, TRA QUESTE SERIE DI ESAMI DI IMAGING, È LA PIU' CORRETTA PER VISUALIZZARE IL POSSIBILE ADENOMA PARATIROIDEO?

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- B. RMN COLLO-TORACE, SCINTIGRAFIA CON 99MTC-SESTAMIBI, ECOGRAFIA DEL COLLO, TAC COLLO-TORACE.
- C. ECOGRAFIA DEL COLLO CON FNAB E DOSAGGIO DEL PTH NEL LIQUIDO DI LAVAGGIO IN CASO DI LESIONE ECOGRAFICA SOSPETTA PER ADENOMA, BEN EVIDENTE ALL'ECOGRAFIA, A SEGUIRE LE EVENTUALI ALTRE METODICHE UTILI.

D. RX TORACE +TAC DEL COLLO.

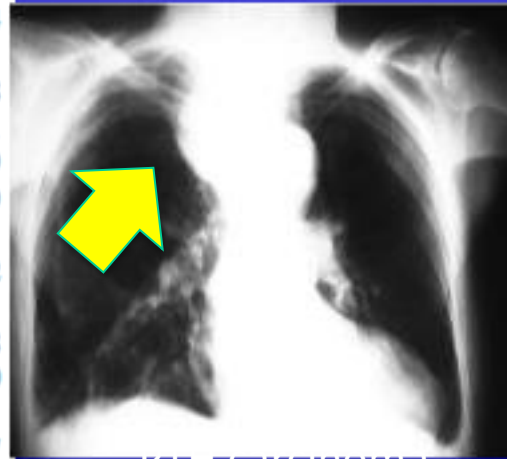
DONNA DI 41 ANNI, CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 11.8 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 2.4 MG/DL, V.N.:2.5-5.1) ED IPERPTH (220 PG/ML; V.N.:15-90).

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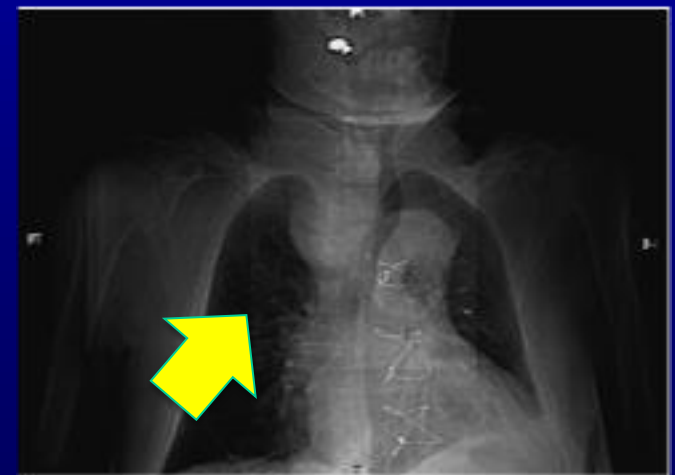
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Occasionally, a routine chest x-ray may reveal a parathyroid mass at X-ray films



PTH carcinoma

Vazquez et al. Singapore Med J 2007



McKay et al. ANZ J Surg 2007

DONNA DI 41 ANNI, CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 11.8 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 2.4 MG/DL, V.N.:2.5-5.1) ED IPERPTH (220 PG/ML; V.N.:15-90).

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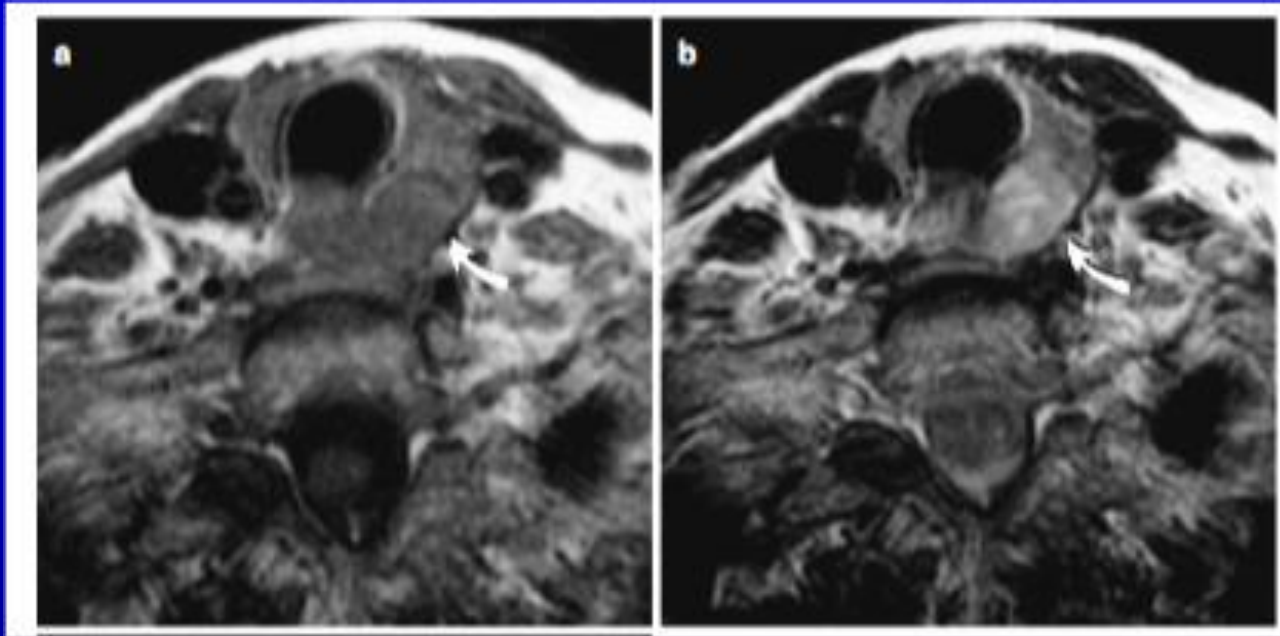
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C. ECOGRAFIA DEL COLLO CON FNAB E DOSAGGIO DEL PTH NEL LIQUIDO DI LAVAGGIO IN CASO DI LESIONE ECOGRAFICA SOSPETTA PER ADENOMA, BEN EVIDENTE ALL'ECOGRAFIA, A SEGUIRE LE EVENTUALI ALTRE METODICHE UTILI.

D. RX TORACE +TAC DEL COLLO.

PARATHYROID ADENOMA LOCATED IN THE MEDIASTINUM

ROLE OF MRI



False Positive

Parathyroid Adenoma
at MRI corresponding
to positive imaging at
SESTAMIBI:

Postoperative diagnosis
Thyroid adenoma

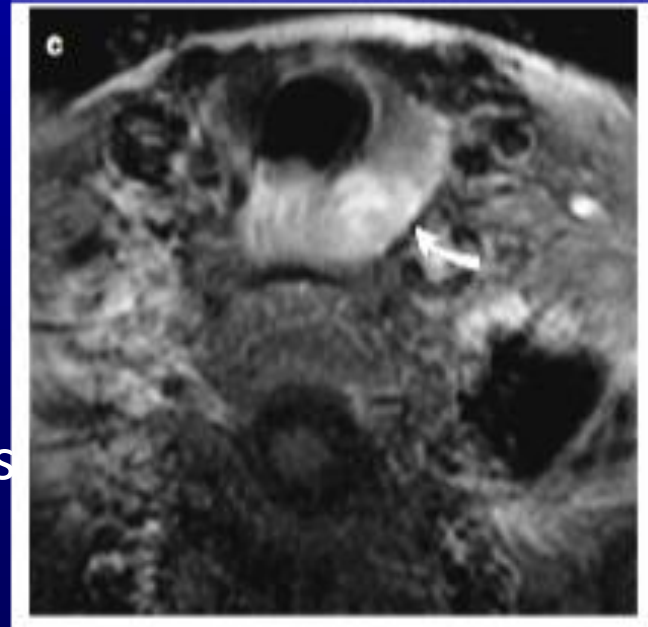
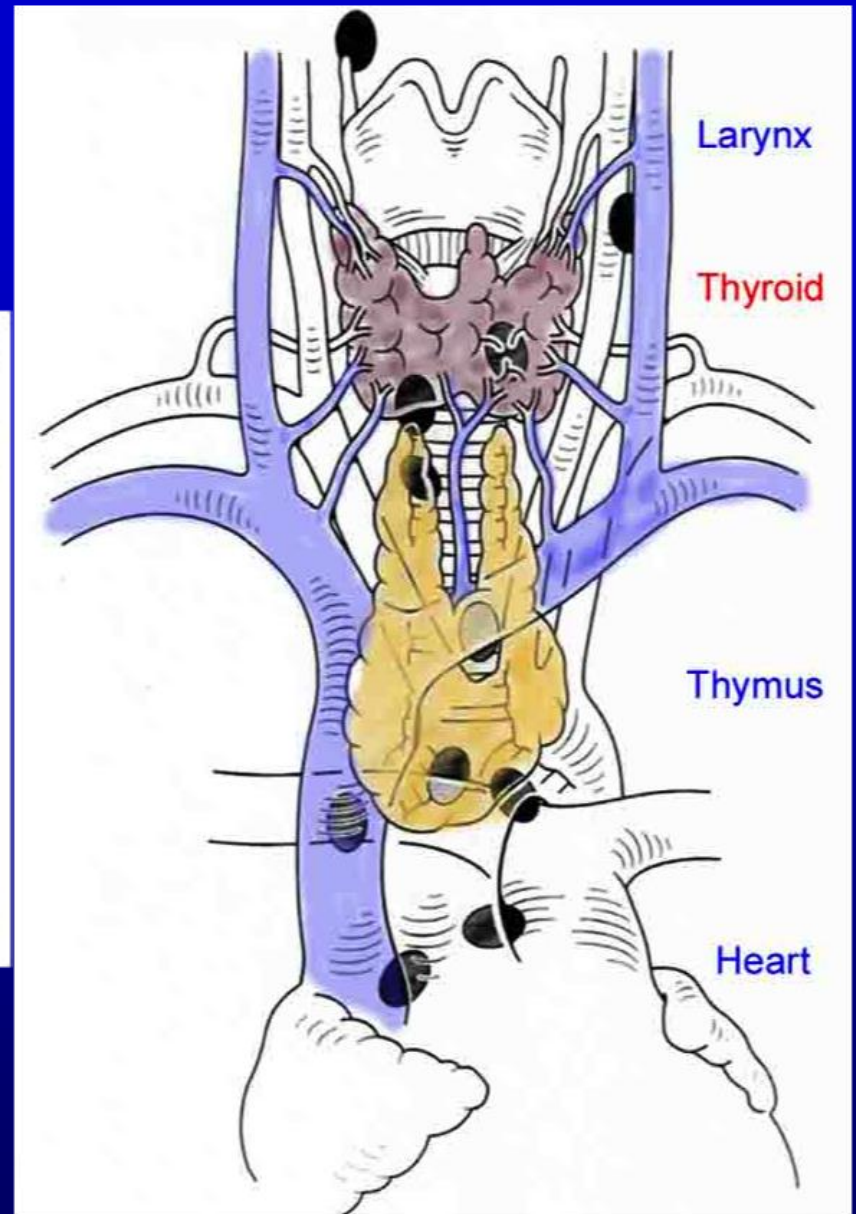


Table 2.1 Location of 54 ectopic parathyroid glands identified by Shen and coworkers [14]

Location	Number
High cervical	1
Aorticopulmonary window	2
Posterior mediastinum	3
Carotid sheath	5
Intrathyroid	6
Anterior mediastinum (nonthymic)	9
Intrathymic	13
Paraesophageal (neck)	15

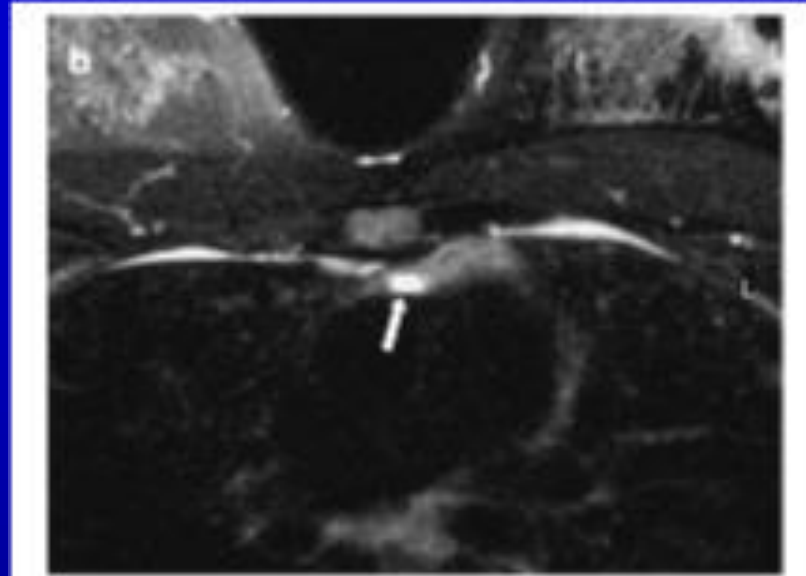
Shen et al. Arch Surg 1996



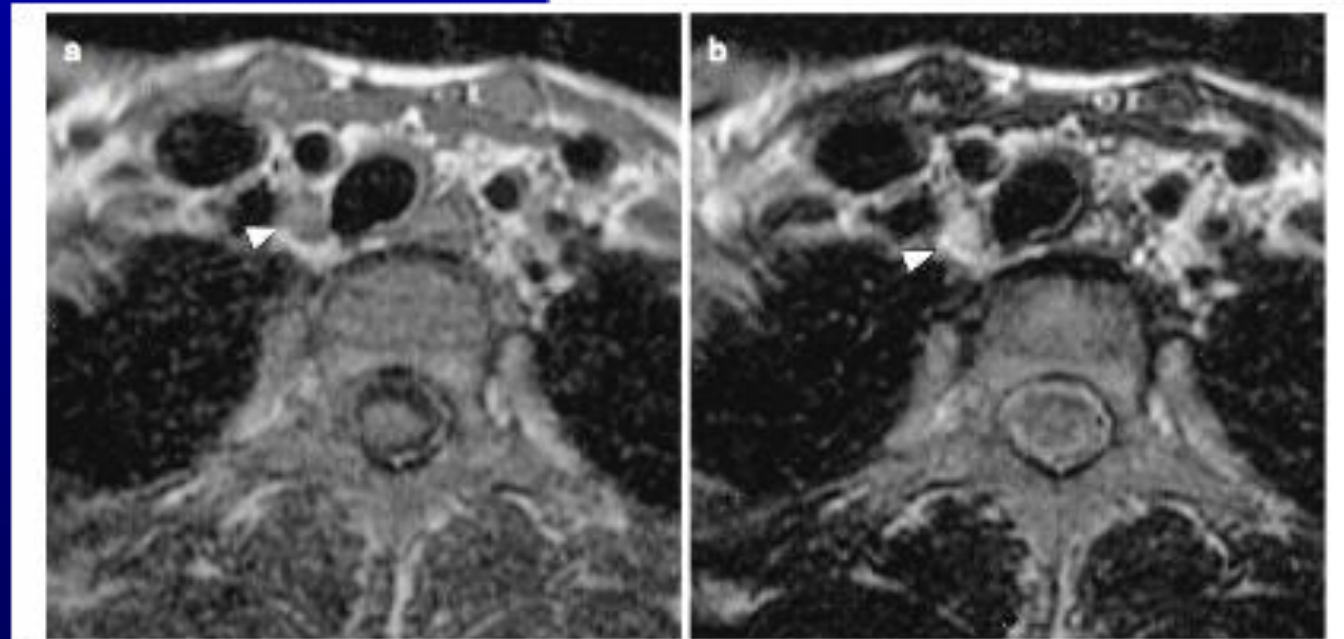
PARATHYROID ADENOMA LOCATED IN THE MEDIASTINUM

ROLE OF MRI

Mediastinic Adenoma



Recurrent
Adenoma



PARATHYROID ADENOMA LOCATED IN THE MEDIASTINUM ROLE OF SESTAMIBI

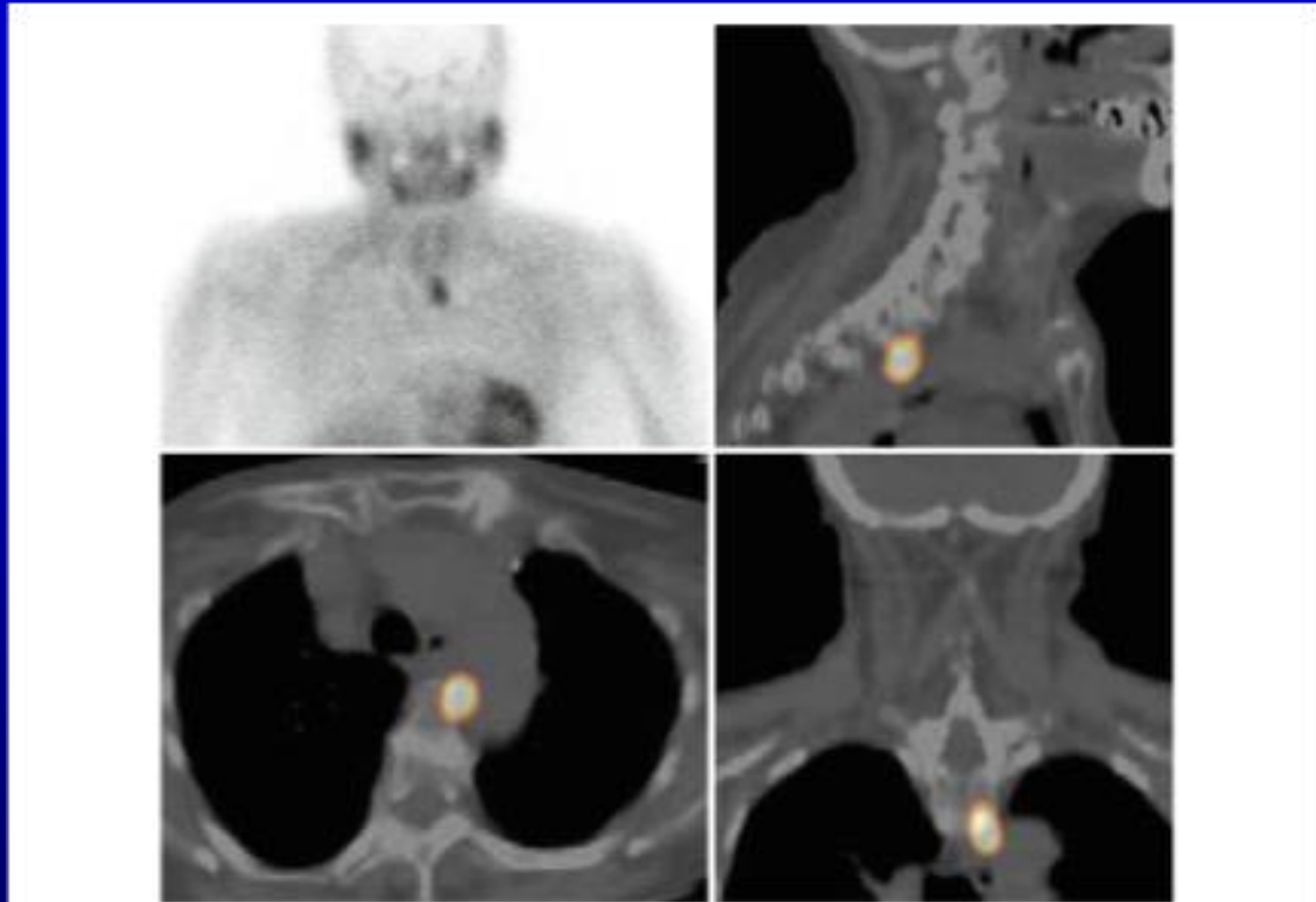


Fig. 10.9 ^{99m}Tc -sestamibi scintigraphy images of a left superior parathyroid adenoma which has migrated towards the posterosuperior mediastinum by gravity. Planar image

finds a left parathyroid adenoma. SPECT images (sagittal, axial, and coronal imaging planes) help in the diagnosis of left paroesophageal location

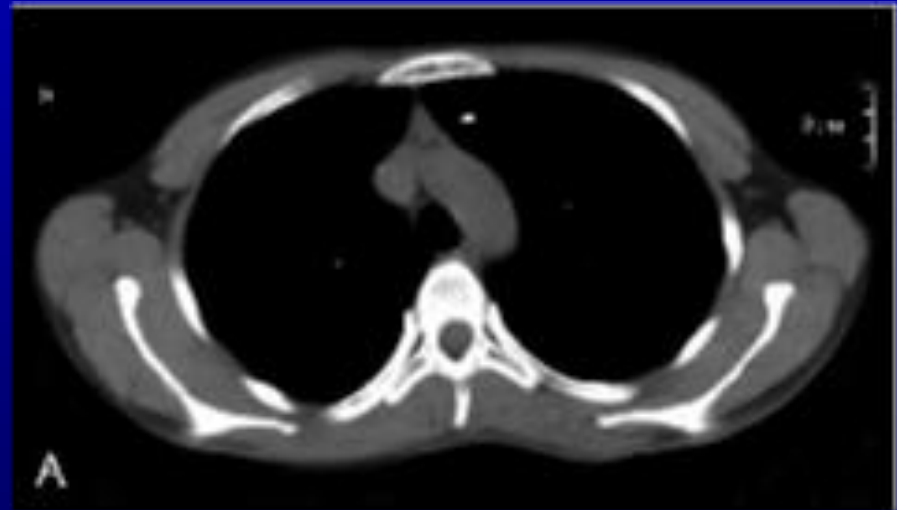
PARATHYROID ADENOMA LOCATED IN THE MEDIASTINUM ROLE OF CT SCAN

SPECIAL FEATURE

Clinical Case Seminar

A Case of Primary Hyperparathyroidism due to Ectopic Parathyroid Adenoma in the Thymus, Accompanied With Vitamin D Deficiency

Guoxing Wang,* Haijuan Xiao,* Zhenyang Gu, and Tongfeng Zhao



Wang et al. JCE&M 2013

Parathyroid Localization and Implications for Clinical Management

John W. Kunstman, Jonathan D. Kirsch, Amit Mahajan, and Robert Udelsman

Table 2. Comparison of Features, Radiation Dose, and Cost for Parathyroid Imaging

	Relative Advantages	Relative Disadvantages	Calculated Effective Radiation Dose (Ref.)	Medicare Reimbursement
Cervical ultrasound	Widely available, no radiation	User-dependent interpretation, limited evaluation ectopic glands	None	\$125.10
Sestamibi scintigraphy	Ease of interpretation, assessment for ectopic glands	Radiation, cannot assess thyroid	Sestamibi/SPECT, 6.7–7.8 mSv (58, 71); SPECT/CT, +.9 mSv (72)	Sestamibi/SPECT, \$546.76; sestamibi alone, \$262.53
CT	Assessment for ectopic glands	Radiation, limited sensitivity	~3–6 mSv (71); varies by protocol	\$371.83
4D-CT	Increased anatomical detail, assessment for ectopic glands	Significant radiation to thyroid, not widely available	10.4 mSv (58)	\$424.51
MR	Assessment for ectopic glands	Limited sensitivity	None	\$644.33

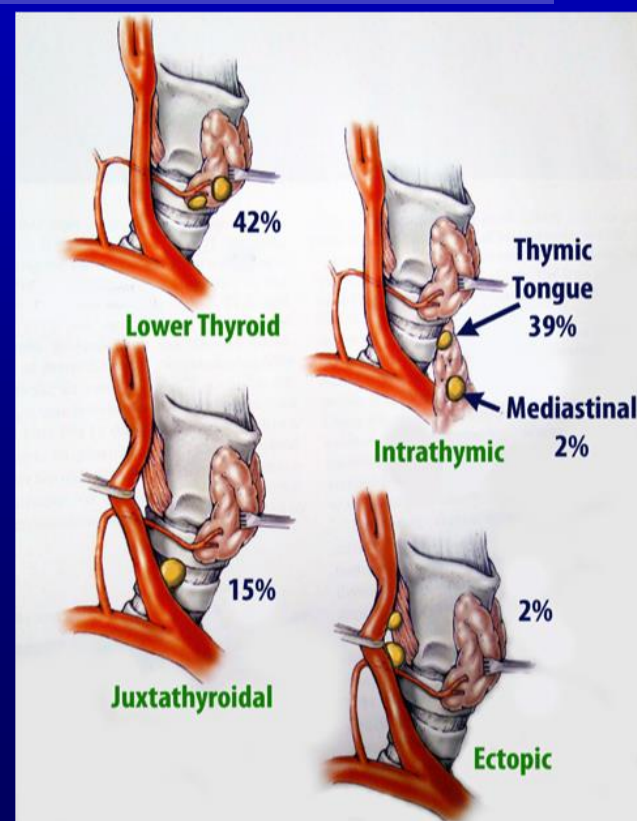
Table 2.1 Characteristics of noninvasive methods of topical diagnosis of primary hyperparathyroidism (Gonzales and Patricio 1997)

Indices	US	CT	MRI	Scintigraphy with ^{201}Tl - $^{99\text{m}}\text{Tc}$	Scintigraphy with $^{99\text{m}}\text{Tc}$ -sestamibi
Sensitivity, %	22–82	47–76	50–80	45–68	70–90
Costs	+	+++	++++	++	++
Operator-dependence	+++	+	++	–	–
Radiation load	–	++	–	+	+
Zone of better imaging	Near the thyroid	Ectopias	Ectopias	Near the thyroid	–
Zone of poor imaging	Mediastinum	Thyroid	–	Mediastinum, deep in the neck	–

Gonzales & Patricio 1997

Kunstman et al. JCE&M 2013

Kalinin et al. The Parathyroid Gland, Springer, 2013



F18-Choline, a Novel PET Tracer for Parathyroid Adenoma?

Elske Quak, Stéphanie Lheureux, Yves Reznik, Stéphane Bardet, and Nicolas Aide

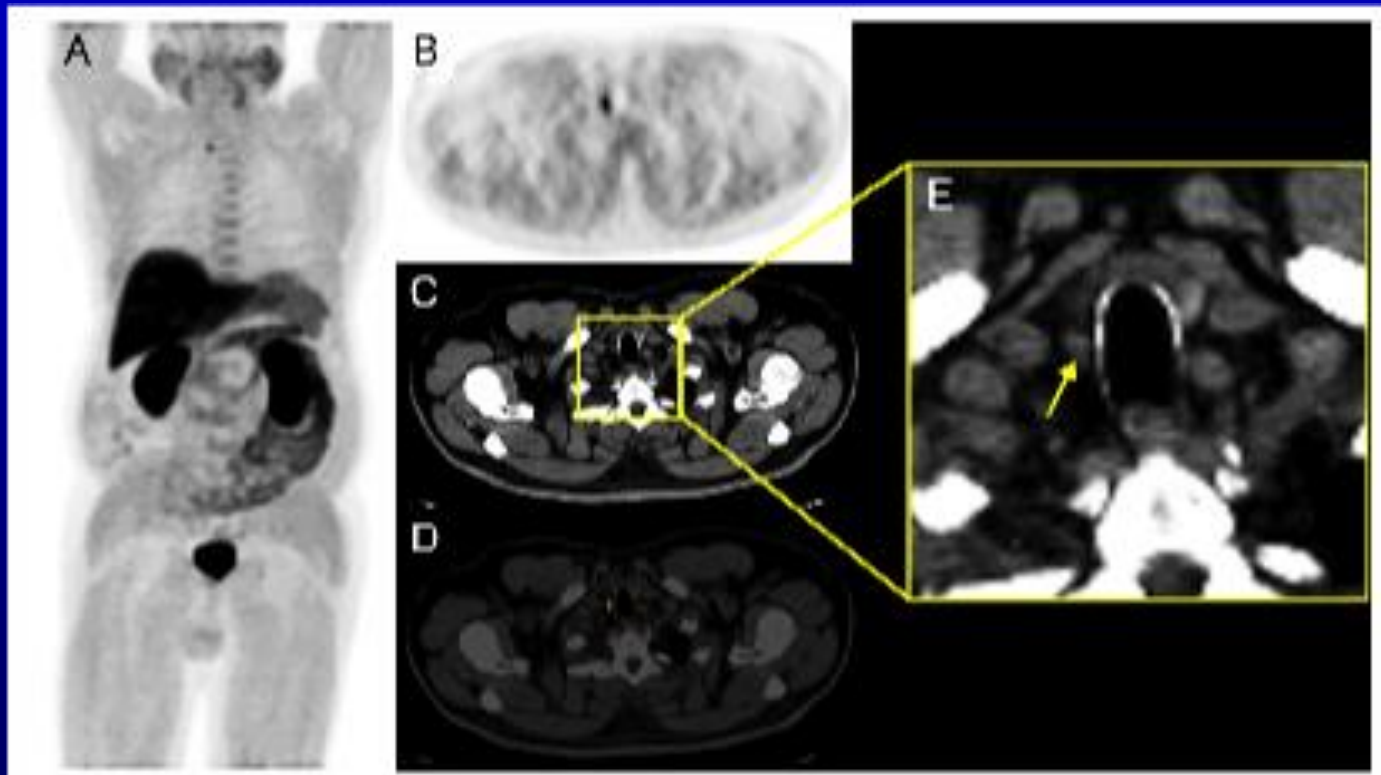




Fig. 1.8 Sir Richard Owen (1804–1892) was a pioneering British comparative anatomist who coined the term *dinosauria*.



Fig. 1.9 Ivar Sandström (Reprinted with permission from *Organ* [38], p. 284)

sie

Società Italiana
Endocrinologia

VARIATION IN SIZE AND SHAPE OF NORMAL AND PATHOLOGIC PARATHYROIDS

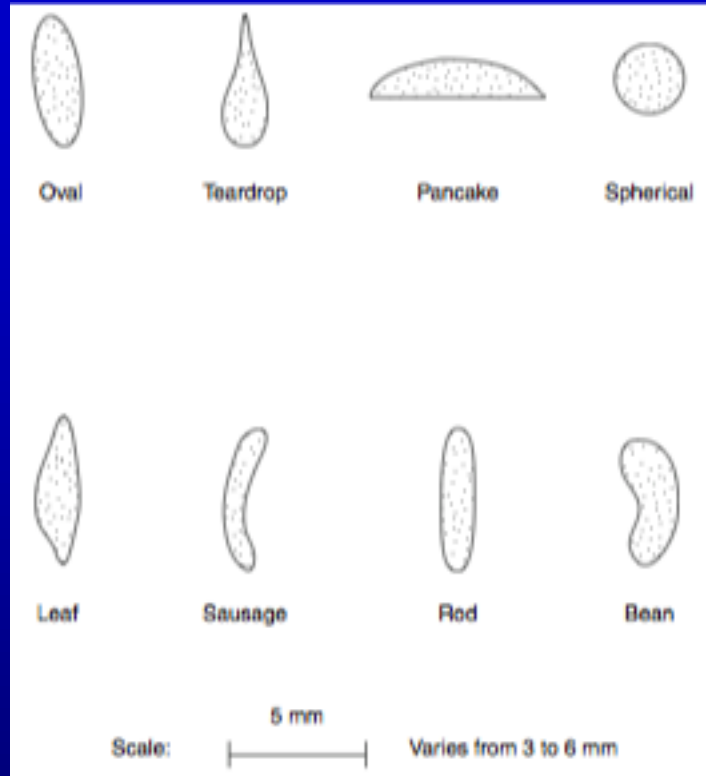


Fig. 2.23 Variations in shape of normal parathyroid glands (Wang 1976)

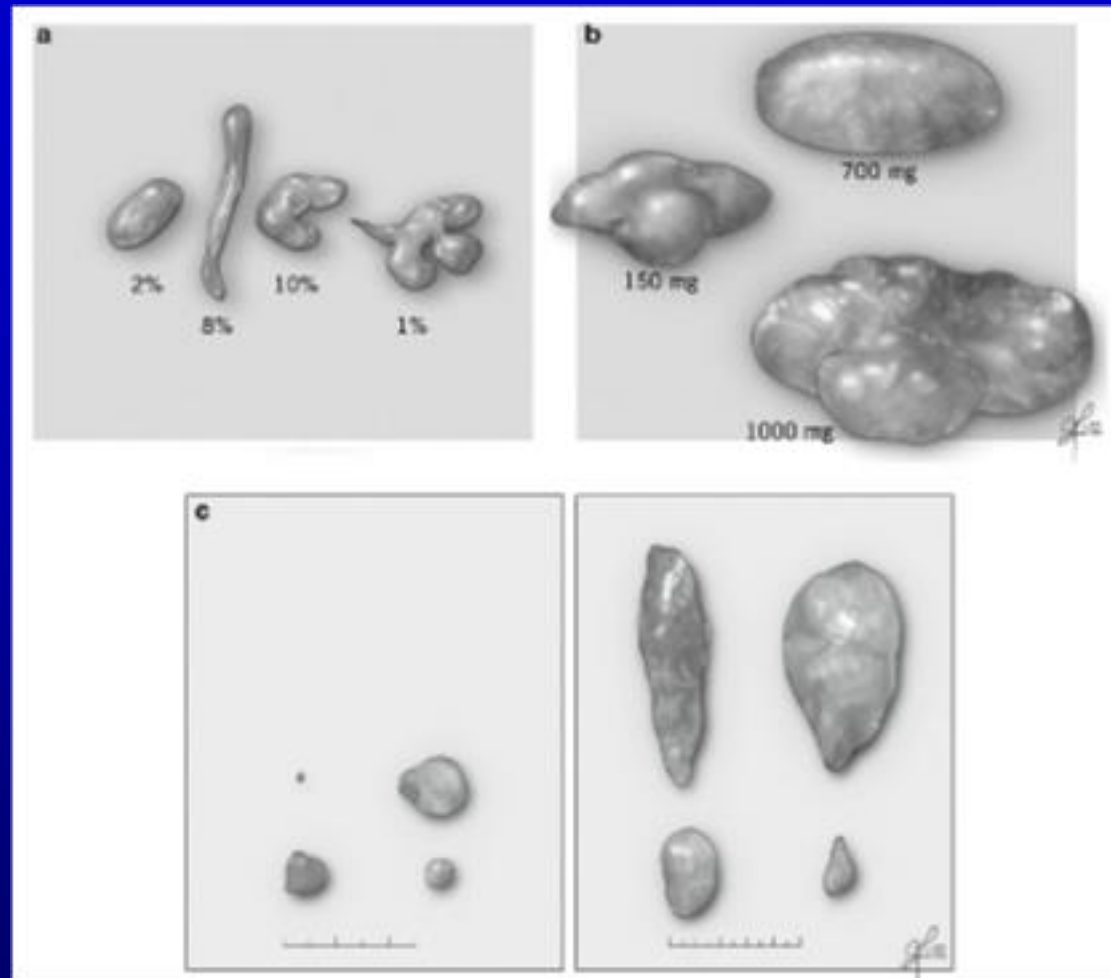


Fig. 20.2 Variable morphology of normal parathyroid glands (a), abnormal parathyroid glands (b), and parathyroid hyperplasia by illustrations (c) and in a surgical examples (d) of multigland disease (left) and single

DONNA DI 41 ANNI, CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 11.8 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 2.4 MG/DL, V.N.:2.5-5.1) ED IPERPTH (220 PG/ML; V.N.:15-90).

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- B. RMN COLLO-TORACE, SCINTIGRAFIA CON 99MTC-SESTAMIBI, ECOGRAFIA DEL COLLO, TAC COLLO-TORACE.**
- C. ECOGRAFIA DEL COLLO CON FNAB E DOSAGGIO DEL PTH NEL LIQUIDO DI LAVAGGIO IN CASO DI LESIONE ECOGRAFICA SOSPETTA PER ADENOMA, BEN EVIDENTE ALL'ECOGRAFIA, A SEGUIRE LE EVENTUALI ALTRE METODICHE UTILI.**
- D. RX TORACE +TAC DEL COLLO.**

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	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

Comparison among different imaging techniques used for localizing parathyroid adenomas

Table 2.2 The results of localizing methods in hyperparathyroidism

Method	Number of patients	Results			Sensitivity, %	Positive prognostic value, %	Cost, UK £
		TP	FP	FN			
Ultrasound	191	50	10	31	82.9	93.8	40
Scintigraphy with ^{201}Tl -/ $^{99\text{m}}\text{Tc}$ -pertechnetate	144	112	10	22	83.6	91.8	120
Scintigraphy with $^{99\text{m}}\text{Tc}$ -sestamibi/ $^{99\text{m}}\text{Tc}$ -pertechnetate	90	74	3	1	85.1	96.1	120
CT	2	74	1	17	81.3	98.7	100
MRI	6	4	1	1	80.0	80.0	300
Selective blood sampling to detect PTH level	30	17	4	9	65.4	80.9	600

TP true-positive, *FP* false-positive, *FN* false-negative

Sensitivity of Tc⁹⁹-sestamibi and high-resolution US

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

Statements from the 2002 vs. 2008 Workshops on asymptomatic pHPT What is the role of preoperative imaging?

2002

⁹⁹Tc-Sestamibi is the first procedure. US, MRI and CT helpful at times

2008

Sestamibi and US the most commonly employed techniques

CT and MRI sometimes used. Angiography and venous sampling selectively used.

US-guided biopsy and FNA-PTH useful in remedial surgery. Not recommended for routine de novo cases

Sensitivity of Tc⁹⁹-sestamibi and high-resolution ultrasound

Diagnostic test	Sensitivity (%)
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- D. RX TORACE +TAC DEL COLLO.

Accuracy of imaging for the localization of parathyroid Adenomas

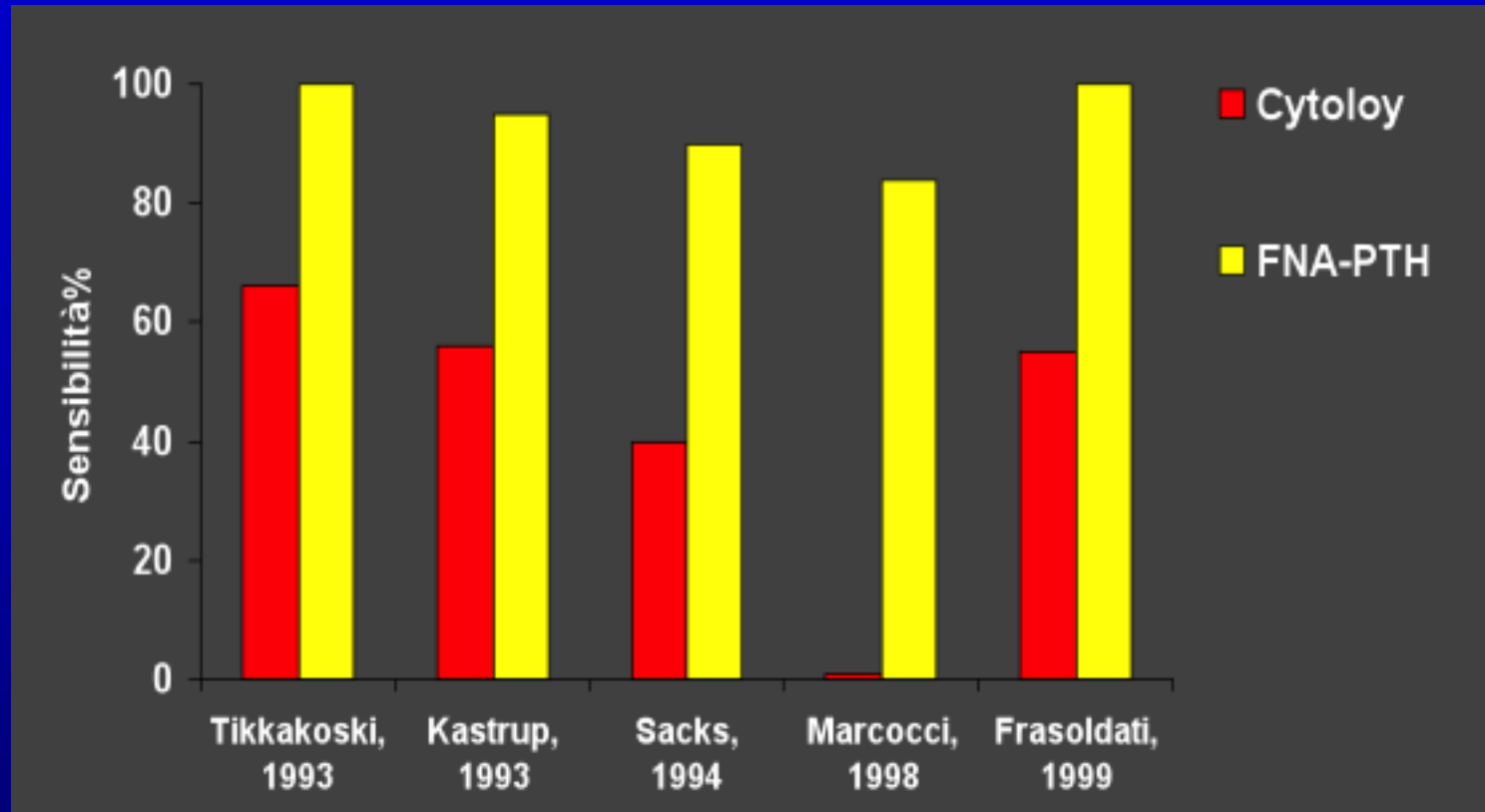
TABLE I.
Accuracy of Ultrasound Versus Sestamibi for Preoperative Parathyroid Adenoma Localization to Correct Quadrant.

	Ultrasound (%)	Sestamibi (%)
Sensitivity	87	58
Specificity	95	95
PPV	85	78
NPV	96	87

Correct quadrant localization includes right versus left and superior versus inferior. $P < .0001$ for significant difference in sensitivity by McNemar test.

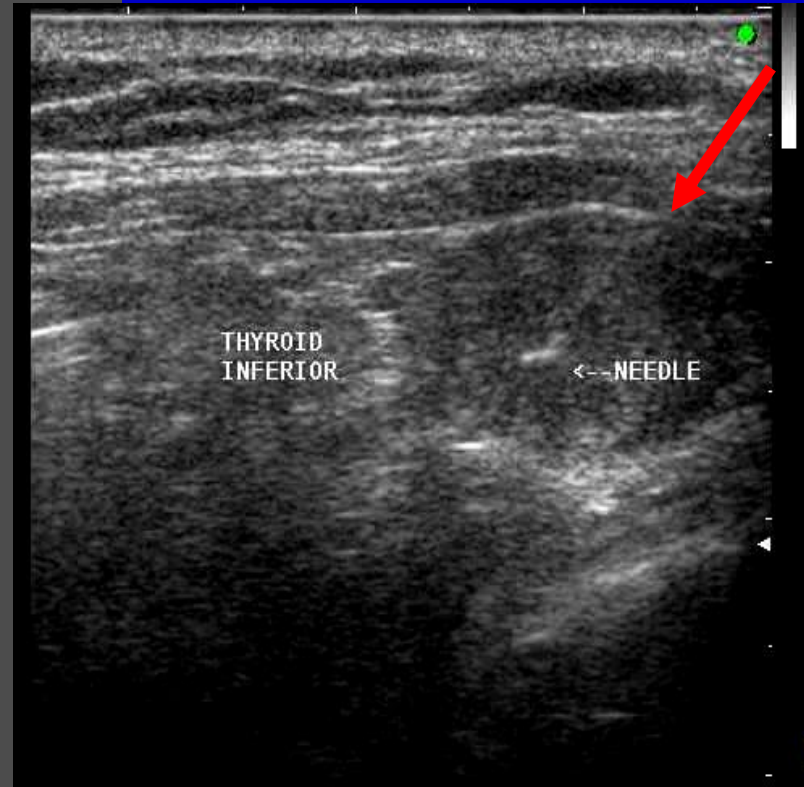
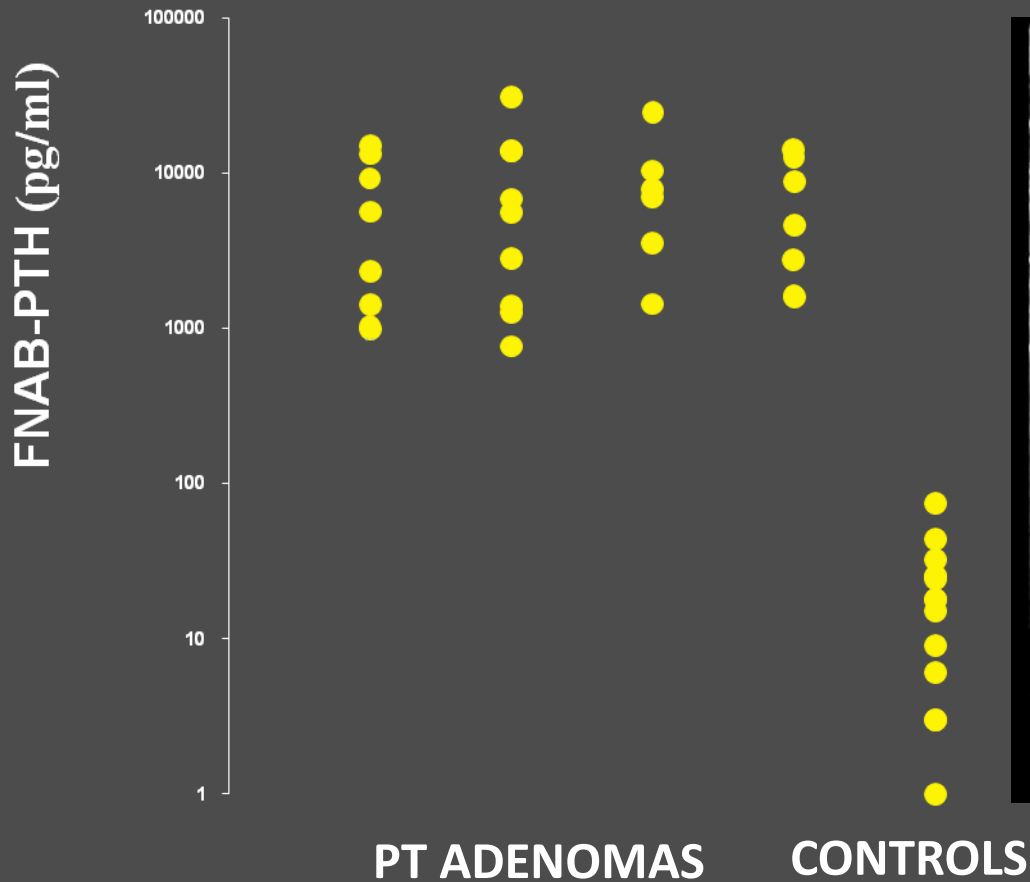
PPV = positive predictive value; NPV = Negative predictive value.

Pitfalls in parathyroid cytology



~ 30% non diagnostic

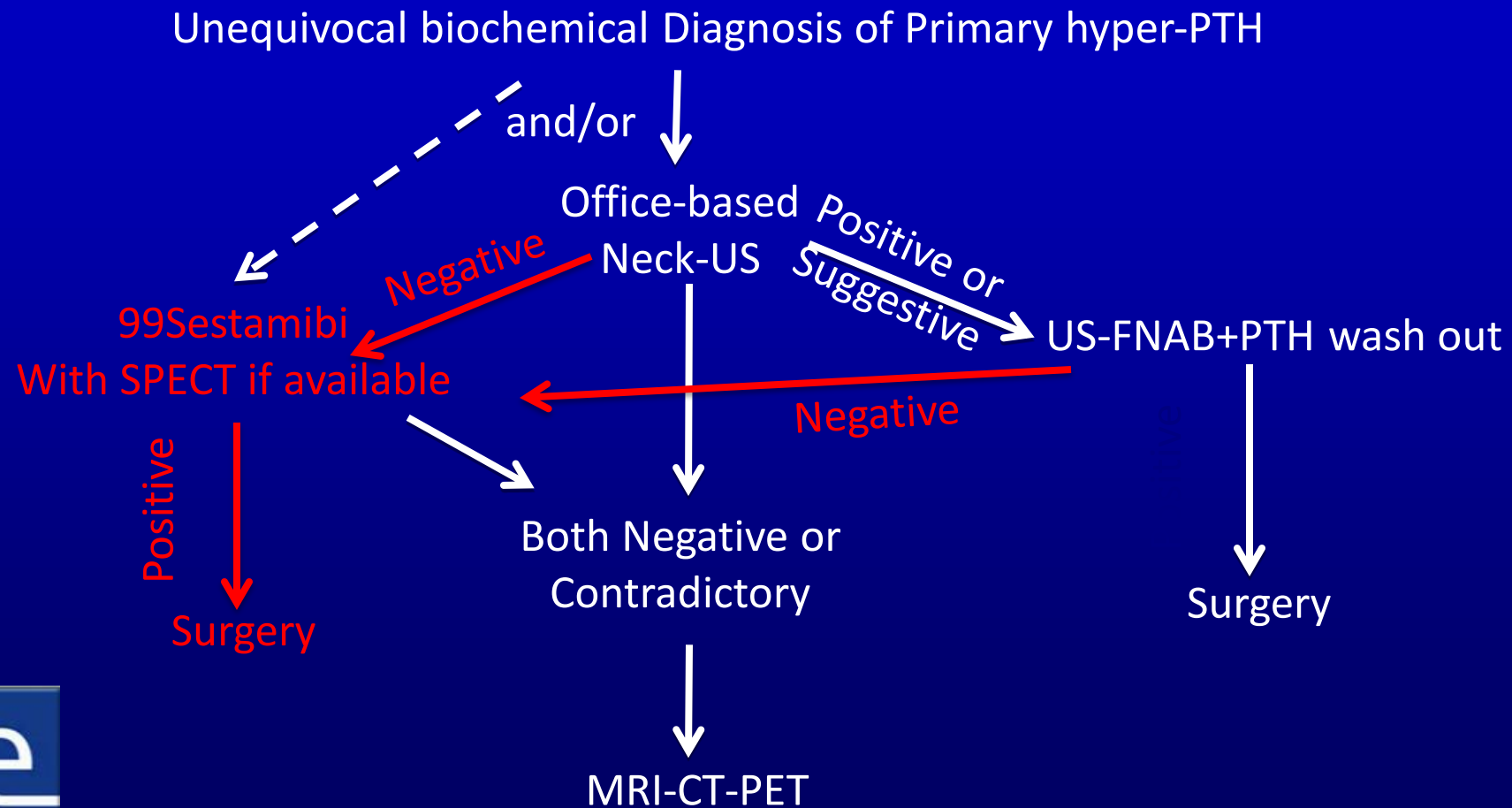
FNAB + FNAB-PTH



Frasoldati, et al, J Clin Ultrasound 1999

Parathyroid Localization and Implications for Clinical Management

John W. Kunstman, Jonathan D. Kirsch, Amit Mahajan, and Robert Udelsman



DONNA DI 71 ANNI, DIMESSA DAL P.S. (ACCESSO PER DELIRIUM) CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 16.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 1.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (320 PG/ML; V.N.:15-90) E CON DIAGNOSI DI DISTURBI COGNITIVI IN ENCEFALOPATIA MULTI-INFARTUALE.

QUALI TRA QUESTE INFORMAZIONI SONO ALTAMENTE SOSPETTE PER CARCINOMA PARATIROIDEO ?

- A. CITOLOGIA SOSPETTA PER CARCINOMA DELLE PARATIROIDI.
- B. DOCUMENTATE LESIONI RADIOGRAFICHE SOSPETTE PER METASTASI (ES. NODULI POLMONARI).
- C. LA SEVERITÀ DELL'IPERPARATIROIDISMO (Ca^{++} E PTH MOLTO ELEVATI) E DOCUMENTATA LESIONE ALL'ECOGRAFIA RIFERIBILE A PARATIROIDE CARATTERIZZATA DA MARCATA DISOMOGENEITÀ E PREVALENZA DEL DIAMETRO ANTERO-POSTERIORE RISPETTO AL DIAMETRO TRASVERSO DELLA LESIONE (MORE TALL THAN WIDTH LESION).
- D. IL SESSO FEMMINILE, L'ETÀ AVANZATA E LA SEVERITÀ DELL'IPERPARATIROIDISMO (Ca^{++} E PTH MOLTO ELEVATI).

DONNA DI 71 ANNI, DIMESSA DAL P.S. (ACCESSO PER DELIRIUM) CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 16.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 1.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (320 PG/ML; V.N.:15-90) E CON DIAGNOSI DI DISTURBI COGNITIVI IN ENCEFALOPATIA MULTI-INFARTUALE.

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D. IL SESSO FEMMINILE, L'ETÀ AVANZATA E LA SEVERITÀ DELL'IPERPARATIROIDISMO (CA⁺⁺ E PTH MOLTO ELEVATI).

Parathyroid Carcinoma – Recurrences (33%-78%)

Cervical Lymph nodes (30%)

Lung (40%)

Liver (10%)

Other (20%)

Bone

Pancreas

Pleura

DONNA DI 71 ANNI, DIMESSA DAL P.S. (ACCESSO PER DELIRIUM) CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 16.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 1.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (320 PG/ML; V.N.:15-90) E CON DIAGNOSI DI DISTURBI COGNITIVI IN ENCEFALOPATIA MULTI-INFARTUALE.

QUALI TRA QUESTE INFORMAZIONI SONO ALTAMENTE SOSPETTE PER CARCINOMA PARATIROIDEO ?

A. CITOLOGIA SOSPETTA PER CARCINOMA DELLE PARATIROIDI.

B. DOCUMENTATE LESIONI RADIOGRAFICHE SOSPETTE PER METASTASI (ES. NODULI POLMONARI).

C. LA SEVERITÀ DELL'IPERPARATIROIDISMO (CA⁺⁺ E PTH MOLTO ELEVATI) E DOCUMENTATA LESIONE ALL'ECOGRAFIA RIFERIBILE A PARATIROIDE CARATTERIZZATA DA MARCATA DISOMOGENEITÀ E PREVALENZA DEL DIAMETRO ANTERO-POSTERIORE RISPETTO AL DIAMETRO TRASVERSO DELLA LESIONE (MORE TALL THAN WIDTH LESION).

Cytologic (FNA) and histologic findings in parathyroid lesions

	PT adenoma	PT hyperplasia	PT carcinoma
PT lesion	2	-	-
Cellular lesion NOS	9	4	-
Follicular neoplasm	2	1	-
PTC	3	-	1
Hurtle cell neoplasm	2	1	-
Thyroiditis		1	-
Thyroid hyperplasia	1	1	-
MTC		-	1

Tseleni-Balfouta et al., Cancer Cytopatol. 2007; 111:130-136

PARATHYROID CANCER CANNOT BE DIAGNOSED PREOPERATIVELY

PARATHYROID CANCER COULD BE ONLY SUSPECTED BY THE MEAN OF A TRIAD OF CLINICAL, LABORATORY, AND RADIOLOGICAL EXAMINATIONS

- ✓ Parathyroid benign and malignant disease cannot be differentiated on cytology.
- ✓ FNAb cytology of a suspected parathyroid carcinoma is not recommended.
- ✓ Potential risk of track seeding a case with cutaneous spread described [Spinelli JEI 2000];

Licata & Lerma Diseases of the parathyroid glands Springer 2012

DONNA DI 71 ANNI, DIMESSA DAL P.S. (ACCESSO PER DELIRIUM) CON DOCUMENTATA IPERCALCEMIA (CALCIO SIERICO DI 16.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 1.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (320 PG/ML; V.N.:15-90) E CON DIAGNOSI DI DISTURBI COGNITIVI IN ENCEFALOPATIA MULTI-INFARTUALE.

QUALI TRA QUESTE INFORMAZIONI SONO ALTAMENTE SOSPETTE PER CARCINOMA PARATIROIDEO ?

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- D.IL SESSO FEMMINILE, L'ETÀ AVANZATA E LA SEVERITÀ DELL'IPERPARATIROIDISMO (Ca^{++} E PTH MOLTO ELEVATI).**

Benign vs Malignant parathyroid lesions

Table 8.2 Clinical features in benign versus malignant parathyroid tumors

	Benign primary hyperparathyroidism	Parathyroid carcinoma
Age at presentation	50–60 years	40–50 years
Women:men ratio	>3:1	1:1

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Benign vs Malignant parathyroid lesions

Table 8.2 Clinical features in benign versus malignant parathyroid tumors

	Benign primary hyperparathyroidism	Parathyroid carcinoma
Age at presentation	50–60 years	40–50 years
Women:men ratio	>3:1	1:1
Serum calcium	Mildly elevated	Markedly elevated
Serum PTH	Mildly elevated	Markedly elevated
Palpable neck mass	Very rare	Common (15–70%)
Renal involvement	<20%	>50%
Severe bone involvement	Rare (<5%)	Common (>50%)
Concomitant bone and renal involvement	Rare	Common
Hypercalcemic crisis	Very rare	Very common
Asymptomatic	Very common	Very rare

Licata & Lerma Diseases of the parathyroid glands Springer 2012

Benign vs Malignant parathyroid lesions

Table 38.1 The clinical and biochemical feature of parathyroid carcinoma compared to benign primary hyperparathyroidism

	Benign HPTH	Parathyroid carcinoma
Female to male	4 to 1	1 to 1
Average calcium (mmol/L)	2.7-2.9	3.75-4.0
Average PTH (ng/L)	<2x normal	>3-10x normal
Average age	Sixth decade	Fifth decade
Palpable mass (%)	<2	30-76
Osteitis fibrosa cystica (%)	5	40-75
Nephrolithiasis (%)	10-15	40
Renal and bone disease (%)	Rare	40-50
Asymptomatic (%)	80	2

IN 60% OF CASES OF CARCINOMAS THE LESION APPEARS AT US AS A MORE TALLER THAN WIDTH LESION.

Parathyroid Carcinoma: A 43-Year Outcome and Survival Analysis

Avital Harari, Avantika Waring, Gustavo Fernandez-Ranvier, Jimmy Hwang, Insoo Suh, Elliot Mitmaker, Wen Shen, Jessica Gosnell, Quan-Yang Duh, and Orlo Clark

PREOPERATIVELY, IT IS OFTEN DIFFICULT TO DIAGNOSE

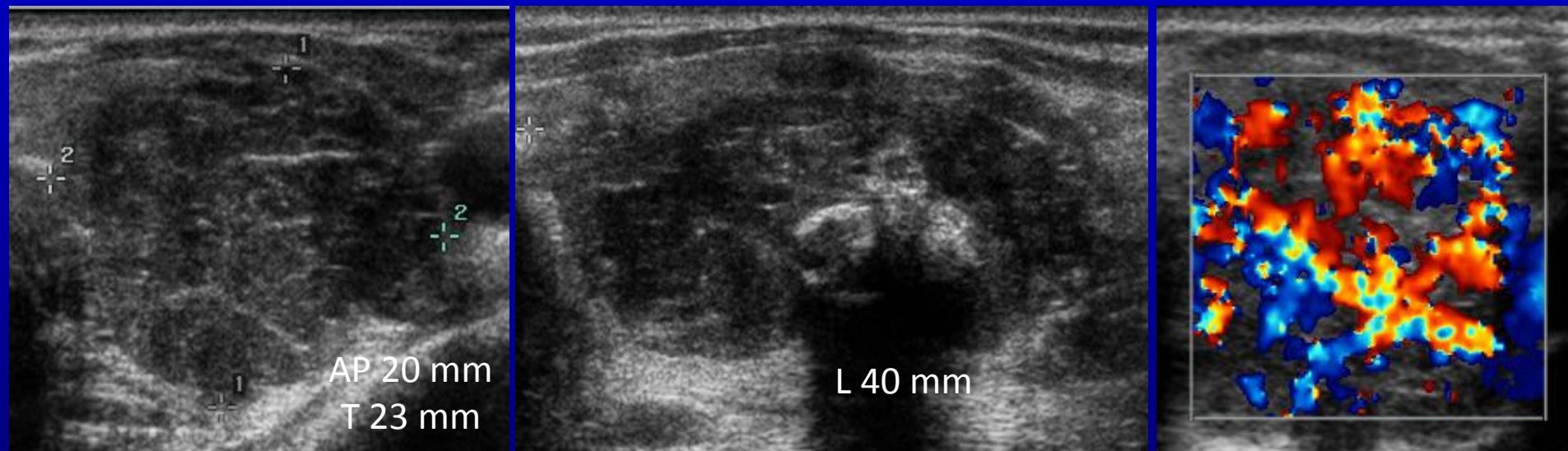
WHEN HYPER-PTH IS PRESENT , THERE ARE SOME CLUES THAT SUGGEST THAT CANCER IS MORE LIKELY

Markedly elevated calcium level (typically above 14 mg/dl)

Palpable mass

Donna di 71 anni - NECK US

Hypoechoic area, pattern 3 at color-doppler near the inferior limit of the left lobe of the thyroid



UOMO DI 49 ANNI, 'MONORENE' (PREGRESSO INTERVENTO DI NEFRECTOMIA DX PER CARCINOMA RENALE A CELLULE CHIARE) CON DOCUMENTATO IPERPARATIROIDISMO PRIMARIO, NORMOCALCEMIA (CALCIO SIERICO DI 10.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 3.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (145 PG/ML; V.N.:15-90). GFR-CLEARANCE DELLA CREATININA 50 ML/MIN, BMD: OSTEOPENIA (t-SCORE -1.9), IPERTENSIONE ARTERIOSA (155/95 IN MEDIA) NON TRATTATA, RECENTE CRISI IPERTENSIVA (190/115) ED ACCESSO IN P.S.

IL PAZIENTE E' IN OSSERVAZIONE DA DUE ANNI: E' CORRETTO IN QUESTO PAZIENTE TALE APPROCCIO 'WAIT AND SEE' ?

- A. SI. SE SI TIENE CONTO DELLA COMPLIANCE DEL PAZIENTE ED IL RELATIVO RIFIUTO DELL'INTERVENTO DI PARATIROIDECTOMIA.
- B. SI. PERCHÉ HA UN SOLO RENE E L'INTERVENTO DI PARATIROIDECTOMIA POTREBBE ULTERIORMENTE COMPROMETTERNE LA FUNZIONALITÀ.
- C. NO. CI SONO PIU' CRITERI CHE IMPONGONO LA PARATIROIDECTOMIA.
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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

TABLE 2. Biochemical changes in asymptomatic patients followed up without parathyroidectomy (n = 49)

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
Serum creatinine (mg/dl)	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.2	0.8 ± 0.1
Urinary calcium (mg/dl)	238 ± 19	215 ± 23	185 ± 32	247 ± 36	202 ± 36
Serum 25-(OH) vitamin D (ng/ml)	21 ± 1	22 ± 2	22 ± 3	21 ± 3	19 ± 4
Serum 1,25-(OH) ₂ vitamin D (pg/ml)	56 ± 2	58 ± 3	54 ± 5	40 ± 5 ^a	48 ± 7

Rubin et al. JCE&M 2008

UOMO DI 49 ANNI, 'MONORENE' (PREGRESSO INTERVENTO DI NEFRECTOMIA DX PER CARCINOMA RENALE A CELLULE CHIARE) CON DOCUMENTATO IPERPARATIROIDISMO PRIMARIO, NORMOCALCEMIA (CALCIO SIERICO DI 10.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 3.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (145 PG/ML; V.N.:15-90). GFR-CLEARANCE DELLA CREATININA 50 ML/MIN, BMD: OSTEOPENIA (t-SCORE -1.9), IPERTENSIONE ARTERIOSA (155/95 IN MEDIA) NON TRATTATA, RECENTE CRISI IPERTENSIVA (190/115) ED ACCESSO IN P.S.

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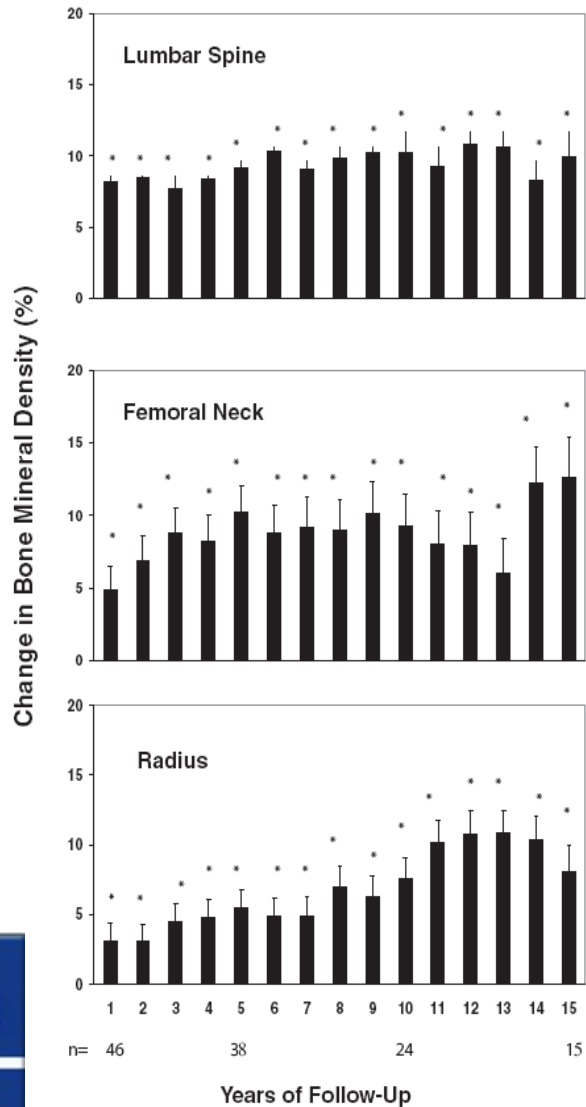
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The Natural History of Primary Hyperparathyroidism with or without Parathyroid Surgery after 15 Years

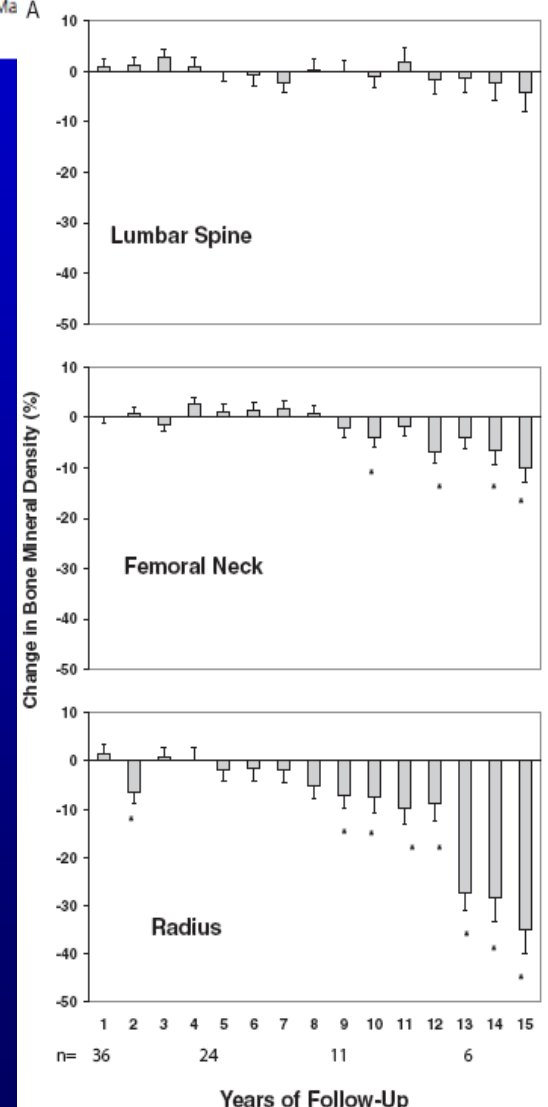
John P. Bilezikian, Donald J. McMahon, Jeffrey A. sky, and Shonni J. Silverberg



+ 12%

+ 10%

+ 7%



0%

- 10%

- 35%

Parathyroidectomy

No Surgery



Rubin et al., JCE&M 2009; 93:2642

UOMO DI 49 ANNI, 'MONORENE' (PREGRESSO INTERVENTO DI NEFRECTOMIA DX PER CARCINOMA RENALE A CELLULE CHIARE) CON DOCUMENTATO IPERPARATIROIDISMO PRIMARIO, NORMOCALCEMIA (CALCIO SIERICO DI 10.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 3.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (145 PG/ML; V.N.:15-90). GFR-CLEARANCE DELLA CREATININA 50 ML/MIN, BMD: OSTEOPENIA (t-SCORE -1.9), IPERTENSIONE ARTERIOSA (155/95 IN MEDIA) NON TRATTATA, RECENTE CRISI IPERTENSIVA (190/115) ED ACCESSO IN P.S.

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Guidelines for parathyroid surgery in asymptomatic PHPT

Comparison of new and old



Measurement	1990	2002	2008
Serum calcium (>upper limit of normal)	1–1.6 mg/dl (0.25–0.4 mmol/L)	1.0 mg/dl (0.25mmol/L)	1.0 mg/dl (0.25 mmol/L)
24-h urine for calcium	>400 mg/d (>10 mmol/d)	>400 mg/d (>10 mmol/d)	Not indicated
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	T-score <–2.5 at any site and/or previous fracture fragility
Age (yr)	<50	<50	<50

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QUALE WORK-UP CARDIOLOGICO CONSIGLIERESTE ?

- A. ECG, E SE ANOMALO ALTRE INDAGINI.
- B. MONITORAGGIO DELLA PRESSIONE ARTERIOSA, ECG E CONSULENZA O VISITA CARDIOLOGICA.
- C. ECG, ECOCARDIOGRAMMA, DOPPLER TSA, ECG SFORZO E SPESSORE INTIMA/MEDIA CAROTIDEO.
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- D. ECOCARDIOGRAMMA E RMN CARDIACA.**

TABLE 1. Participant characteristics and cardiovascular risk factors

Variable	PHPT (n = 51)	Controls (n = 49)	P value
Age (yr)	61.4 ± 1.0	63.4 ± 0.8	0.13
Race/ethnicity			
Caucasian (%)	100	96	0.24
Hispanic (%)	12	7	0.49
African-American (%)	0	4	0.24
Male (%)	20	24	0.56
Coronary artery disease (%)	8	4	0.43
Hypercholesterolemia (%)	41	45	0.71
Hypertension (%)	29	22	0.43
Diabetes mellitus (%)	2	4	0.53
Ever smoke	49	51	0.84
Body mass index (kg/m ²)	25 ± 0.6	27 ± 0.9	<0.05
Systolic blood pressure (mm Hg)	124 ± 2.6	138 ± 3.1	<0.01
Diastolic blood pressure (mm Hg)	75 ± 1.6	81 ± 1.7	<0.05
Total cholesterol (mg/dl)	211 ± 4.9	218 ± 5.7	0.35
Triglycerides (mg/dl)	98 ± 7.8	70 ± 7.4	<0.05
High-density lipoprotein (mg/dl)	69 ± 2.5	66 ± 2.5	0.41
Low-density lipoprotein (mg/dl)	122 ± 4.4	138 ± 5.2	<0.05
Glomerular filtration rate (ml/min · 1.73 m ²)	76 ± 2.6	73 ± 2.1	0.37

Aortic Valve Calcification in Mild Primary Hyperparathyroidism

Shinichi Iwata, Marcella Donovan Walker, Marco R. Di Tullio, Eiichi Hyodo, Zhezhen Jin, Rui Liu, Ralph L. Sacco, Shunichi Homma, and Shonni J. Silverberg

MILD PHPT IS ASSOCIATED WITH
SUBCLINICAL AORTIC VALVE
CALCIFICATION

TABLE 2. Echocardiographic data

Variable	PHPT (n = 51)	Controls (n = 49)	Normal range	P value
Left ventricle end-diastolic dimension, (mm)	45.0 ± 0.6	44.4 ± 0.6	39–54	0.51
Left ventricle end-systolic dimension, (mm)	27.6 ± 0.6	28.0 ± 0.6		0.62
Ventricular septum, (mm)	10.9 ± 0.2	11.0 ± 0.2	6–10	0.74
Posterior left ventricle wall, (mm)	10.6 ± 0.2	10.9 ± 0.2	6–10	0.26
Mean transaortic pressure gradient, (mm Hg)	2.8 ± 0.2	3.2 ± 0.2		0.16
Peak transaortic pressure gradient, (mm Hg)	5.6 ± 0.3	6.0 ± 0.3	<25.0	0.39
Aortic valve calcification area (cm ²)	0.24 ± 0.02	0.17 ± 0.02		<0.01

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CLASSICAL ECG FEATURES OF HYPERCALCEMIA, SUCH AS A SHORT QT INTERVAL, ARE USUALLY REPORTED IN PATIENTS WITH PHPT

Hedback G & Oden A. Eur J Clin Invest 1998

Chang CJ et al. Pacing Clin Electrophysiol 2000

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Carotid Vascular Abnormalities in Primary Hyperparathyroidism

M. D. Walker, J. Fleischer, T. Rundek, D. J. McMahon, S. Homma, R. Sacco, and S. J. Silverberg

TABLE 1. Participant characteristics and cardiovascular risk factors

Variables	All participants		P value
	PHPT, n = 49	Controls, n = 991	
Age (yr)	61.6 ± 7.4	63.6 ± 6.0	0.07
Male (%)	16	42	<0.0001
BMI (kg/m ²)	25.6 ± 4.1	28.3 ± 4.9	<0.001
Coronary artery disease (%)	8	9.6	1.00
Hypercholesterolemia (%)	38	42	0.46
Hypertension (%)	35	46	0.12
Diabetes (%)	2	15	<0.01
Tobacco ever use (%)	55	51	0.55
Systolic blood pressure (mm Hg)	127 ± 19	142 ± 21	<0.0001
Diastolic blood pressure (mm Hg)	75 ± 11	85 ± 11	<0.0001
Calcium (mg/dl)	10.5 ± 0.5	9.1 ± 0.4	<0.0001
Total cholesterol (mg/dl)	211 ± 34	203 ± 39	0.18
Low-density lipoprotein (mg/dl)	124 ± 30	131 ± 35	0.17
Triglycerides (mg/dl)	98 ± 56	144 ± 84	<0.0001

Results are mean ± SD unless indicated otherwise.

MILD PHPT IS ASSOCIATED WITH INCREASED MEDIA THICKNESS

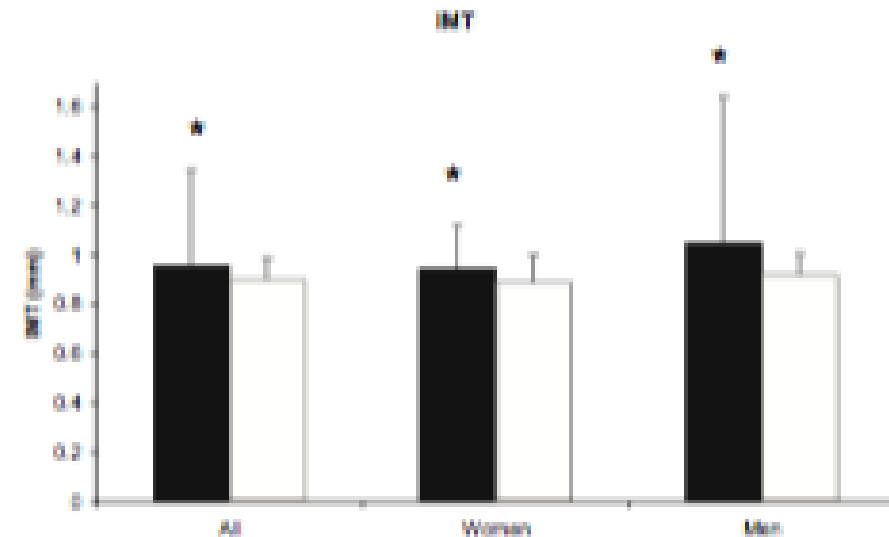


FIG. 1. Comparison of carotid IMT between PHPT (black bar) and control (white bar) subjects. IMT was higher in PHPT than control in all subjects ($P < 0.0001$), non-Hispanic Caucasian women

Arrhythmias in primary hyperparathyroidism evaluated by exercise test

Jessica Pepe, Mario Curione, Sergio Morelli, Marco Colotto, Marisa Varrenti, Claudia Castro, Antonella D'Angelo, Cristiana Cipriani, Sara Piemonte, Elisabetta Romagnoli and Salvatore Minisola

IN PATIENTS WITH PHPT, AN INCREASED OCCURRENCE OF VPBS AND A DIFFERENT QTC ADAPTATION DURING ET WERE OBSERVED AND MAY REPRESENT RISK FACTORS FOR MAJOR ARRHYTHMIAS

Table 4 Length of QTc interval (msec) in V5 lead and VPBs during every stages of exercise test in patients with PHPT and controls

	PHPT	Controls	P
QTc at rest	401.0 ± 24.8	417.8 ± 25.1	0.01
VPBs (% of subjects)	3.3%	0%	0.99
QTc at peak exercise	396.29 ± 20.1	403.38 ± 28.6	0.2
VPBs (% of subjects)	23.3%	3.3%	0.02
QTc at 1st stage of recovery	389.5 ± 27.7	405.5 ± 16.5	0.008
VPBs (% of subjects)	20%	6.3%	0.20
QTc at 5th stage of recovery	399.0 ± 19.2	414.5 ± 21.2	0.004
VPBs (% of subjects)	20%	6.3%	0.20

UOMO DI 49 ANNI, 'MONORENE' (PREGRESSO INTERVENTO DI NEFRECTOMIA DX PER CARCINOMA RENALE A CELLULE CHIARE) CON DOCUMENTATO IPERPARATIROIDISMO PRIMARIO, COMPLIANCE ASSENTE, NORMOCALCEMIA (CALCIO SIERICO DI 10.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 3.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (145 PG/ML; V.N.:15-90). GFR-CLEARANCE DELLA CREATININA 50 ML/MIN, BMD: OSTEOPENIA (t-SCORE - 1.9), IPERTENSIONE ARTERIOSA (155/95 IN MEDIA) DA ANNI NON TRATTATA, RECENTE CRISI IPERTENSIVA (190/115) ED ACCESSO IN P.S.

QUALE WORK-UP CARDIOLOGICO CONSIGLIERESTE ?

A. ECG, E SE ANOMALO ALTRE INDAGINI.

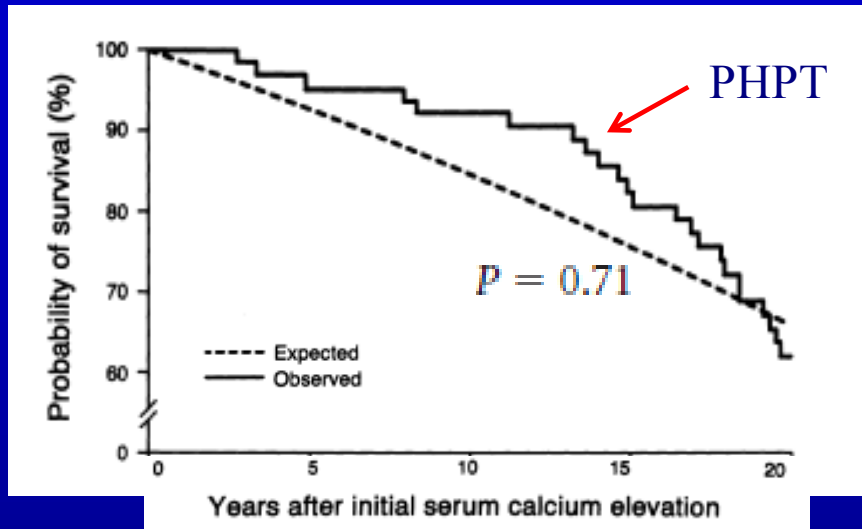
B. MONITORAGGIO DELLA PRESSIONE ARTERIOSA, ECG E CONSULENZA O VISITA CARDIOLOGICA.

C. ECG, ECOCARDIOGRAMMA, DOPPLER TSA, ECG SFORZO E SPESSORE INTIMA/MEDIA CAROTIDEO.

D. ECOCARDIOGRAMMA E RMN CARDIACA.

SURVIVAL AND PHPT

SURVIVAL IN PHPT HIGHER THAN THAT EXPECTED IN THE GENERAL POPULATION FOR CARDIOVASCULAR DISEASES AND CANCER



pre-screening

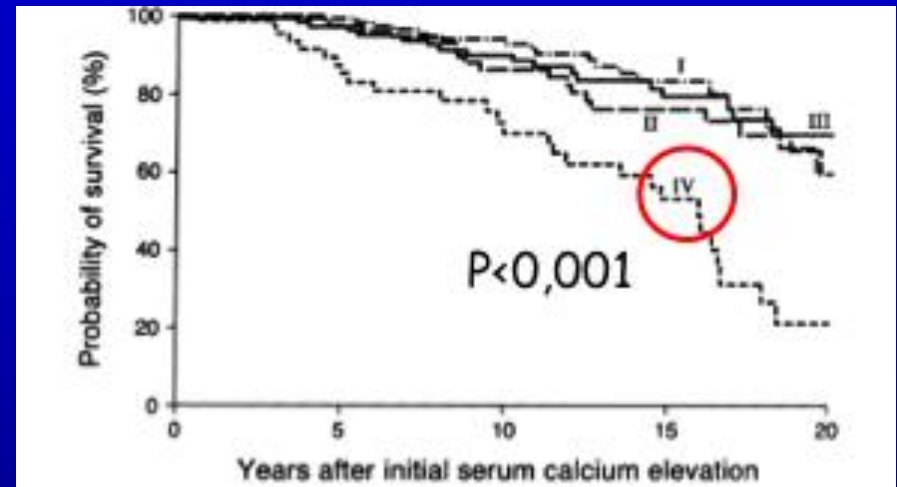


Figure 3. Survival as a function of quartile of serum calcium levels (I = 10.2 to 10.5 mg/dL; II = 10.6 to 10.7 mg/dL; III = 10.8 to 11.1 mg/dL; and IV = 11.2 to 16.0 mg/dL) among Rochester, Minnesota residents with primary hyperparathyroidism. Group IV had significantly reduced survival ($P < 0.001$) compared with the other 3 groups.

Wermers R et al., Am J med 1998

SOPRAVVIVENZA

TREPCALCEMIA

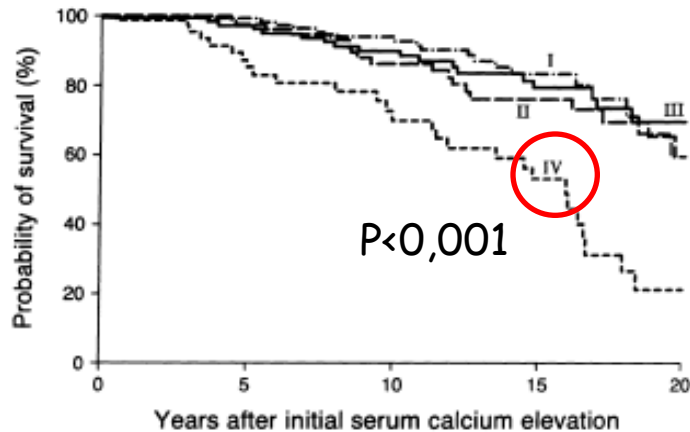
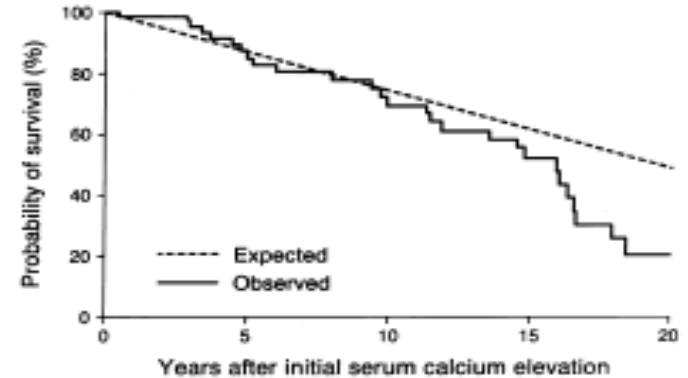


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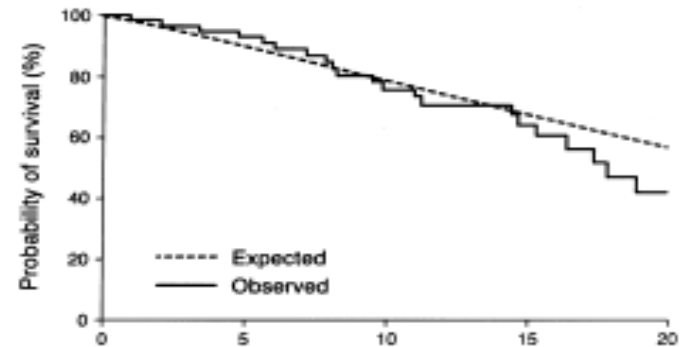
IV quartile

75% Ca: 11,2-11,8 mg/dL

25% Ca: 11,8-16 mg/dL



(A)



(B)

Confrontando la sopravvivenza dei soggetti nel IV quartile con quella attesa (aggiustando per età e sesso) non è emersa diff. significativa (pre-chirurgia $P=0,91$; post-chirurgia $P=0,41$)

Presentation of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

Shonni J. Silverberg, E. Michael Lewiecki, Leif Mosekilde, Munro Peacock, and Mishaela R. Rubin

Consensus response

Despite the strong evidence that PHPT associated with marked hypercalcemia has deleterious cardiovascular consequences, data on the extent and nature of cardiovascular involvement in those with mild disease are too limited to provide a complete picture. There is evidence for subtle cardiovascular manifestations in mild disease, such as changes in endothelial function, increased vascular stiffness, and perhaps diastolic dysfunction, which must be confirmed and extended. It will be important to ascertain, to the extent possible, the association of any cardiovascular abnormalities with hypercalcemia or elevated PTH levels. The implications of subtle cardiovascular manifestations of asymptomatic PHPT, some of which are indirect surrogates for disease outcomes, are unknown at this time. However, demonstration of significant reversible cardiovascular abnormalities in asymptomatic PHPT could change the recommendation for parathyroidectomy.

Silverberg et al. JCE&M 2009

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Endocrinologia

Monitoring asymptomatic patients (2008 guidelines)

Measurement	Frequency
Serum calcium	Annually
24-hour urinary calcium	Not recommended*
Creatinine clearance	Not recommended*
Serum creatinine	Annually†
Bone mineral density	Every 1-2 year ^a (3 sites; lumbar spine, hip, forearm)
Abdominal X-ray (± ultrasound)	Not recommended*

*Except at the time of initial evaluation.

†If the serum creatinine concentration suggests a change in the creatinine clearance when the Cockcroft-Gault equation is applied.

^a This recommendation acknowledges country-specific advisories as well as the need for more frequent monitoring if the clinical situation is appropriate.

DONNA DI 37 ANNI, IPERPARATIROIDISMO PRIMARIO IN TERAPIA CON MIMPARA DA 3 ANNI (RIFIUTO DELL'INTERVENTO), ADENOMA PARATIROIDEO BEN VISUALIZZABILE ALL'ECOGRAFIA CONFERMATO DA PTH >1800 PG/ML NEL WASH-OUT DA FNA-B ECOGUIDATO, NORMOCALCEMIA (CALCIO SIERICO DI 10.3 MG/DL, V.N.: 8.5-11.0; FOSFORO SIERICO DI 3.7 MG/DL, V.N.:2.5-5.1) ED IPERPTH (145 PG/ML; V.N.:15-90), NEFROLITIASI. NON VARIAZIONI DEL QUADRO DOPO RECENTE INTERVENTO DI PARATIROIDECTOMIA

QUALI TRA QUESTI ASPETTI AVREBBE POTUTO CONDIZIONARE IN POSITIVO L'ESITO DELLA TERAPIA CHIRURGICA?

- A. LA LOCALIZZAZIONE PREOPERATORIA (ECOGRAFICA O SCINTIGRAFICA) E' UN'OTTIMA PREMessa PER LA RIUSCITA DELL'INTERVENTO CHIRURGICO.
- B. L'ABILITÀ DEL CHIRURGO NELL'ESPLORAZIONE MANUALE.
- C. L'UTILIZZO DELLA CHIRURGIA ROBOTICA.
- D. L'APPROCCIO MULTIDISCIPLINARE PERIOPERATORIO.

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FUTURE PERSPECTIVES

Evolution of new methods for localization or robotic surgery may be challenging for the improvement of parathyroid surgery

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UNILATERAL NECK EXPLORATION (UNE) and BILATERAL NECK EXPLORATION (BNE)



Image-directed exploration (IDP), also known as minimal access or minimally invasive parathyroidectomy has surpassed UNE and BNE as the procedure of choice.

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PREOPERATORY IMAGING AND SURGICAL OUTCOMES

Image-directed exploration (IDP), also known as minimal access or minimally invasive parathyroidectomy, involves a focused approach to the single abnormal parathyroid gland seen on preoperative imaging

Palazzo & Delbridge et al. Surg Clin North Am 2004

The evolution of IDP has relied upon two important developments:

1. the refinement of accurate preoperative localization techniques
2. the introduction of iPTH

Udelsman et al. JCE&M 2009

Khan et al. Handbook of parathyroid diseases, Springer 2012

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MULTIDISCIPLINARE

Surgery for Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

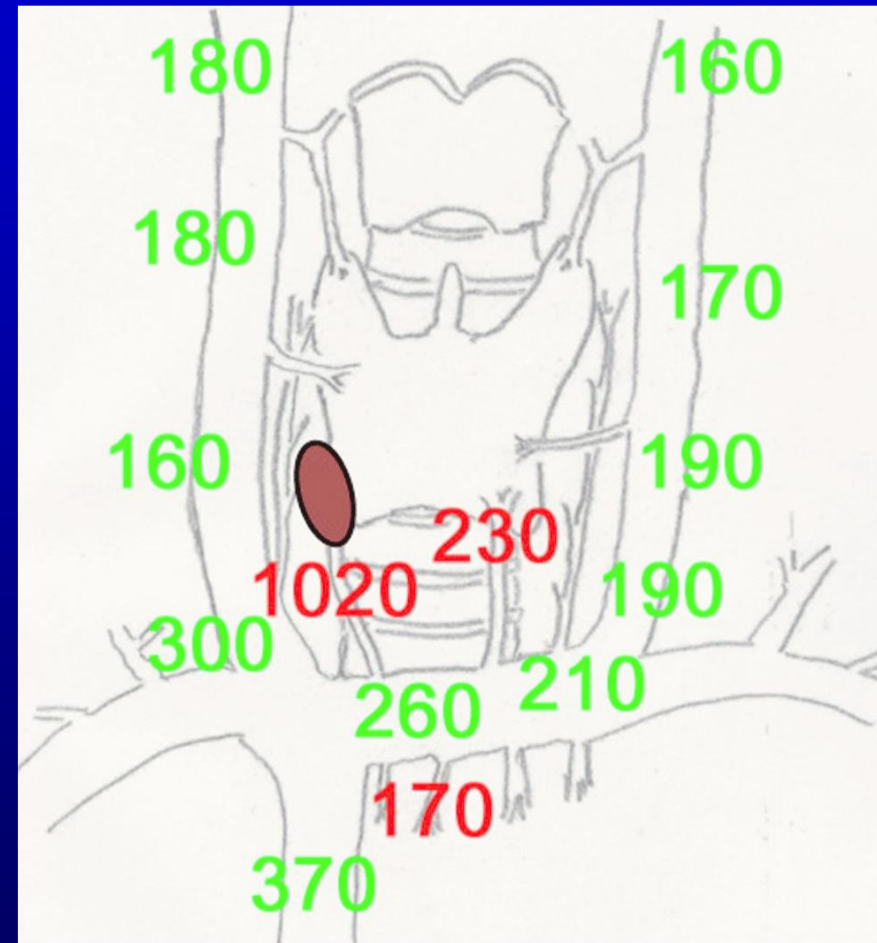
Robert Udelsman, Janice L. Pasieka, Cord Sturgeon, J. E. M. Young, and Orlo H. Clark

Question 5. What operative adjuncts are available to assist the surgeon?

A variety of operative adjuncts are available in specialized centers, including rapid intraoperative PTH assays, employment of a gamma probe in conjunction with a preoperative sestamibi injection, intraoperative ultrasound, and the ability to perform intraoperative internal jugular vein sampling to measure PTH and determine the presence of an ipsilateral venous gradient. All of these techniques are highly institution specific. Most experts agree that the intraoperative PTH assay is the most useful of these techniques (60). Intraoperative venous sampling is reserved for cases where the surgeon is unable to locate the abnormal parathyroid gland and has immediate availability of an intraoperative PTH assay.

Intraoperative internal jugular vein sampling to measure PTH

Superselective venous sampling of parathyroid hormone (PTH) levels helping regionalizing a parathyroid adenoma responsible for hypercalcemia



Surgeon performed US for preoperative localization of abnormal PTs

	Sensitivity %	Specificity %	PPV %	NPV%
Radiologist Performed US	10.5	93.1	50.0	61.4
Surgeon Performed US	59.8	96.4	92.5	96.4

Kairys et al., 2006

The neck-US in the hands of experienced endocrinologist reaches high level of diagnostic value

Teams & Teamwork



TEAMWORK

Titanus distribuzione

MARIO CECCHI GORI presenta

L'ARMATA BRANCALEONE

VITTORIO GASSMAN
CATHERINE SPAAK



FOLCO LULLI

con GIAN MARIA VOLONTE'

MARIA GRAZIA BUCCELLA

BARBARA STEELE

con ENRICO MARIA SALERNO

SOGGETTO E SCENEGGIATURA DI
AGE & SCARPELLI

DIRETTORE DALLA FOTOGRAFIA MARIO MONICELLI

UNA PRODUZIONE FAIR FILM S.P.A.

DIRETTORE DELLA FOTOGRAFIA CARLO DI PALMA

TECHNICOLOR

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Società Italiana
Endocrinologia

PERIOPERATIVE MULTIDISCIPLINAR APPROACH

PRE-PERIOPERATIVE IMAGING

Revision of radiological outcomes
Perform a new neck-US if positive

INTRAOPERATIVE PROCEDURES

Intraoperative US
iPTH
PTH Gradient

ENDOCRINOLO
GIST

Pre-operative
Imaging

SURGEON

ENDOCRINOLO
GIST

Intra-operative
Procedures

SURGEON