

Funzionalità paratiroidea: nuove frontiere della diagnostica
13° Simposio annuale ELAS-Italia

Bologna - 20 Novembre 2007

**Significato clinico del dosaggio del
Paratormone**

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DIMI - DISEM

**Azienda Ospedale Università San Martino
Università degli Studi di Genova**



Calcio corporeo

CALCIO TOTALE :

99% extracellulare (legato al fosfato nello scheletro -idrossiapatite)

1 % intracellulare (funzioni cellulari, signaling)

0.1 % sierico (2.2-2.6 mmol/l)

40%

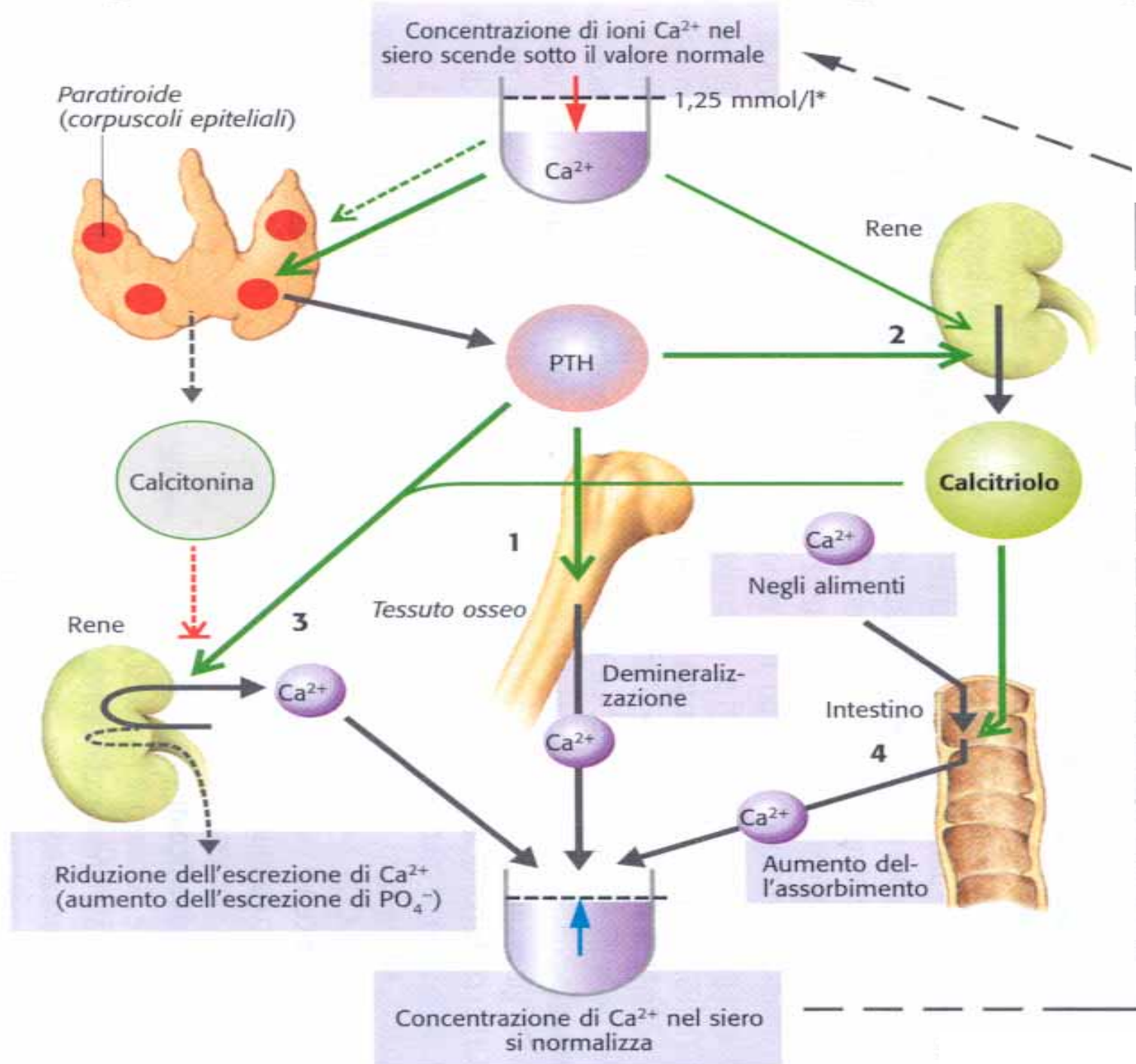
legato a proteine
(90% albumina
resto : globuline)

60%

unbound

- **50% ionizzato (1.1-1.3 mmol/l)**
= **frazione biologicamente attiva**
- 10% legato a complessi: fosfati, citrati)

Frazione attiva : calcio ionizzato



IPERCALCEMIA

(= calcio plasmatico totale $> 10.3 \text{ mg/dl}$)

~ 1% di pazienti ospedalizzati

CAUSE principali :

1) TUMORI MALIGNI : 60% dei casi (!) (spec. K bronchiale, K mammario, plasmocitoma)

a) ipercalcemia osteolitica

(metastasi ossee o plasmocitoma : $\text{TGF}\alpha$, TNF, IL-1...stimolano gli osteoclasti)

b) ipercalcemia paraneoplastica \Rightarrow PTHrP \uparrow

2) CAUSE ENDOCRINE : iperparatiroidismo primitivo (~20%), tireotossicosi...

3) FARMACI (intossicazione con vit D, tiazidi, tamoxifene, litio...)

4) SARCOIDOSI (produzione di $1,25(\text{OH})_2 \text{ Vit D}_3$ nei macrofagi)

ORMONE PARATIROIDEO

84 aminoacidi (pre-pro-ormone: 115 aminoacidi)

REGOLAZIONE DELLA SECREZIONE : Ca^{++}

a) PTH \uparrow

- Bassa concentrazione o diminuzione della concentrazione di $\text{Ca}^{++} \Rightarrow \uparrow$ PTH **entro pochi secondi**
- $\text{Ca}^{++} \downarrow$ **per ore** \Rightarrow PTH – mRNA \uparrow
- $\text{Ca}^{++} \downarrow$ **per mesi – anni** \Rightarrow ipertrofia paratiroidea
(----- \rightarrow eventuale autonomizzazione)

b) PTH \downarrow

Ca^{++} e $1,25(\text{OH})_2\text{-Vit D}_3$ (mRNA \downarrow , e riduz. massa ghiandolare)

ORMONE PARATIROIDEO

Funzioni:

- ↑ riassorbimento **osseo** (calcio ↑, fosfato ↑ nel plasma)
- **rene** : - escrezione Ca^{++} ↓ \Rightarrow Ca ↑ nel plasma
 - escrezione fosfato ↑ \Rightarrow fosfato ↓ nel plasma
 - conversione :
 $25(\text{OH})\text{-Vit D}_3 \rightarrow 1,25(\text{OH})_2\text{-Vit D}_3 = \text{calcitriolo}$

emivita: < 4 minuti

poi : rapida clearance (epatica > renale) che genera *frammenti C-terminali* con emivita + lunga che possono essere escreti solo dal rene

IPERPARATIROIDISMO

a) PRIMITIVO : (ipercalcemia)

- iperplasia 15%
- adenoma singolo 80%
- adenomi multipli 5%
- carcinoma (< 1%)

} paratiroidei

b) SECONDARIO :

insufficienza renale cronica (normo – o ipocalcemia)

↳ calcio ↓
fosfato ↑
vitamina D₃ ↑ } • Iperplasia paratiroidea
• PTH ↑

c) TERZIARIO : (ipercalcemia)

Autonomizzazione della ghiandola paratiroidea ipertrofica dopo lunga stimolazione (per es. in insufficienza renale cronica)

IPERPARATIROIDISMO PRIMITIVO

Raramente < 15 aa età

spesso > 40aa età

f : m = 3.5 : 1

prevalenza ~ 1: 1000

- 80% **asintomatici** con ipercalcemia lieve
- **sintomatici**: nefrolitiasi è spesso l'unico reperto
- **iperparatiroidismo normocalcemico** (spesso ipoalbuminemia, altrimenti tende ad aumentare nel tempo, diagn.diff.: iperparatiroidismo secondario)
- **iperparatiroidismo acuto**

CLINICAL STUDY

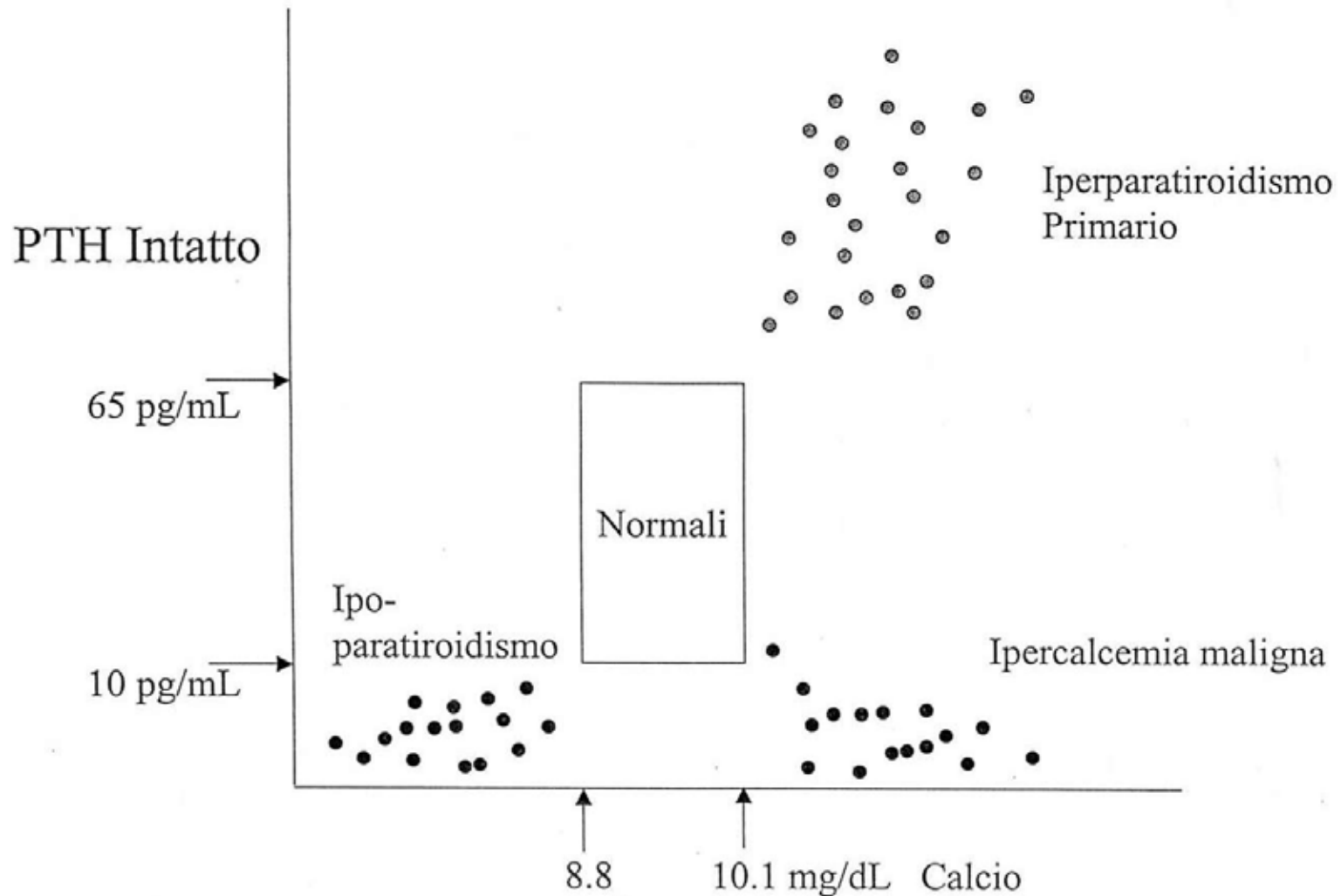
Retrospective analysis of the association of nodular goiter with primary and secondary hyperparathyroidism

L dell'Erba¹, S Baldari², N Borsato³, G Bruno⁴, G Calò-Gabrieli¹, M Carletto⁵, A Ciampolillo⁶, M Dondi⁷, P Erba⁵, P Gerundini⁴, S Lastoria⁸, P Marinelli³, M Santoro⁷, B Scarano⁹, P Zagni¹⁰, M Bagnasco¹¹ and G Mariani⁵

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Diagnosi differenziale



Summary Statement from a Workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century

John P. Bilezikian, John T. Potts, Jr., Ghada El-Hajj Fuleihan, Michael Kleerekoper, Robert Neer, Munro Peacock, Jonas Rastad, Shonni J. Silverberg, Robert Udelsman and Samuel A. Wells

The first generation immunoradiometric assay for PTH (IRMA PTH-Intact) has proved useful because the majority of patients with primary hyperparathyroidism have elevated levels.

.....

The normal range for the IRMA PTH-intact assay (generally 10–65 pg/ml) does not take into account the facts that PTH levels rise with age and differ between Caucasians and African-Americans. In African-Americans, normal PTH levels are typically higher than those in Caucasians. On the other hand, PTH levels are typically lower in younger adults.

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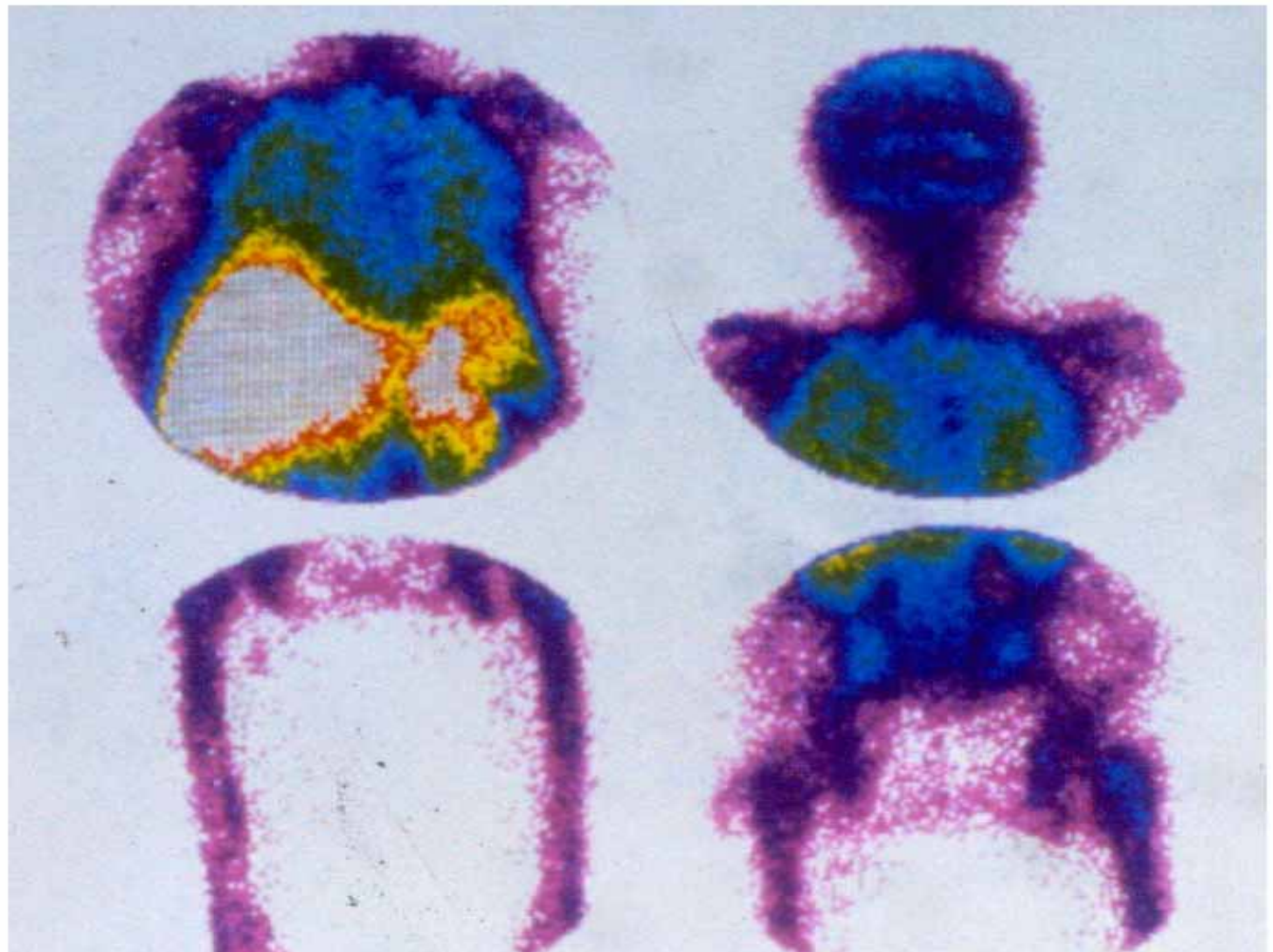
John P. Bilezikian, John T. Potts, Jr., Ghada El-Hajj Fuleihan, Michael Kleerekoper, Robert Neer, Munro Peacock, Jonas Rastad, Shonni J. Silverberg, Robert Udelsman and Samuel A. Wells

Primary hyperparathyroidism can also present as part of familial multiple endocrine neoplasia syndromes, but these patients constitute a small minority of patients with primary hyperparathyroidism. This possibility should be suspected in settings of a family history of hypercalcemia or other endocrine neoplasias and when primary hyperparathyroidism occurs in young subjects.

“Abnormal Bone Scintigraphy and Acute-Onset Severe Primary Hyperparathyroidism”

L. dell’Erba, S. Palermo, E. Orunesu, M. Bagnasco.

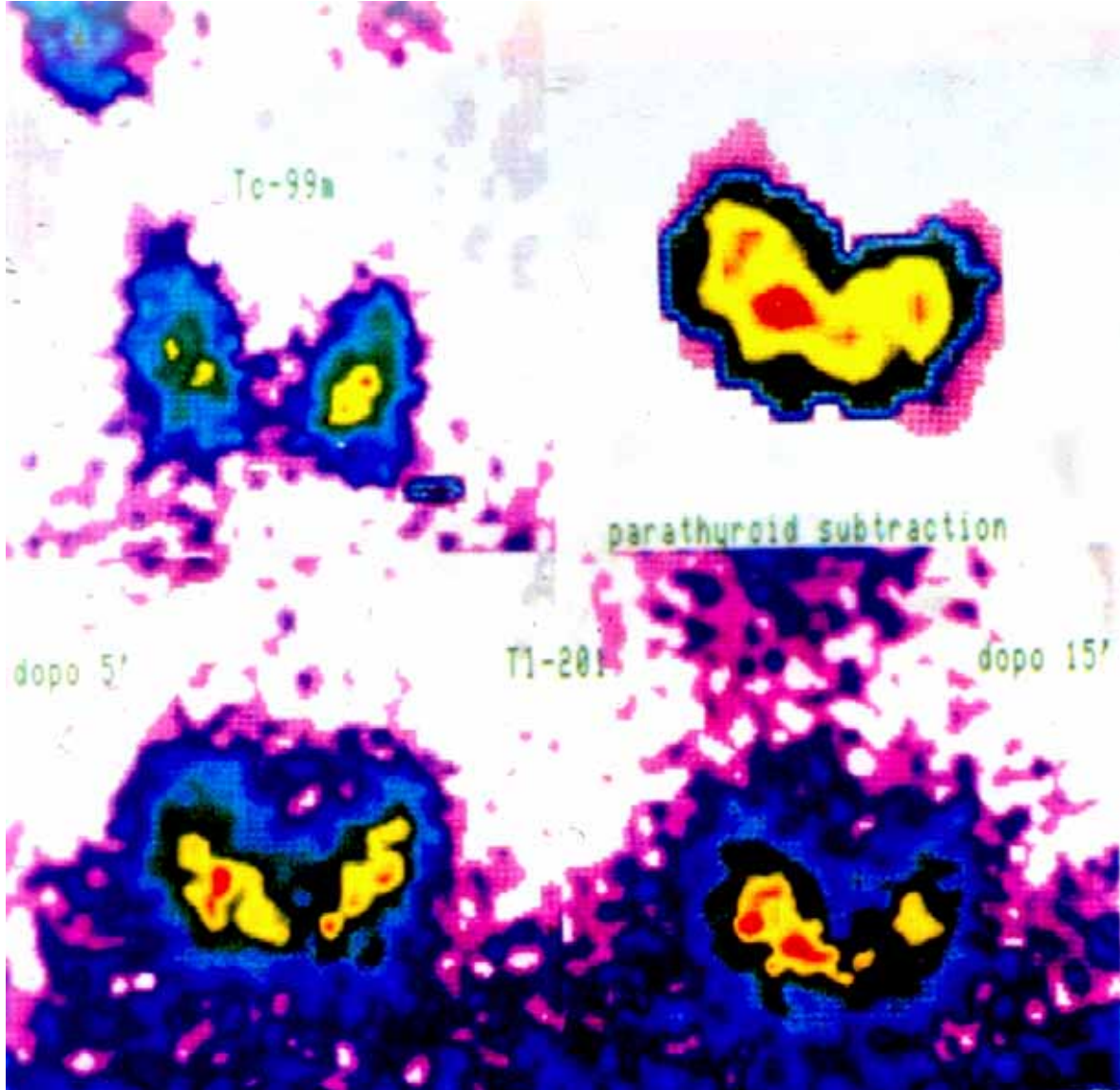
J Endocrinol Invest, in press



"Abnormal Bone Scintigraphy and Acute-Onset Severe Primary Hyperparathyroidism"

L. dell'Erba, S. Palermo, E. Orunesu, M. Bagnasco.

J Endocrinol Invest, in press



Dilemma clinico

"Parathyroidectomy for asymptomatic primary hyperparathyroidism (PHPT): is it worth the risk?"

YES

Rastad J.

J Endocrinol Invest 2001 Jan;24(1):56-61

"Parathyroidectomy for asymptomatic primary hyperparathyroidism (PHPT): is it worth the risk? "

NO

Rao DS.

J Endocrinol Invest 2001 Feb;24(2):131-4

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TABLE 1. A comparison of new and old guidelines for parathyroid surgery in asymptomatic primary hyperparathyroidism

Measurement	Guidelines (1990)	Guidelines (2002)
Serum calcium (above upper limit of normal)	1-1.6 mg/dl	1.0 mg/dl
24-h urinary calcium	>400 mg	>400 mg
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

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

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TABLE 2. A comparison of new and old management guidelines for patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroid surgery

Measurement	Older guidelines	Newer guidelines
Serum calcium	Biannually	Biannually
24-h urinary calcium	Annually	Not recommended ^a
Creatinine clearance	Annually	Not recommended ^a
Serum creatinine	Annually	Annually ^b
Bone density	Annually (forearm)	Annually (three sites: lumbar spine, hip, forearm)
Abdominal x-ray (±ultrasound)	Annually	Not recommended ^a

^a Except at the time of the initial evaluation.

^b If the serum creatinine concentration suggests a change in the creatinine clearance, when the Cockcroft-Gault equation is applied (see text), further, more direct, assessments of the creatinine clearance are recommended.

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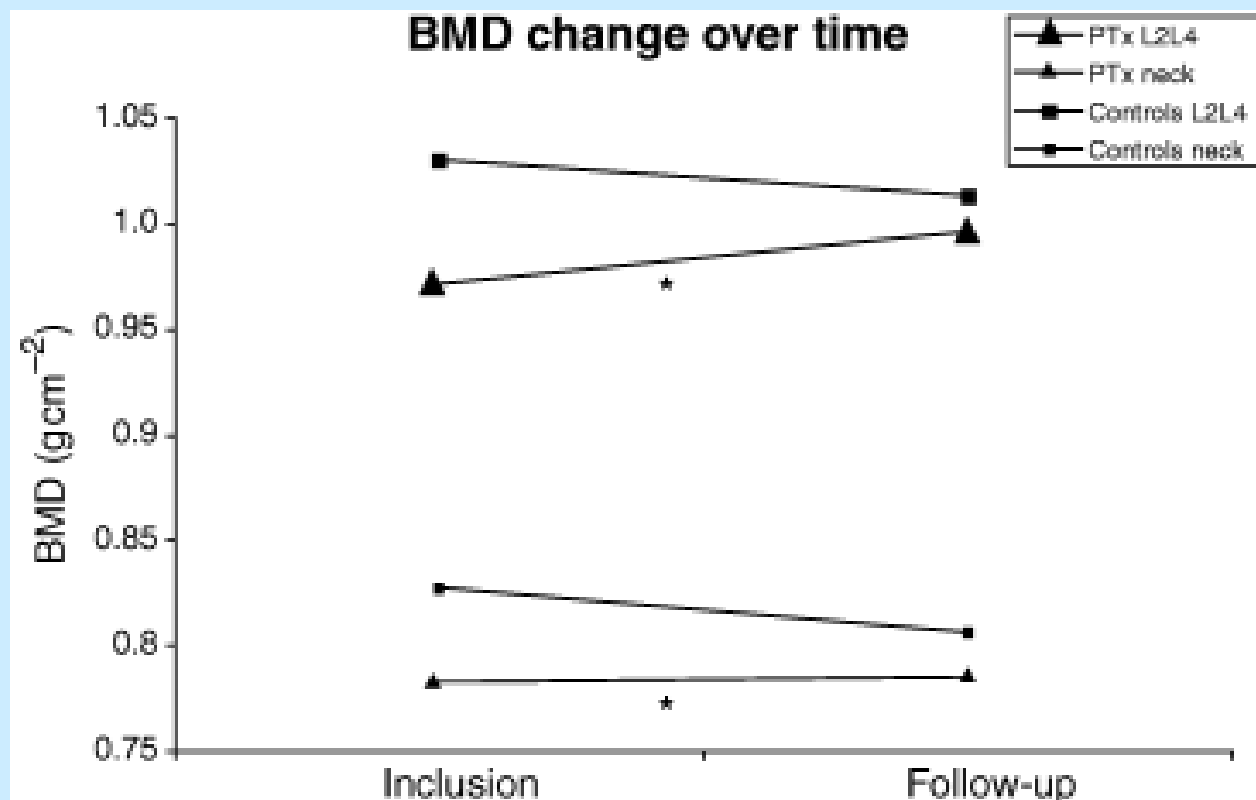
John P. Bilezikian, John T. Potts, Jr., Ghada El-Hajj Fuleihan, Michael Kleerekoper, Robert Neer, Munro Peacock, Jonas Rastad, Shonni J. Silverberg, Robert Udelsman and Samuel A. Wells

These patients with normal serum calcium concentrations are being discovered when PTH is measured in the course of evaluations for skeletal health or in the context of testing for osteoporosis. They are described as patients with normocalcemic primary hyperparathyroidism. This diagnostic consideration requires that all potential causes of secondary elevations of PTH be ruled out, particularly low calcium intake due to a gastrointestinal disorder, renal insufficiency, vitamin D deficiency (as defined by serum levels of 25-hydroxyvitamin D <20 ng/ml), or hypercalciuria of renal origin.

Positive effect of parathyroidectomy on bone mineral density in mild asymptomatic primary hyperparathyroidism*

E. HAGSTRÖM¹, E. LUNDGREN¹, H. MALLMIN¹, J. RÅSTAD^{1,2} & P. HELLMAN¹

From the ¹Department of Surgical Sciences, Uppsala University Hospital, Uppsala; and ²Clinical Science, AstraZeneca R & D, Södertälje; Sweden



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From the ¹Department of Surgical Sciences, Uppsala University Hospital, Uppsala; and ²Clinical Science, AstraZeneca R & D, Södertälje; Sweden

We conclude that it is feasible to conduct a randomized, controlled clinical trial of parathyroidectomy in patients with mild asymptomatic primary hyperparathyroidism, and measurable benefits of surgery on BMD, quality of life, and psychological function can be demonstrated. However, the small but significant benefits of parathyroidectomy must be weighed against the risks of surgery in these otherwise healthy individuals. (*J Clin Endocrinol Metab* 89: 5415–5422, 2004)

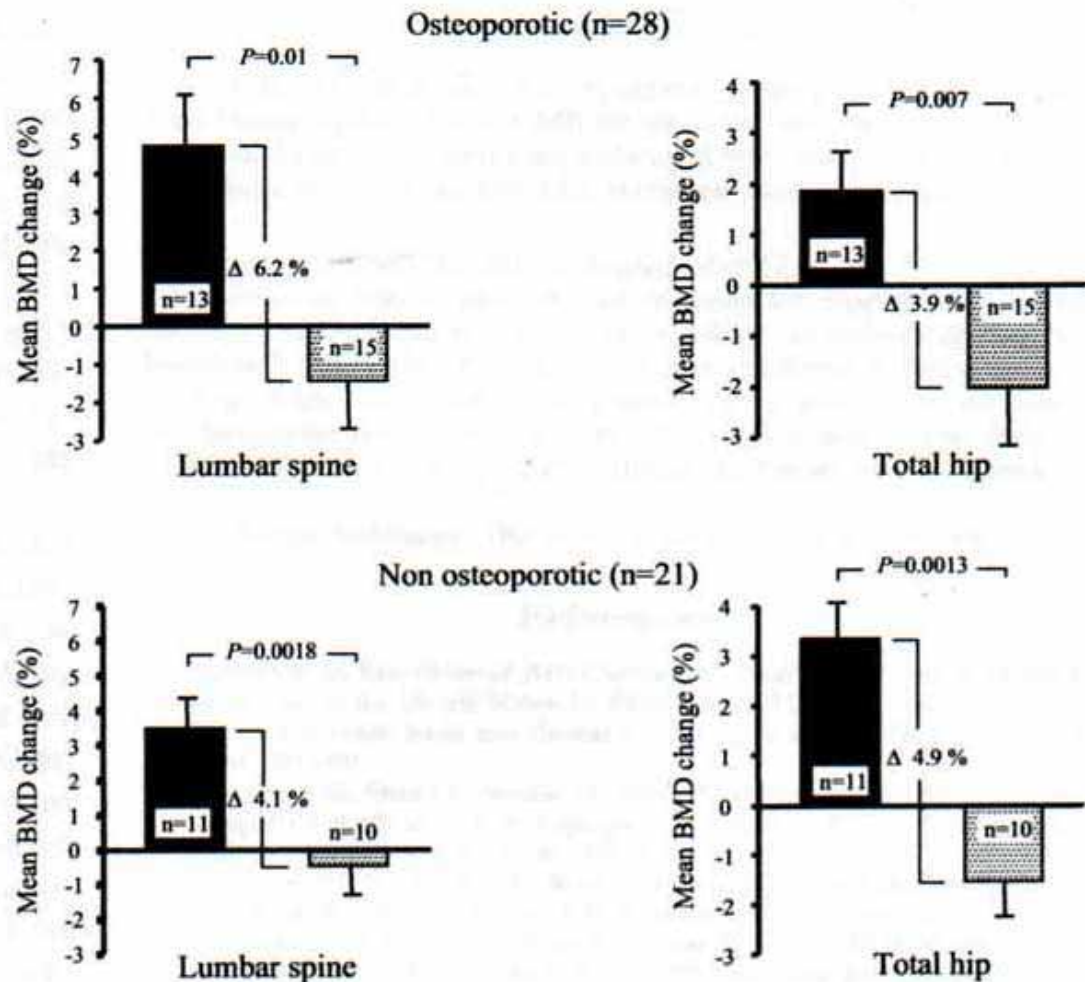
Surgery or Surveillance for Mild Asymptomatic Primary Hyperparathyroidism: A Prospective, Randomized Clinical Trial

Elena Ambrogini,* Filomena Cetani,* Luisella Cianferotti,* Edda Vignali, Chiara Banti, Giuseppe Viccica, Annalisa Oppò, Paolo Miccoli, Piero Berti, John P. Bilezikian, Aldo Pinchera, and Claudio Marcocci

Conclusions: In patients with mild asymptomatic PHPT, successful PTx is followed by an improvement in BMD and quality of life. Most patients followed without surgery did not show evidence of progression. (*J Clin Endocrinol Metab* 92: 3114–3121, 2007)

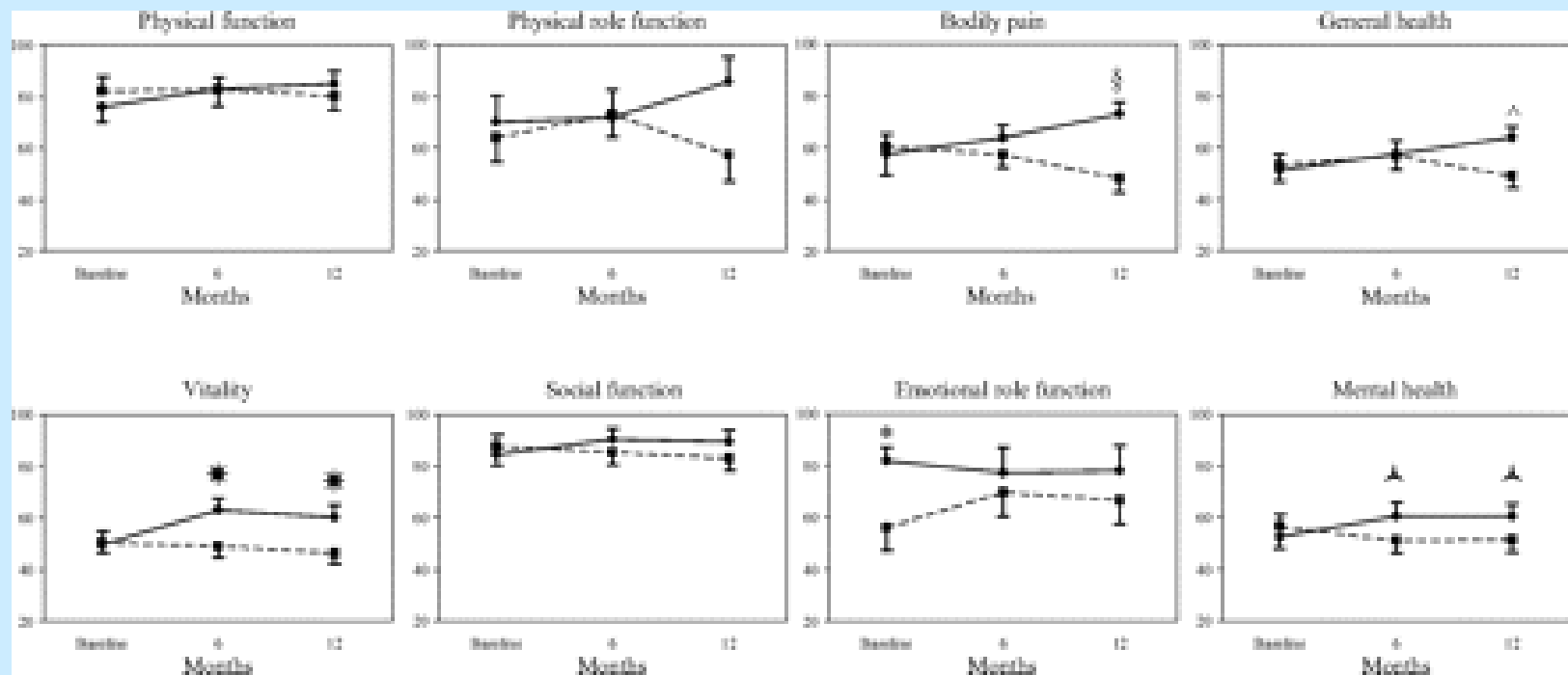
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Possibili criteri per indicazione chirurgica

bibliografia : www.endocrinology.med.ucla.edu, Mark Goodarzi

- 1) Calcio plasmatico > 12 mg/dl
- 2) Ipercalciuria > 400 mg/d
- 3) Manifestazione clinica (es. nefrolitiasi)
- 4) Riduzione di BMD ossea (z-score < -2)
- 5) Riduzione clearance creatinina di natura non identificabile
- 6) Età < 50 anni
- 7) Episodio di iperparatiroidismo acuto

Nel 90% intervento porta a guarigione completa

Dosaggio PTH

- **anni '70-'80** - saggi RIA per :
 - N-terminale*
 - Media-molecola (MM)
 - C-terminalescarsa sensibilità
- **prima metà anni '80** - metodo a due passaggi:
immunoestrazione + RIA (per PTH intatto bioattivo)
- **1987** - primo saggio immunoradiometrico a due siti
"sandwich"

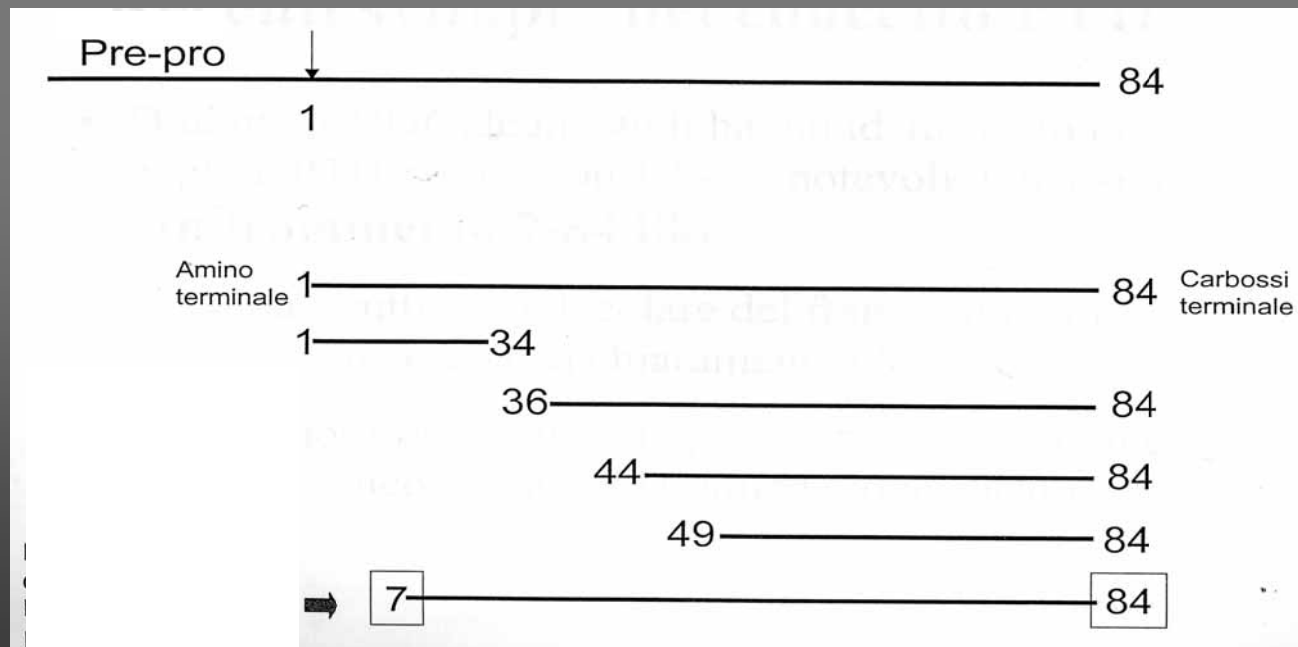
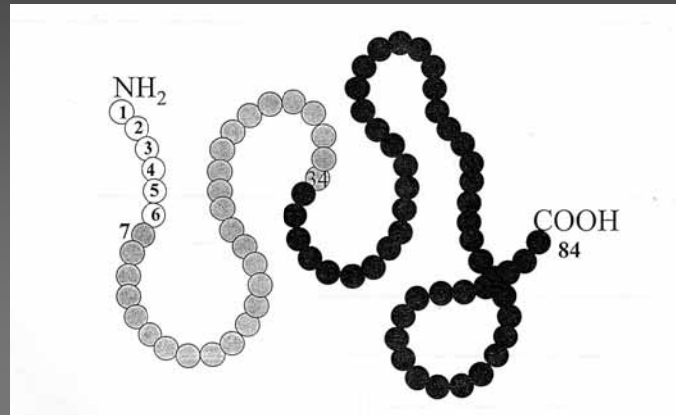
* N-terminale :stessa attività biologica di PTH intatto e stessa breve emivita <5min., però: livelli circolanti molto più bassi

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A second generation IRMA assay for PTH has been developed that appears to measure only the full-length molecule, PTH(1–84). The first generation IRMA PTH-intact assay also detects appreciable quantities of a large fragment(s) of PTH that is apparently missing a portion of the amino terminus of the full-length molecule. It is not known whether the newer IRMA assay, in which large hormone fragments are not detected, will provide increased diagnostic sensitivity in this disorder. Further investigation is warranted, especially in view of some evidence that favors its superiority.

STRUTTURA PTH

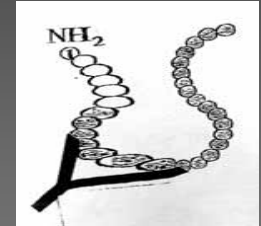
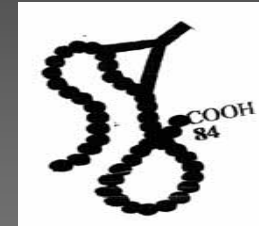


DOSAGGIO DEL PTH

1963 primo dosaggio

1975 dosaggi RIA specifici per frammento C

1981 dosaggi RIA specifici per frammento N



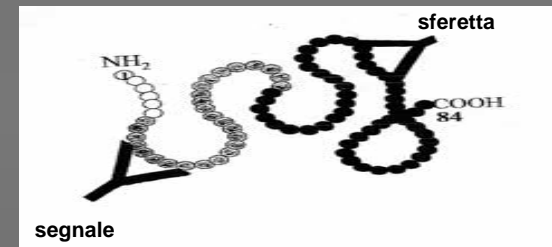
1985 IRMA 24h

1991 Chemiluminescenza 2h

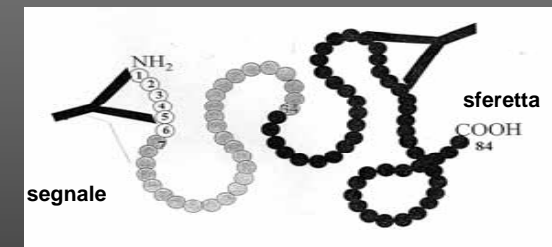
ALTA SPECIFICITA'
(molecola Intatta)



LEGAME SANDWICH



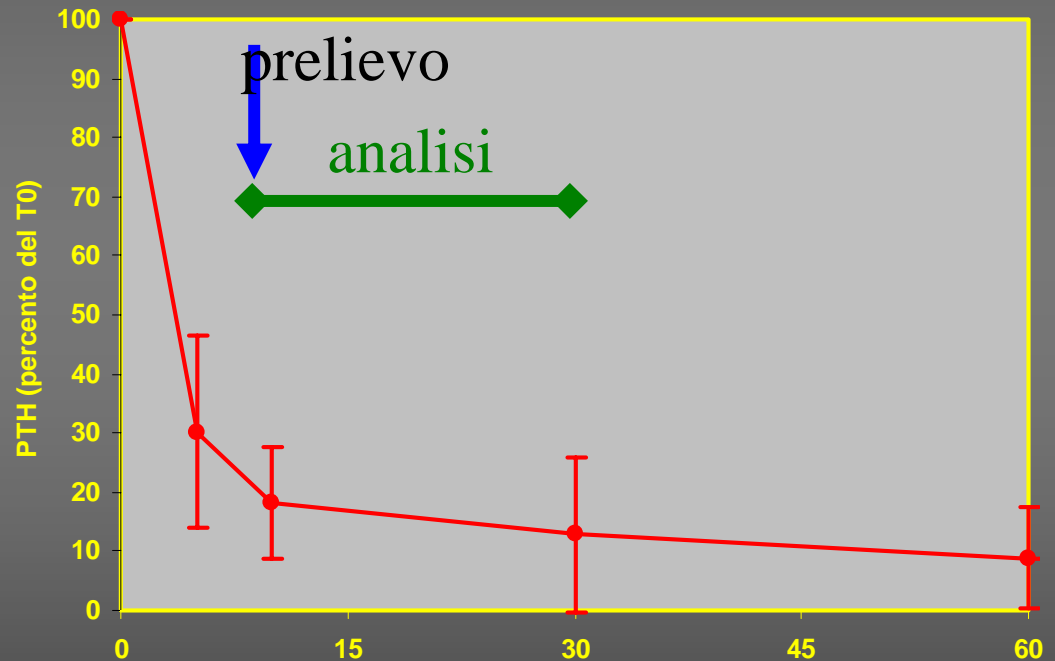
2000 Bio-Intact PTH (1-84)



1995 PTH ultraveloce (10-20 min) → intraoperatorio

Razionale del dosaggio del PTH intraoperatorio

- Emivita molto breve (3-4')
- Procedura di analisi molto veloce (10-20 minuti)



Vantaggi del dosaggio del PTH intraoperatorio

- **Informazione (quasi) immediata del successo operatorio o della necessità di reintervento**
- **Possibilità di accesso mini invasivo**
- **Riduzione dei tempi di intervento**
- **Localizzazione della(e) ghiandola da asportare**
- **Informazione sul rischio di ipocalcemia**



Requisiti per il dosaggio

- **Laboratorio centrale / sala operatoria**
 - **Strumentazione (costo, ingombro)**
 - **Personale**
 - **Distanza**
 - **Frequenza degli interventi**
 - **Tempo di risposta**



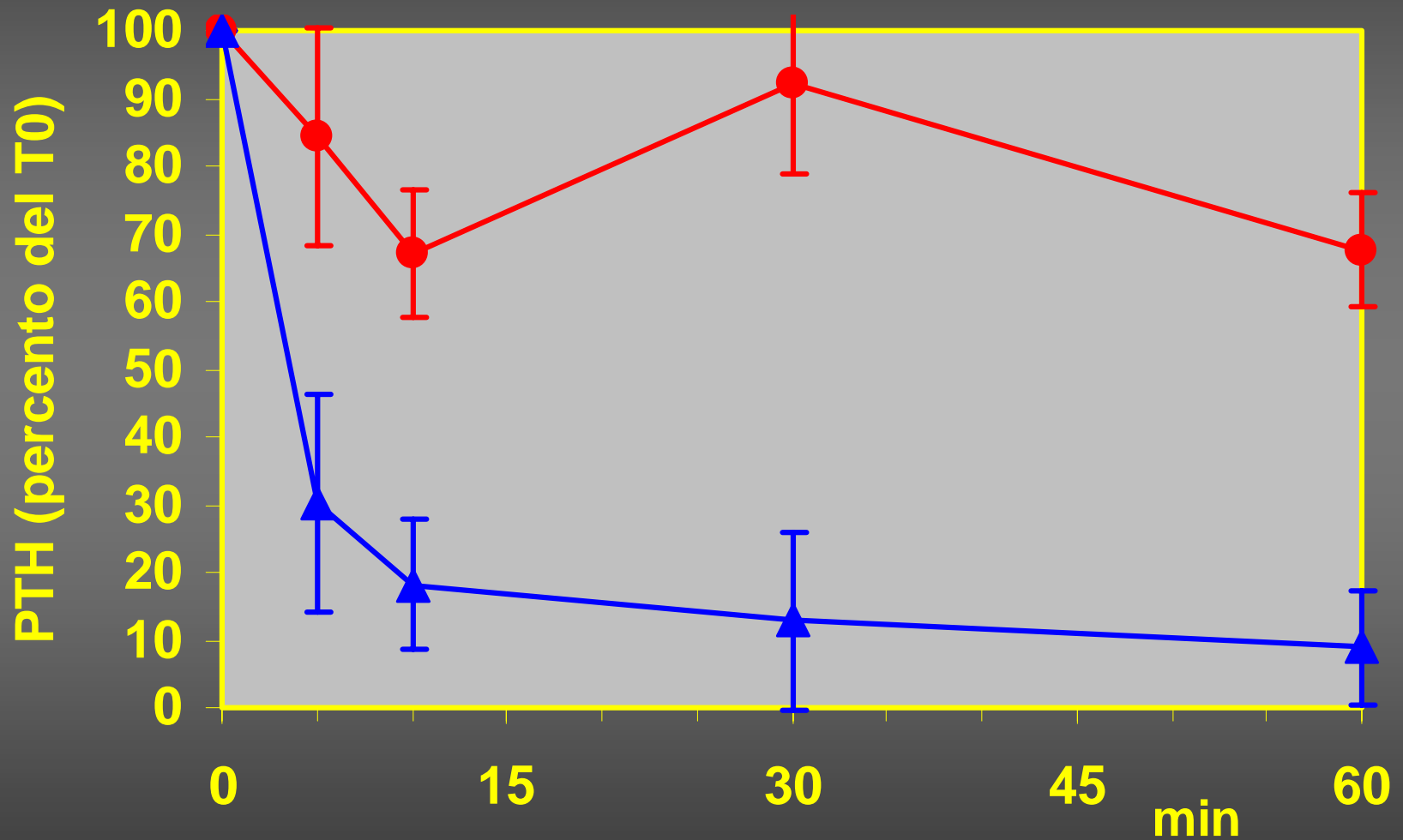
PTH INTRAOPERATORIO

Laura Fazzuoli

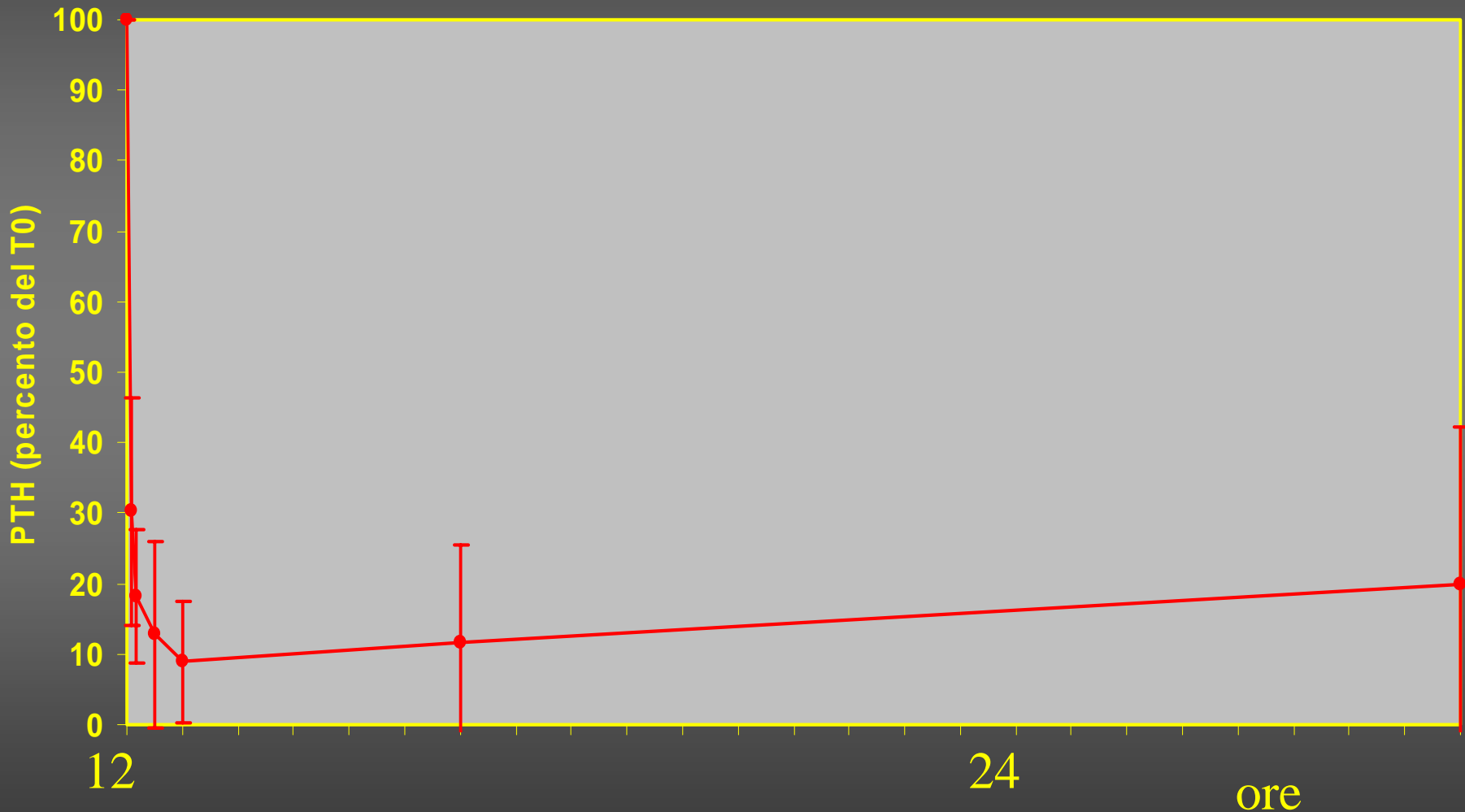
Francesco Minuto



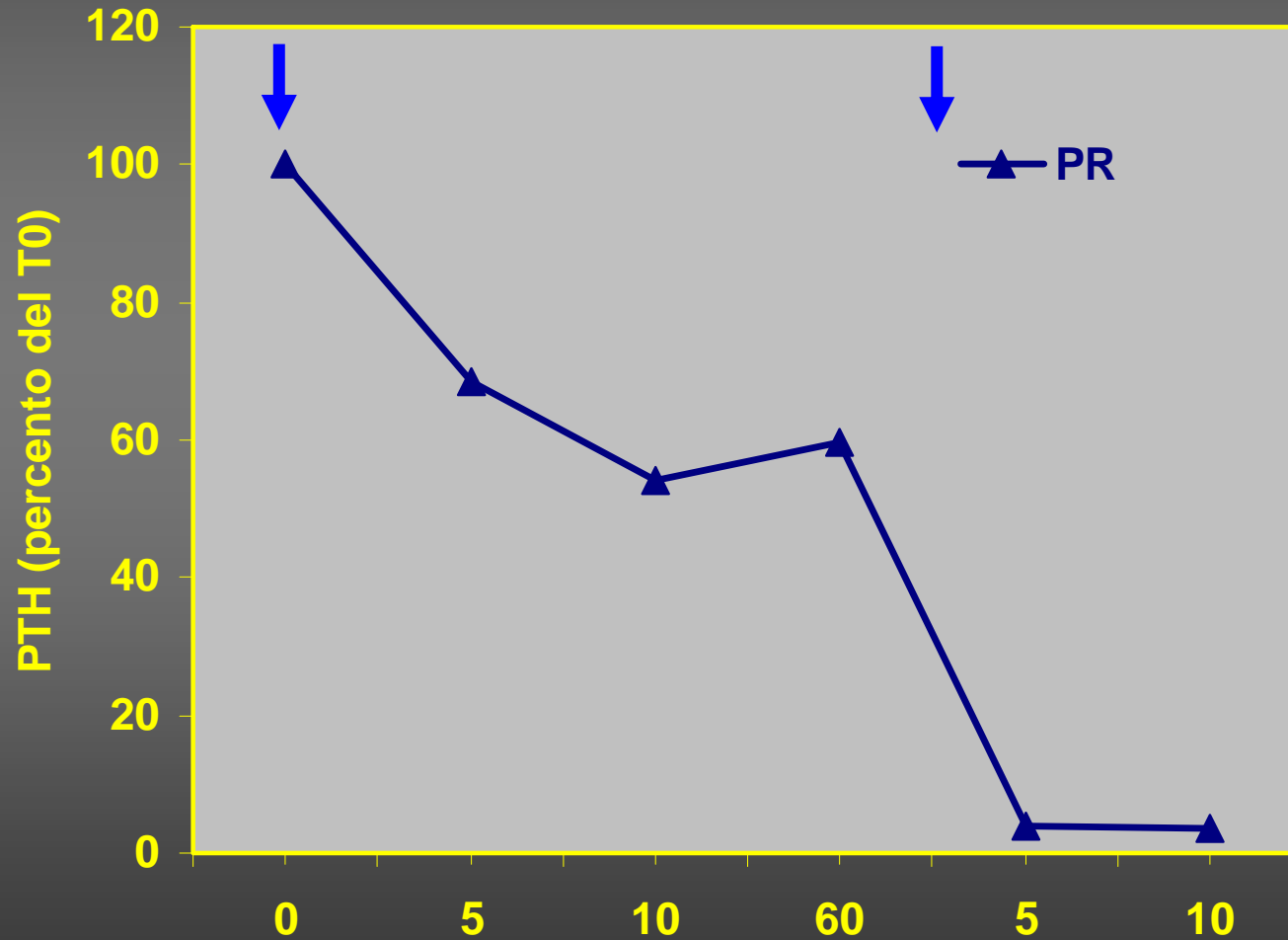
Andamento della concentrazione di PTH dopo la paratiroidectomia



Andamento della concentrazione di PTH dopo la paratiroidectomia



Caso clinico



IL PTH INTRAOPERATORIO

- **Consente la tecnica di PTx mini invasiva**
- **Dà la certezza della riuscita dell'intervento**
- **Riduce tempi e costi dell'intervento**
- **Riduce il rischio di ipoparatiroidismo (?)**

