AACE Italian Chapter
Course 3
Guida all'iperparatiroidismo

Danno d'organo: osso

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

nessuno

PHPT “SINTOMATICO” e “ASINTOMATICO”

SINTOMATICO	ASINTOMATICO
Fratture	Ridotta BMD
Tumori bruni	
Osteite fibroso-cistica	

PHPT "SINTOMATICO"

C.S. anni 40

Visita endocrinologica urgente per

MANO DX Ampia aria di rarefazione ossea che determina rigonfiamento del collo del terzo metacarpo ed assottigliamento delle pareti ma senza interruzione delle pareti (encondroma solitario ?Cisti aneurismatica ?)

"Osteolisi ovalare 25 x 12 testa 3° metacarpo come da tumore bruno da iperPTH"

PHPT "SINTOMATICO"

D.L. anni 41

Già seguita per ipotiroidismo in trattamento con tiroxina.

Viene a controllo con diagnosi istologica di:

TUMORE A CELLULE GIGANTI DELL'OSSO della sinfisi pubica destra

Assume ossicodone

Suggerita "asportazione di adenoma paratiroideo"

PHPT and FRACTURES

Bandeira F, Cassibba S., Curr Rheumatol Rep (2015) 17: 48

Parameter	Symptomatic	Asymptomatic	Normocalcemic
Fracture Vertebral Non-vertebral	↑↑↑ ↑↑↑	↑ ↑	NA NA
BTM	↑↑↑	↑	↑
25OHD	↓↓↓	↓ ↓	↔
LSBMD **FNBMD** **DRBMD**	↓↓↓ ↓↓↓ ↓↓↓	↓ ↓ ↓ ↓↓↓	↓ ↓ ↓
TBS	NA	↓↓↓	NA
HRpQCT Trabecular Cortical	NA	↓↓↓ ↓↓↓	NA
Histomorphometry Trabecular Cortical	NA	↓ ↓↓↓	NA

PHPT and FRACTURES

Khosla S et al., J Bone Min Res 14: 1700-7, 1999

TABLE 2. OBSERVED (OBS) FRACTURES IN COMPARISON WITH EXPECTED NUMBERS (EXP) AND STANDARDIZED INCIDENCE RATIOS (SIRS) AT ALL SKELETAL SITES AMONG 407 ROCHESTER, MINNESOTA, RESIDENTS WITH PRIMARY HPT FIRST DIAGNOSED IN 1965–1992

	Obs	*Exp*	*SIR*	*95% CI*
Vertebral	79	24.6	3.2	2.5–4.0
Distal forearm (Colles')	49	22.1	2.2	1.6–2.9
Proximal femur	37	26.2	1.4	1.0–2.0
Ribs	61	22.3	2.7	2.1–3.5
Skull/face	4	4.8	0.8	0.2–2.1
Cervical spine/posterior elements	4	1.7	2.4	0.6–6.0
Sternum/clavicle/scapula	14	6.3	2.2	1.2–3.7
Proximal humerus	18	11.3	1.6	0.9–2.5
Shaft/distal humerus	4	3.0	1.4	0.4–3.5
Shaft/proximal forearm	2	6.2	0.3	0.0–1.2
Hands/fingers	23	14.6	1.6	1.0–2.4
Pelvis	14	6.8	2.1	1.1–3.5
Shaft/distal femur	1	4.7	0.2	0.0–1.2
Patella	9	4.2	2.1	1.0–4.1
Tibia/fibula/ankle	30	22.8	1.3	0.9–1.9
Feet/toes	29	20.1	1.4	0.9–2.0
Any fracture	202	154.6	1.3	1.1–1.5

PHPT and FRACTURES

Khosla S et al., J Bone Min Res 14: 1700-7, 1999

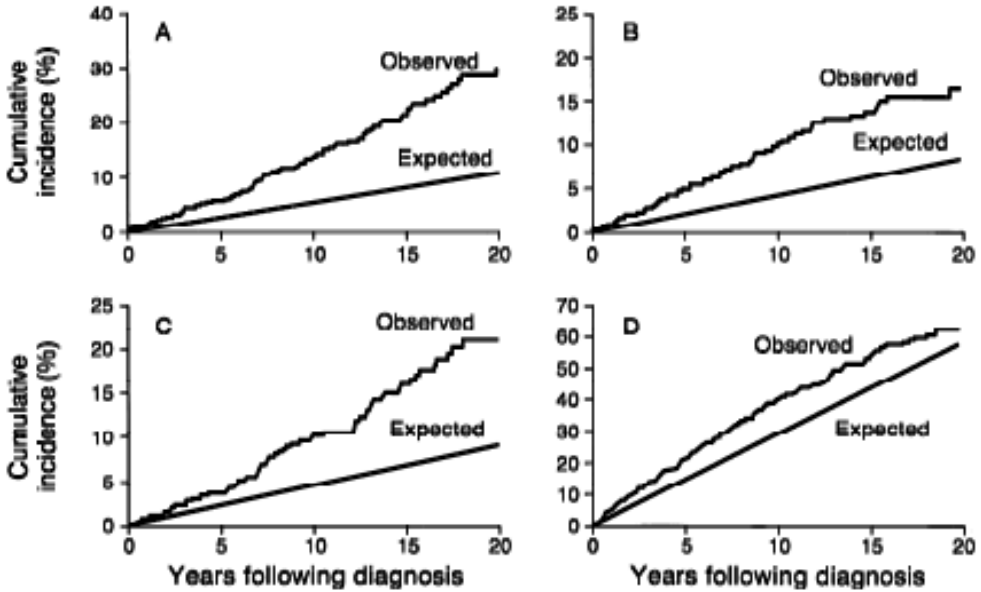


FIG. 2. Observed and expected cumulative incidence (1 minus survival free-of-fracture) of any vertebral fracture (A), distal forearm (Colles') fracture (B), rib fracture (C), and all fractures (D) among 407 Rochester, Minnesota residents following the initial diagnosis of primary HPT in 1965–1992. p values < 0.001 for all of the observed versus expected curves.

The Parathyroid Epidemiology and Audit Research Study (PEARS)

Yu N et al.,
Clinical Endocrinology (2011)
75, 169–176

Outcome	Event (%) Cases	Comparators	HRs	95% CI	*P*-values
Primary outcomes					
All cause mortality	404 (28·4)	992 (13·9)	2·24	1·99–2·51	<0·001
Fatal CVD	162 (11·4)	334 (4·7)	2·67	2·21–3·23	<0·001
Nonfatal CVD	357 (25·1)	544 (7·6)	4·19	3·66–4·79	<0·001
Secondary outcomes					
Cancer deaths	118 (8·3)	241 (3·4)	2·69	2·16–3·56	<0·001
Cerebrovascular	129 (9·1)	212 (3·0)	3·51	2·82–4·37	<0·001
Hypertension	161 (11·3)	188 (2·6)	5·01	4·06–6·19	<0·001
Renal failure	269 (18·9)	84 (1·2)	19·30	15·08–24·70	<0·001
Renal stones	19 (1·3)	23 (0·3)	4·56	2·48–8·38	<0·001
Psychiatric	32 (2·2)	27 (0·4)	6·46	3·87–10·79	<0·001
All fractures	109 (7·7)	284 (4·0)	2·16	1·73–2·69	<0·001
Osteoporotic fractures	81 (5·7)	221 (3·1)	2·06	1·60–2·66	<0·001
Cancer	144 (10·1)	370 (5·2)	2·18	1·80–2·65	<0·001
Diabetes	55 (3·9)	207 (2·9)	1·34	0·99–1·80	0·06

HRs, hazard ratios; CVD, cardiovascular disease; PHPT, primary hyperparathyroidism. The matching term, age and gender was used as a strata variable in all analyses. All secondary outcomes, apart from cancer deaths, were the primary cause of an in-patient hospital admission.

Patients. All patients with diagnosed but untreated, mild PHPT

PHPT and BONE DAMAGE - Evaluation

SPINE X-RAY

- vertebral fractures
- radiological evidence of osteoporosis
- morphometry

DXA

- gold standard method
- distal radius involved > than lumbar spine
- hip region: intermediate
- suitable for follow-up

EVIDENCE INTO PRACTICE

AME statement 2012 – J Endocrinol Invest 35 (suppl. to n. 7): 2-21

We recommend against skeletal X-ray as routine examination in PHPT.

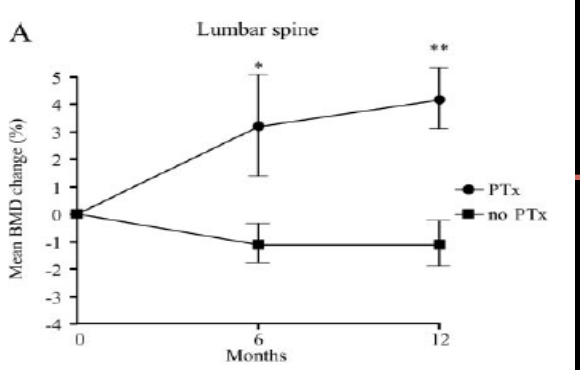
We recommend BMD measurement at diagnosis and at 1-2-yr intervals in individuals with PHPT who do not undergo surgery (for follow-up after PTX see below).

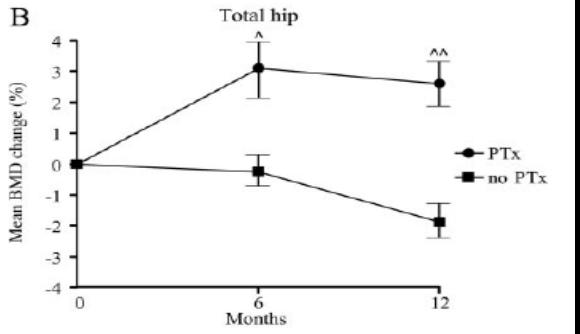
We suggest looking for vertebral fractures by vertebral morphometry in PHPT patients with osteoporosis or related symptoms.

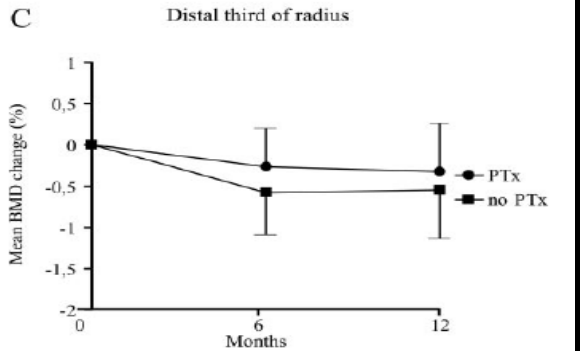
SURGERY for PHPT and BONE DISEASE

Ambrogini E et al., J Clin Endocrinol Metab 92: 3114–3121, 2007

- Most patients followed without surgery did not show evidence of progression.
- In patients with mild asymptomatic hyperparathyroidism, successful parathyroidectomy is followed by an improvement in BMD.

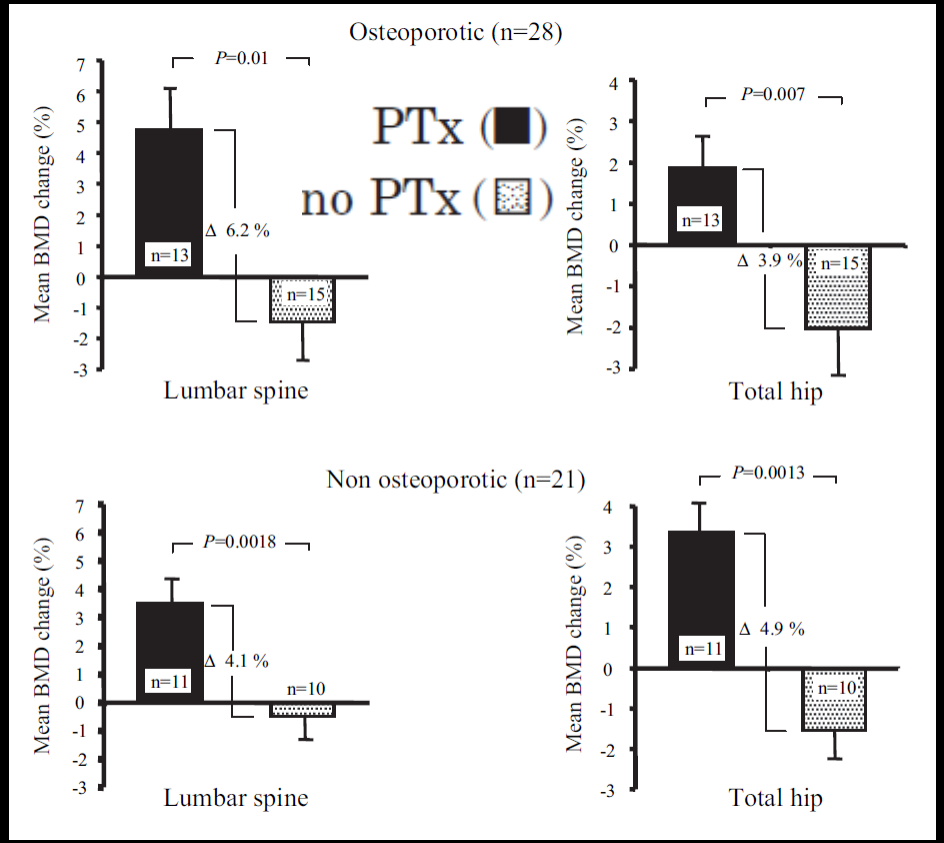






SURGERY for PHPT and BONE DISEASE

Ambrogini E et al., J Clin Endocrinol Metab 92: 3114–3121, 2007



SURGERY for PHPT and FRACTURE RISK

VanderWalde LH et al., World J Surg (2009) 33:406–411

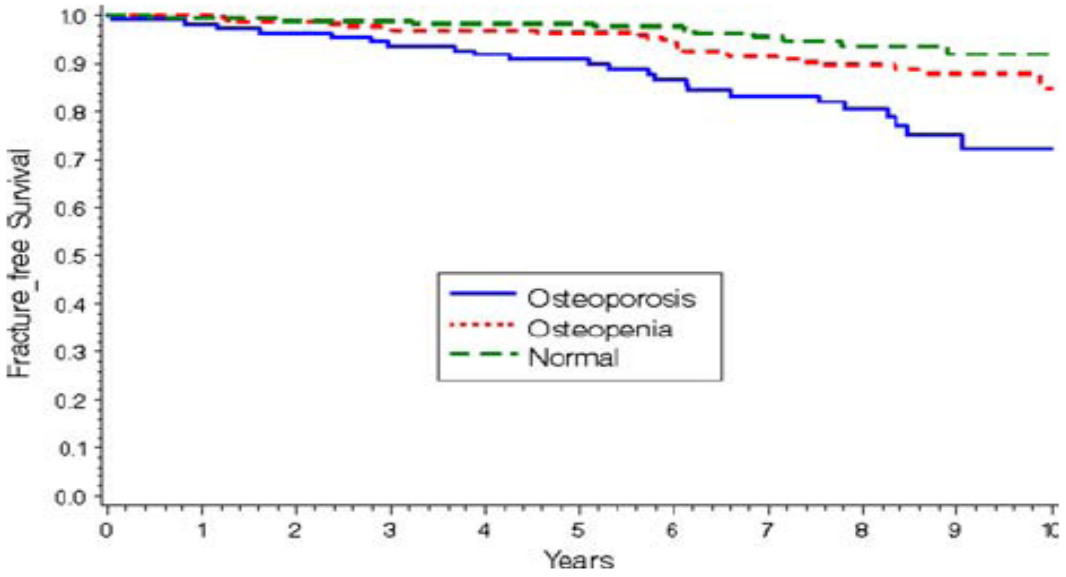
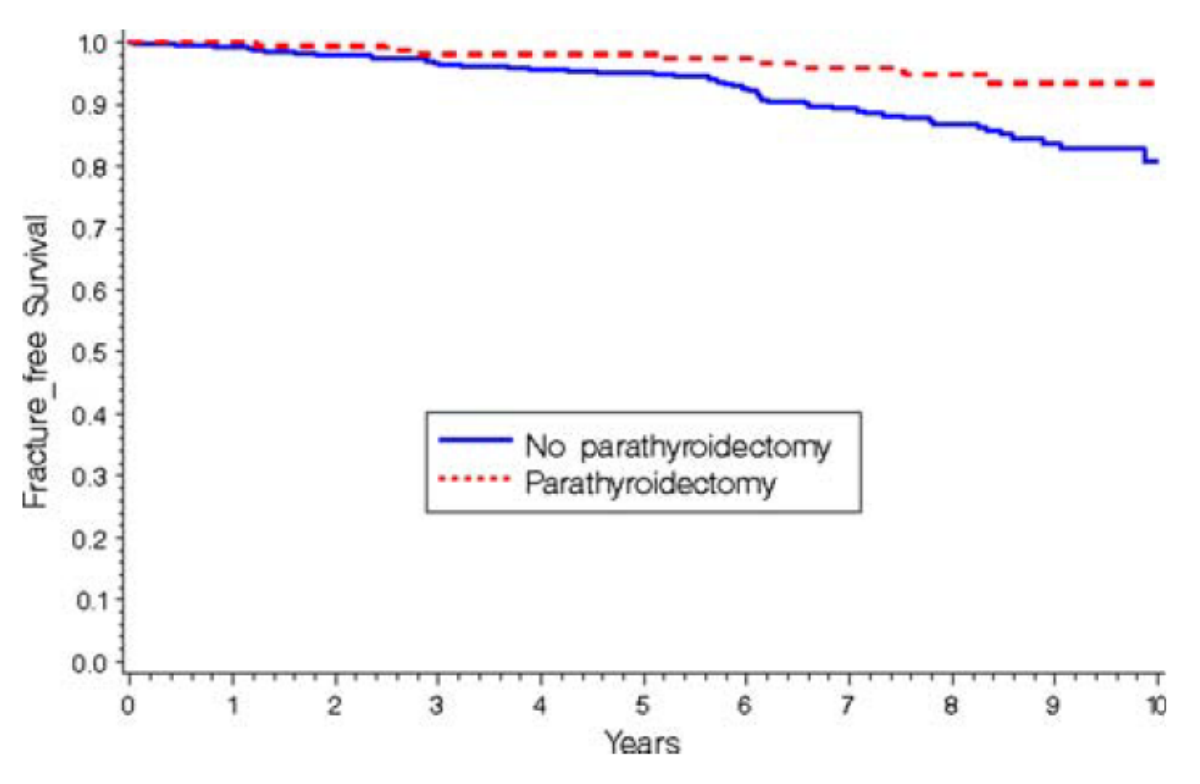


Fig. 1 The 10-year fracture free survival (FFS) of patients with different bone mineral densities. Patients with normal bones (T-score ≥ -1.0) had a 10-year FFS of 92%, compared to 85% in patients with osteopenia (T-score ≤ -1.0, ≥ -2.5) and 72% in patients with osteoporosis (T-score ≥ -2.5)

SURGERY for PHPT and FRACTURE RISK

VanderWalde LH et al., World J Surg (2009) 33:406–411



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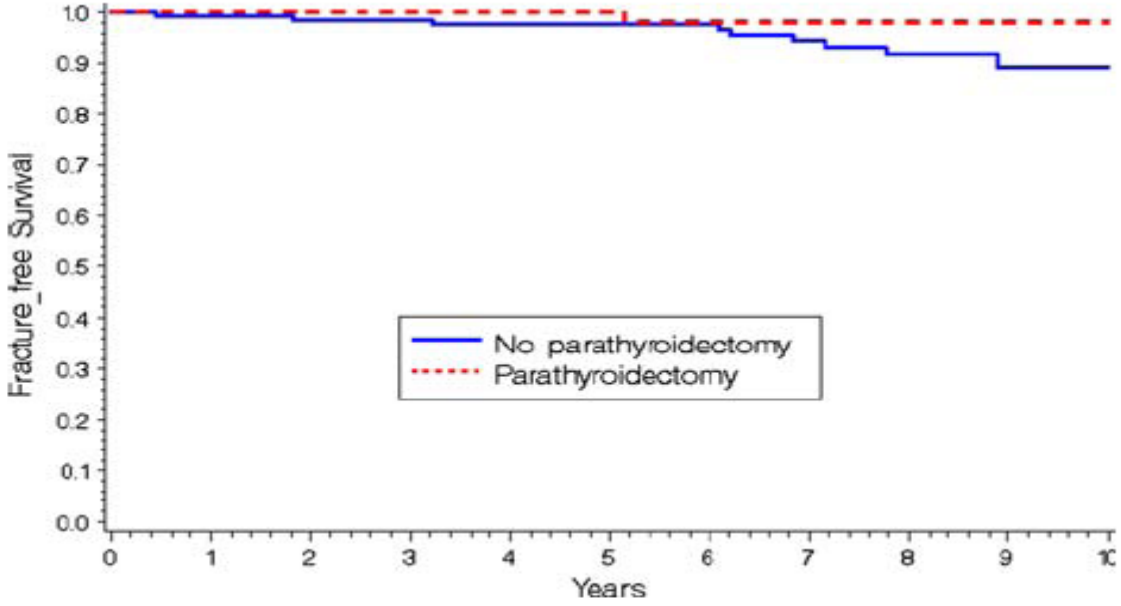


Fig. 3 In patients with normal bones (T-score ≥ -1.0), the 10-year FFS was 98% in patients treated with parathyroidectomy compared to 89% in those observed ($p = 0.99$)

SURGERY for PHPT and FRACTURE RISK

VanderWalde LH et al., World J Surg (2009) 33:406–411

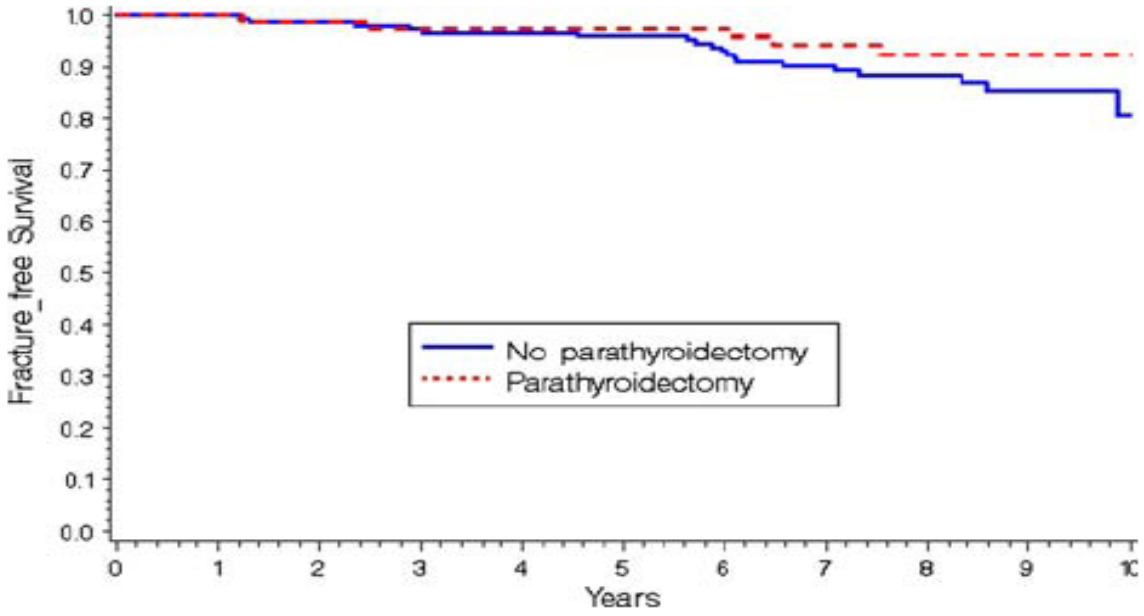


Fig. 4 In patients with osteopenia (T-score $\leq -1.0, \geq -2.5$), the 10-year FFS was 92% in patients treated with parathyroidectomy compared to 80% in those observed ($p = 0.92$)

THERAPY of PHPT and FRACTURE RISK

VanderWalde LH et al., World J Surg (2009) 33:406–411

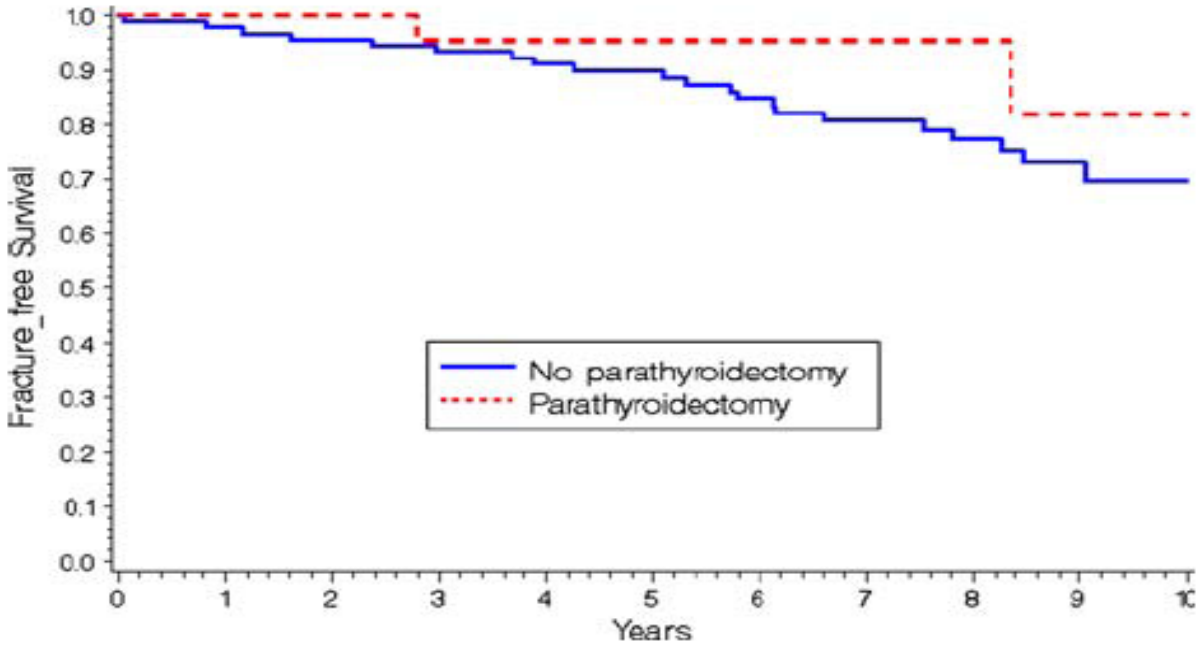


Fig. 5 In patients with osteoporosis (T-score < -2.5), the 10-year FFS was 82% in patients treated with parathyroidectomy compared to 70% in those observed ($p = 0.02$)

SURGERY for PHPT and FRACTURE RISK

Lundstam K et al., J Clin Endocrinol Metab, April 2015, 100(4):1359–1367

Demographics	Observation	Surgery
Number of patients	55	51
New VFs during follow-up		
Number of patients	5 (9.1%)	0
Number of VFs	5	0

Follow-up: 5 yrs

"Parathyroidectomy has a long-term beneficial effect on the skeleton and is probably prudent to refer PHPT patients for surgery in all cases where increased bone fragility is suspected. Bisphosphonates (BPs), mainly alendronate, have been proved as reasonable choices for BMD improvement . Combination of BPs and cinacalcet, is a valid therapeutic approach from a pathophysiological point of view".

Makras P, Anastasilakis AD. Bone Disease in Primary Hyperparathyroidism. Metabolism. 2017 Oct 16.

Medical vs. Surgical Treatment

- There is no controversy that virtually all patients with **symptomatic** biochemically confirmed PHPT should be referred for surgical treatment
- After surgery in symptomatic subjects:
  - bone density improves
  - fracture rate declines
  - cognitive function appears to improve
  - the incidence of kidney stones seems to decline
  - cardiovascular disease and premature death also appear to decrease

Udelsman R et al., J Clin Endocrinol Metab 94: 366–372, 2009

Table 1. Guidelines for Surgery in Asymptomatic PHPT: A Comparison of Current Recommendations With Previous Ones[a]

	1990	2002	2008	2013
Measurement[b]				
Serum calcium (>upper limit of normal)	1–1.6 mg/dL (0.25–0.4 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: Z-score <−2.0 (site unspecified)	BMD by DXA: T-score <−2.5 at any site[b]	BMD by DXA: T-score <−2.5 at any site[b]	A. BMD by DXA: T-score < −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius[b]
			Previous fragility fracture[c]	B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	A. eGFR reduced by >30% from expected B. 24-h urine for calcium >400 mg/d (>10 mmol/d)	A. eGFR reduced by >30% from expected B. 24-h urine for calcium >400 mg/d (>10 mmol/d)	A. eGFR < 60 cc/min B. 24-h urine for calcium not recommended	A. Creatinine clearance < 60 cc/min B. 24-h urine for calcium >400 mg/d (>10 mmol/d) and increased stone risk by biochemical stone risk analysis[d]
				C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Age, y	<50	<50	<50	<50

BONE and ASYMPTOMATIC PHPT

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

Bilezikian JP et al., J Clin Endocrinol Metab. 2014 Oct;99(10):3561-9

EVIDENCE INTO PRACTICE

AME statement 2012 – J Endocrinol Invest 35 (suppl. to n. 7): 2-21

ITALIAN CHAPTER

Chirurgia	Wait and see
pHPT sintomatico	pHPT asintomatico con assenza criteri Workshop 2008 e con localizzazione preoperatoria negativa
pHPT asintomatico con almeno 1 criterio Workshop 2008	
pHPT asintomatico con localizzazione positiva	

→ ***Marco Boniardi !***

Perché non operare

- malattia tendenzialmente stabile
- disponibilità di farmaci efficaci su densità ossea e ipercalcemia

Quando non operare

- forme lievi
- mancata localizzazione preoperatoria dell'adenoma
- pazienti anziani o con alto rischio chirurgico
- pazienti non disponibili

"…asymptomatic patients who do not meet surgical guidelines can be followed safely without surgery, at least for a period of years."

Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop
Bilezikian JP et al., J Clin Endocrinol Metab. 2014 Oct;99(10):3561-9

Il PAZIENTE CON PHPT NON OPERATO

- Target osso
  - osteoporosi
  - fratture
  - lesioni focali
- Target ipercalcemia
  - acuta
  - cronica
- Target rene
  - calcoli
  - funzione glomerulare

→ ***Claudio Marcocci !***

→ ***Sabrina Corbetta !***

VITAMIN D STATUS

Lee JH et al., Osteoporos Int. 2017 May;28(5):1667-1674

	Women			
	25(OH)D, ng/ml			
	<20 ($n = 36$)	≥20 ($n = 16$)	P	P*
LS (g/cm^2)	0.903 ± 0.138	0.998 ± 0.184	0.045	0.035
LS T-score	−1.8 ± 1.2	−1.1 ± 1.5	0.055	0.043
FN (g/cm^2)	0.715 ± 0.084	0.791 ± 0.113	0.009	0.001
FN T-score	−1.5 ± 0.7	−0.9 ± 1.0	0.014	0.002
TH (g/cm^2)	0.777 ± 0.113	0.818 ± 0.144	0.273	0.104
TH T-score	−1.3 ± 0.9	−1.0 ± 1.2	0.271	0.099
LS-TBS	1.258 ± 0.098	1.289 ± 0.112	0.315	0.222

LS lumbar spine, *FN* femur neck, *TH* total hip

79 pts.
with PHPT

EVIDENCE INTO PRACTICE

AME statement 2012 – J Endocrinol Invest 35 (suppl. to n. 7): 2-21

ITALIAN CHAPTER

Nei pazienti con pHPT il deficit di vitamina D è frequente

→ **Misurare sempre i livelli plasmatici di 25-OHD.**

→ **Trattare il deficit di vitamina D**

We suggest vitamin D supplementation in vitamin D-deficient patients with PHPT, as currently done for non-PHPT patients.

PHPT e OSSO: FARMACI vs. CHIRURGIA

Sankaran S et al. Skeletal Effects of Interventions in Mild Primary Hyperparathyroidism: A Meta-Analysis. J Clin Endocrinol Metab 95: 1653–1662, 2010

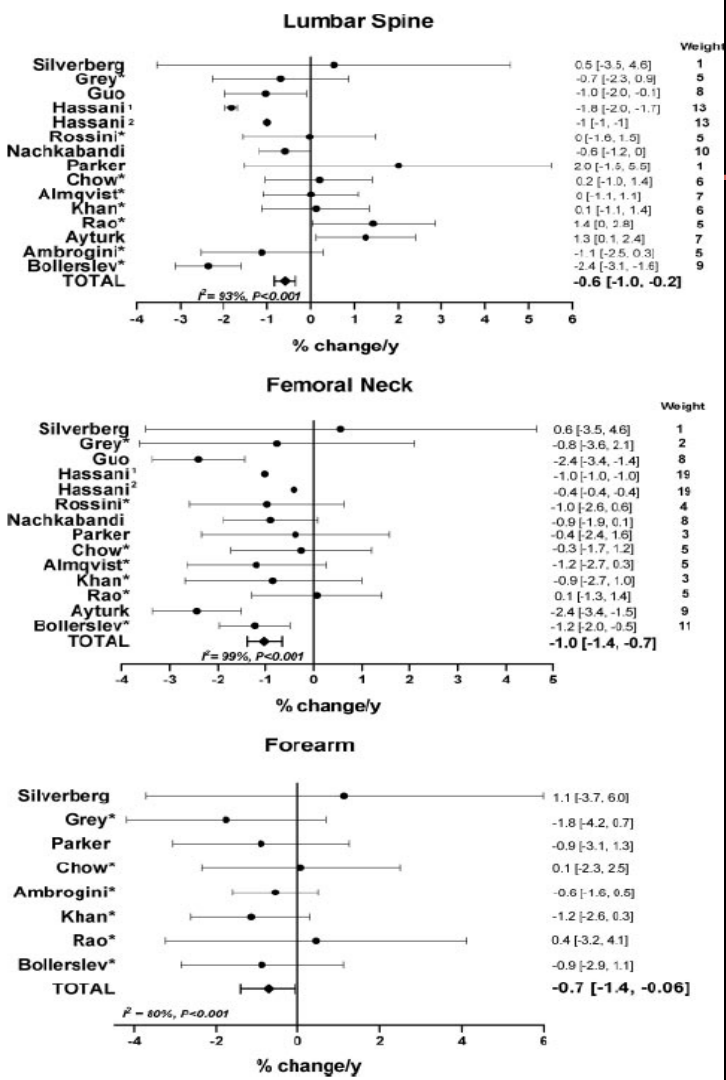


FIG. 4. Meta-analysis of effects of no intervention on BMD in studies of up to 2-yr duration in mild PHPT. *Circles* and *lightface type* represent individual studies; *diamonds* and *boldface type* represent summary statistics. For Hassani *et al.* references: 1, men; 2, women. *, Placebo group from randomized trial. Data are expressed as mean (95% CI) percentage change per year.

PHPT e OSSO: FARMACI vs. CHIRURGIA

Sankaran S et al. Skeletal Effects of Interventions in Mild Primary Hyperparathyroidism: A Meta-Analysis. J Clin Endocrinol Metab 95: 1653–1662, 2010

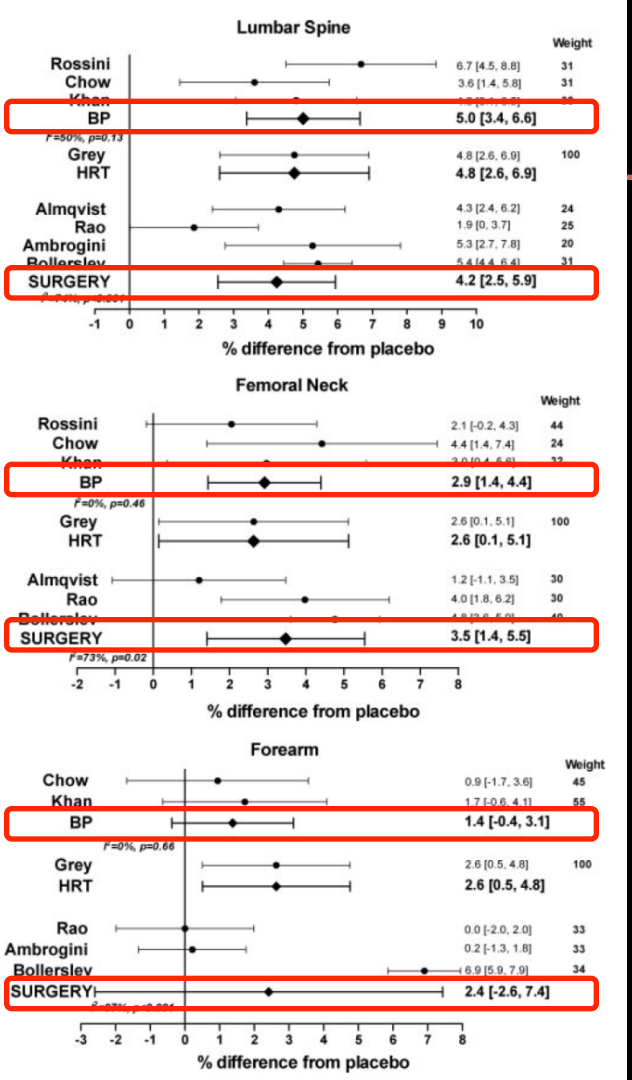
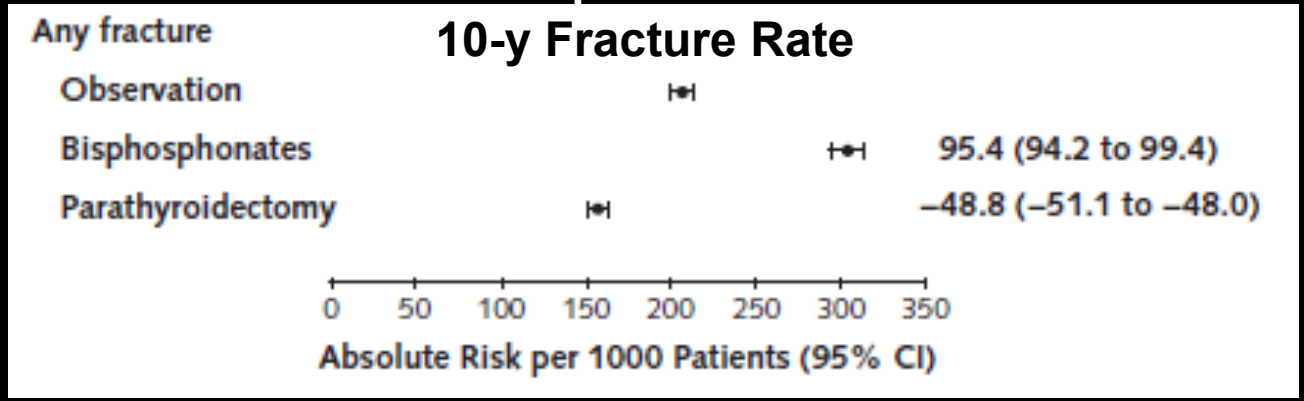


FIG. 2. Meta-analysis of effects of surgical and medical interventions on BMD after 1 yr in RCTs of mild PHPT. *Circles* and *lightface type* represent individual studies; *diamonds* and *boldface type* represent summary statistics. BP, Bisphosphonate. Data are expressed as mean (95% CI) percentage difference from placebo.

PHPT e OSSO: FARMACI vs. CHIRURGIA

Yeh MW et al., Ann Intern Med. 2016;164:715-723.

6272 pts
retrospective cohort
10-y Fracture Rate



EVIDENCE INTO PRACTICE

AME statement 2012 – J Endocrinol Invest 35 (suppl. to n. 7): 2-21

- **Raccomandiamo** di considerare l'uso dell' alendronato nei pazienti con PHPT non operati
  - con BMD nel range di osteoporosi
  - con BMD nel range di osteopenia con fattori di rischio per frattura
- **Suggeriamo** il ricorso all'alendronato anche nei pazienti che dopo la paratiroidectomia non hanno un soddisfacente recupero di densità minerale ossea

IPERPARATIROIDISMO e OSSO

THM (1/2)

- L'iperparatiroidismo espone al rischio di frattura
- Lo stato osseo deve essere valutato al momento della diagnosi di PHPT
  - DXA
  - morfometria vertebrale
- La risoluzione chirurgica del PHPT tende a normalizzare il rischio di frattura

IPERPARATIROIDISMO e OSSO

THM (2/2)

- Una quota minoritaria ma consistente dei pazienti con PHPT non viene operata
- In questi, è ben dimostrata la possibilità di proteggere farmacologicamente l'osso
  - alendronato
  - vitamina D