APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA
REUMATOLOGIA E MALATTIE NEOPLASTICHE

# Morbo di Paget ed Osteosarcoma

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S.C. GERIATRIA E MALATTIE METABOLICHE DELL'OSSO

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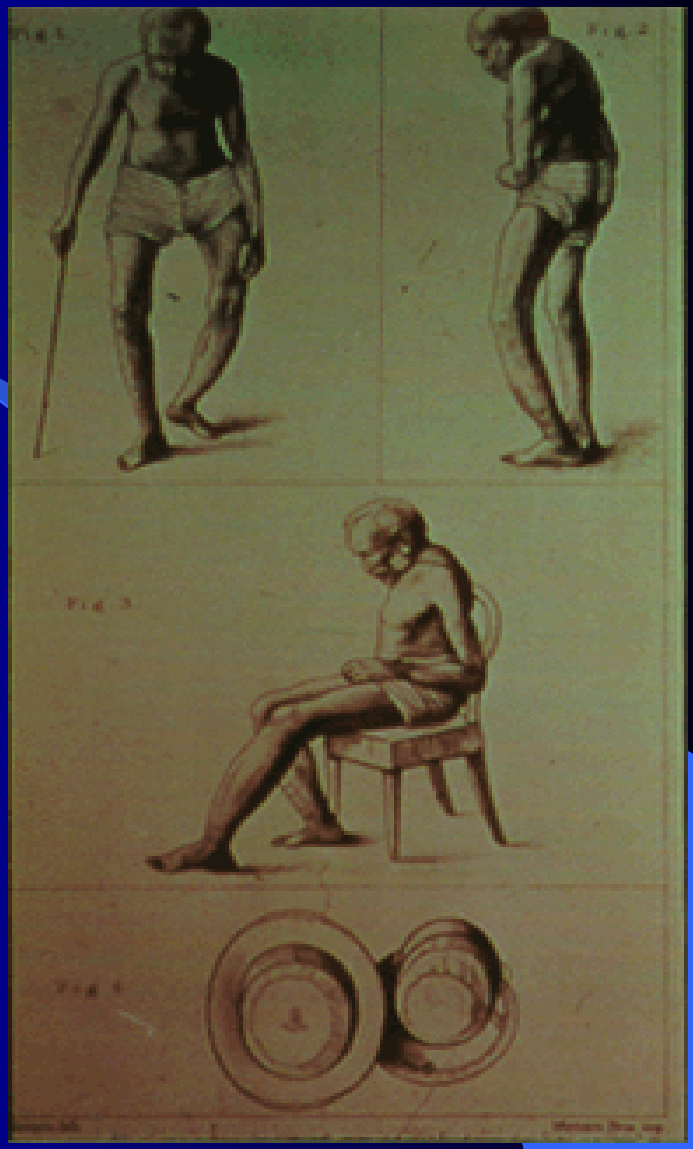
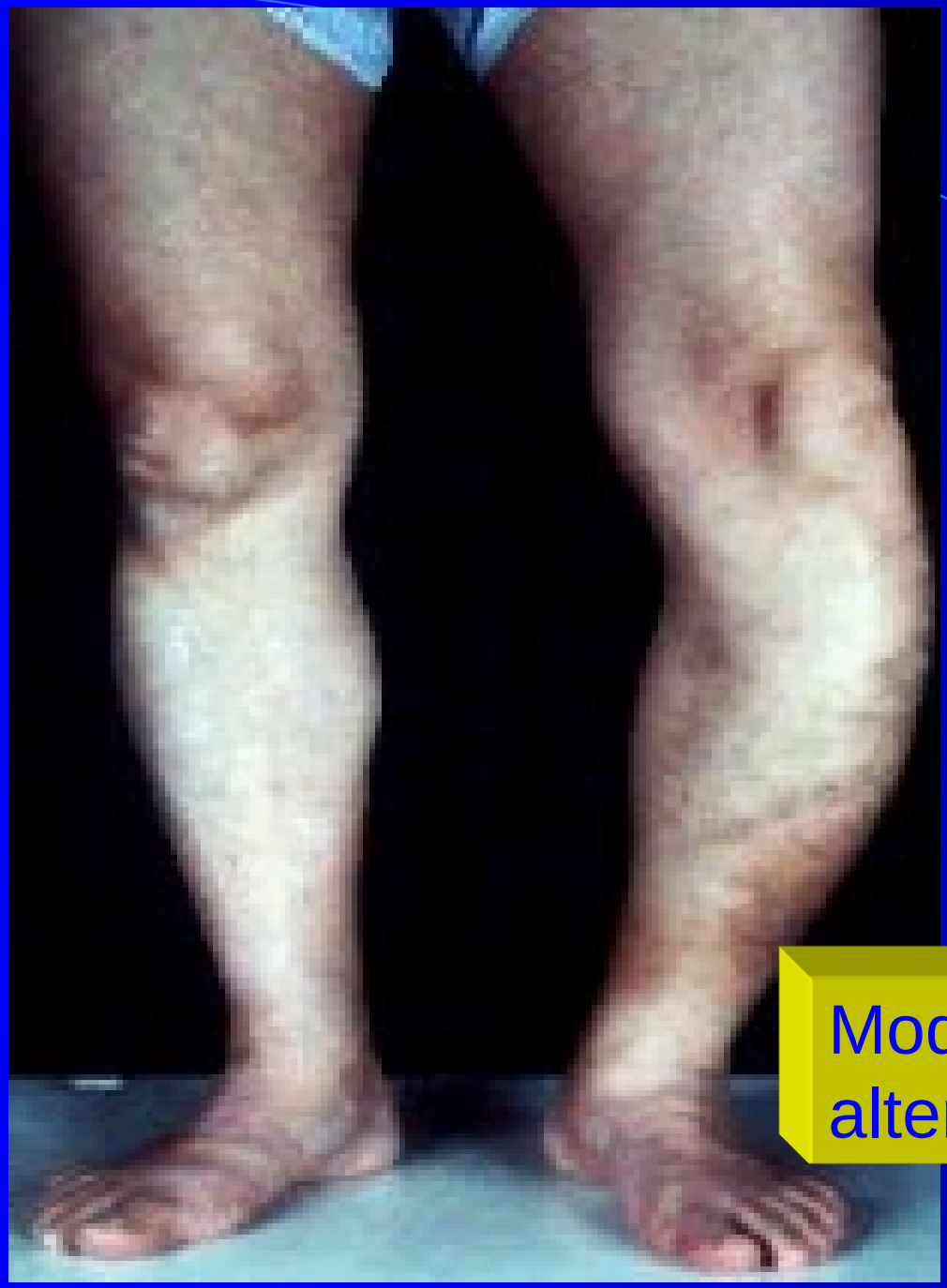
James Paget
1877

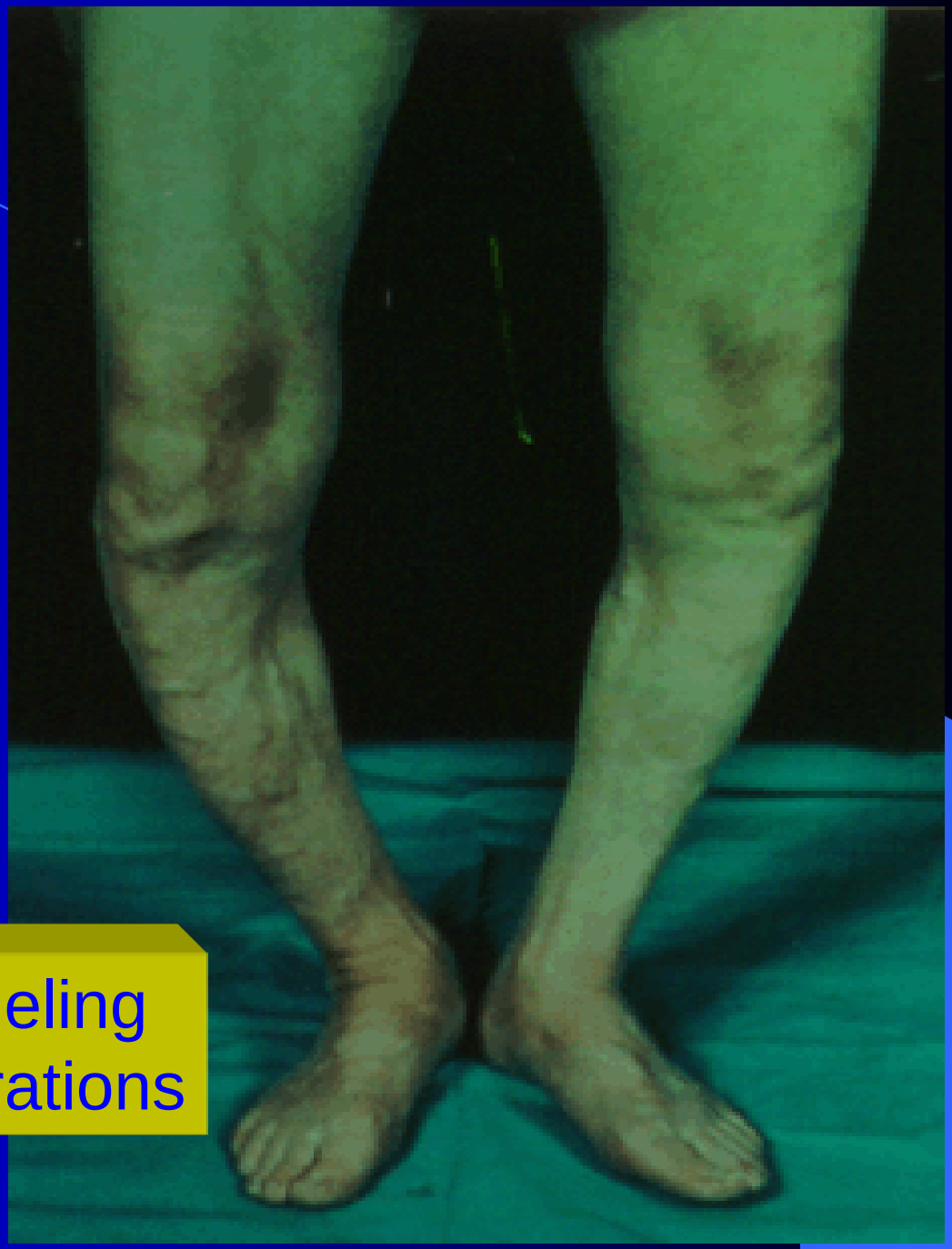


Osteitis deformans

# Paget's disease of bone

- Disorder of bone remodeling in which there is **excessive bone resorption** followed by **excessive bone formation** that results in bone that is architecturally unsound.
- The excess bone lacks the structural stability of normal bone, causing **deformity**, **pain**, and **fracture** in one or more regions of the skeleton

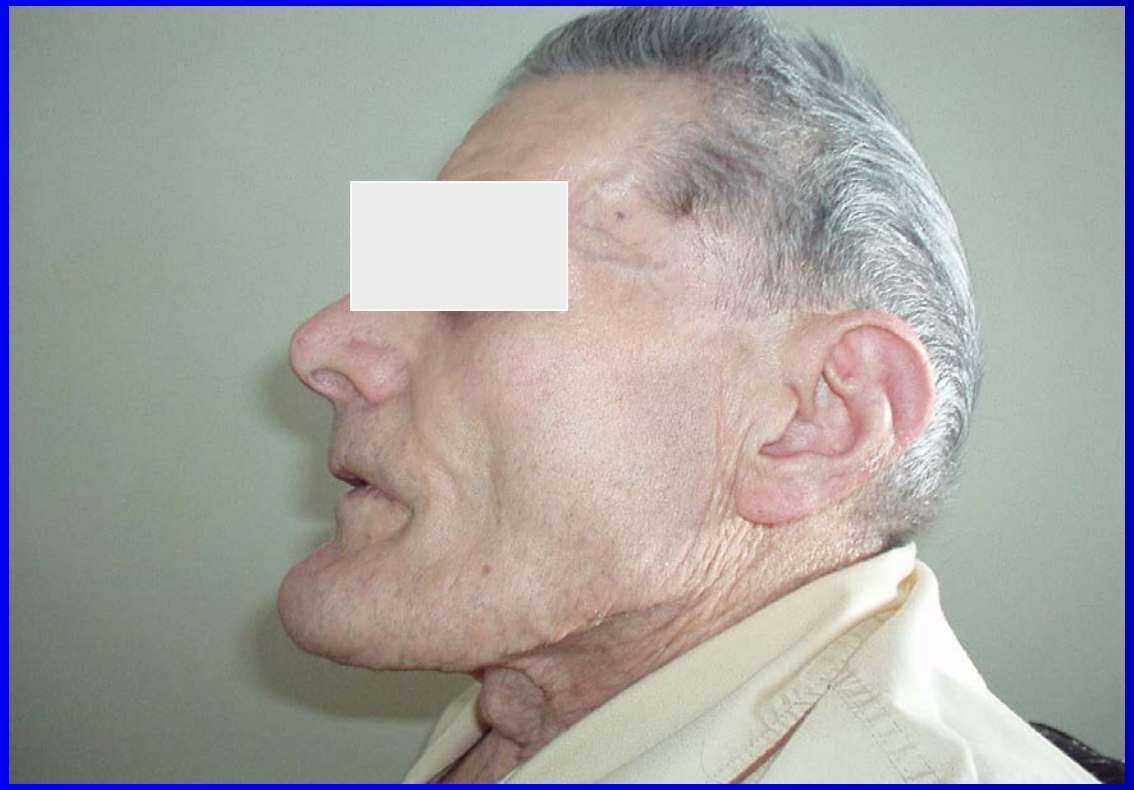


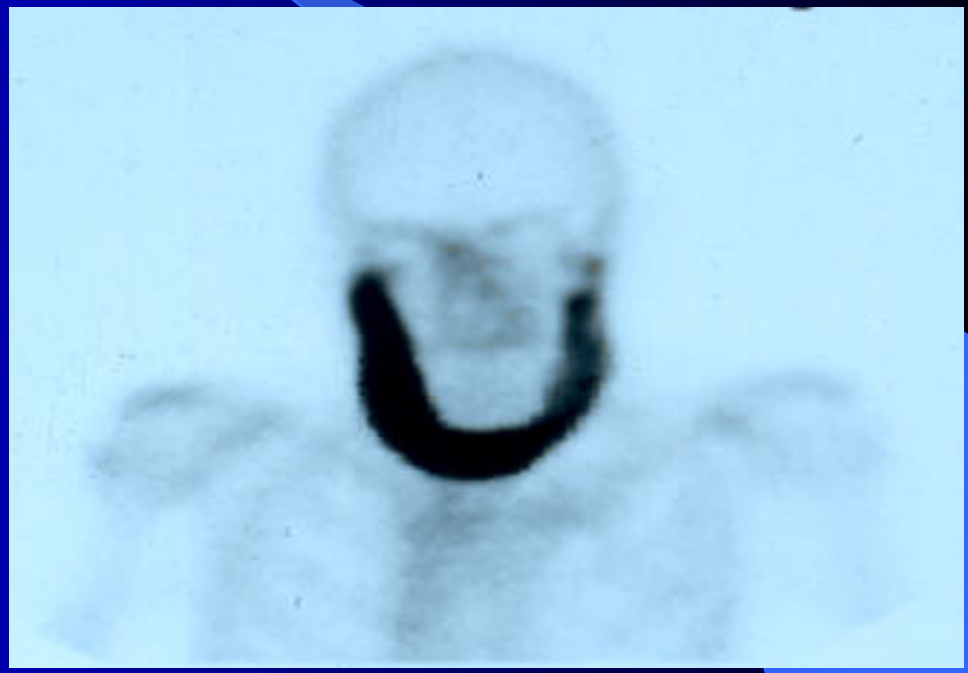


Modeling alterations

# Morbo di Paget

## Localizzazioni cranio-facciali





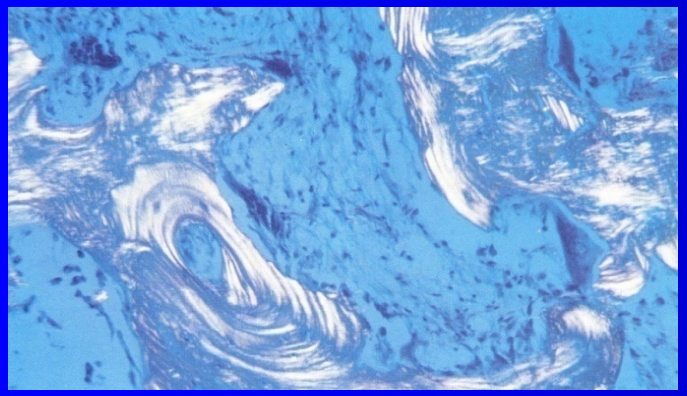
# Paget's disease

- Diagnosis  in the early phase is uncommon
- Often asymptomatic
- Pain attributed to osteoartrhitis
- Serum ALP not correctly evaluated
- In some cases, diagnosis was made after complications are developed

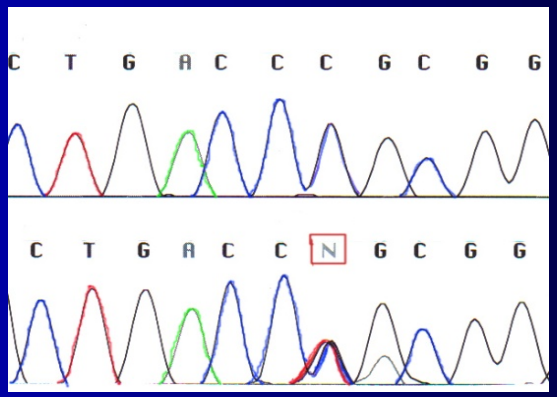
# DIAGNOSIS OF PAGET'S DISEASE OF BONE

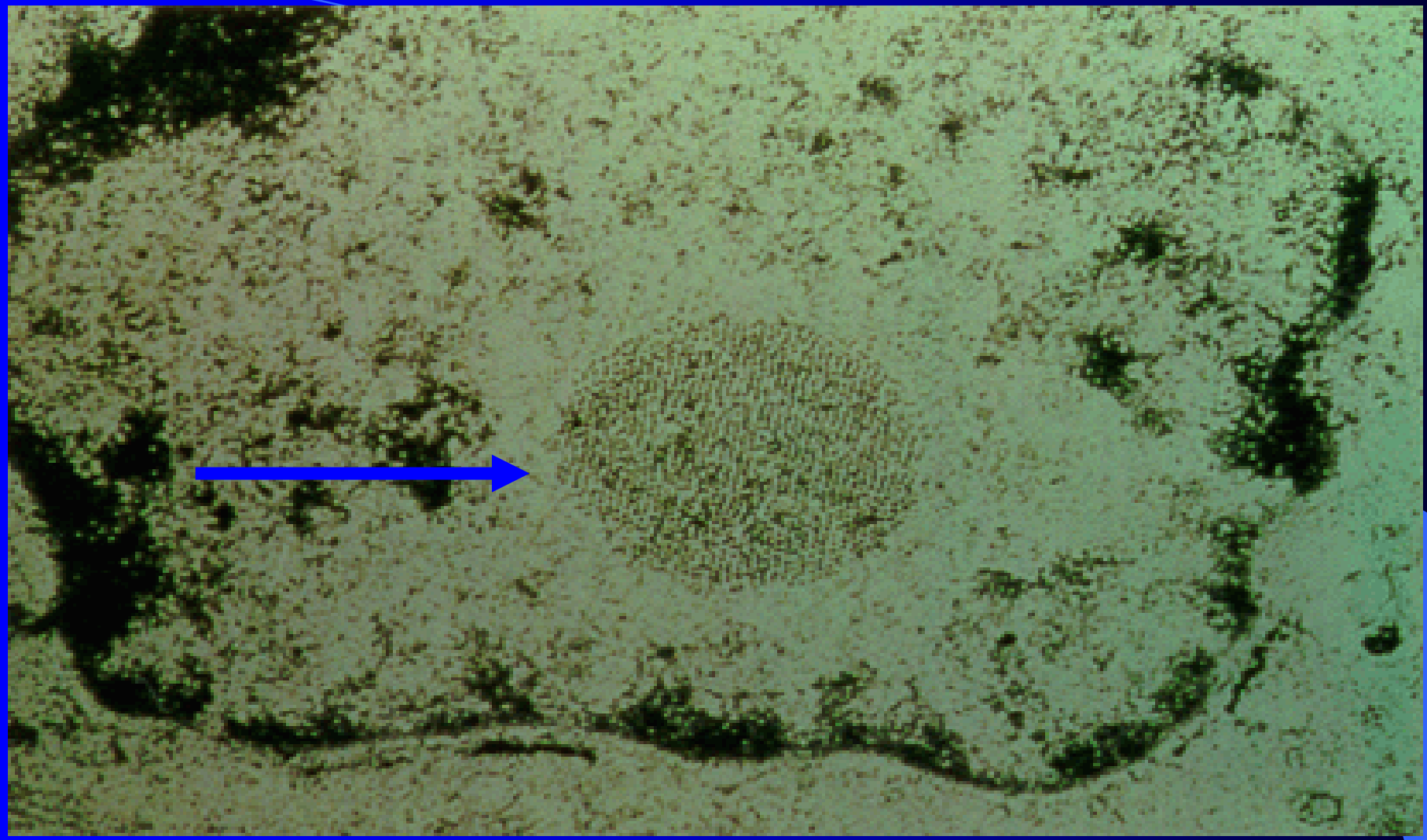
- **Signs and Symptoms** *(bone deformities)*
- **Bone Markers** *(high alkaline phosphatase)*
- **X-rays**
- **Bone Scan** *($^{99m}$Tc-MDP)*
- (CT and/or MRI)

- (Bone Biopsy)



- *SQSTM1* Gene Analysis





The cause of Paget’s disease is still not clear. Research findings suggest that PD may caused by a slow virus infection, possibly related to paramixovirus family

# EZIOLOGIA

- **Familiarità nel 15-30% dei casi.**
- **Nei parenti di primo grado rischio > 7-10 volte.**

**IPOTESI GENETICA**

**la suscettibilità genetica potrebbe non essere condizione sufficiente**

- Penetranza incompleta nelle famiglie con una documentata predisposizione genetica,
- Malattia è altamente localizzata a uno o più particolari distretti ossei piuttosto che interessare l'intero scheletro,
- Cambiamenti nell'incidenza e nella severità nel corso degli ultimi 25 anni,
- Maggiore prevalenza della malattia in aree rurali,

**IPOTESI VIRALE**

# Epidemiologia del Morbo di Paget

- Alta prevalenza:
  - Inghilterra, U.S.A., Australia, Nuova Zelanda, Europa Occidentale
- Bassa prevalenza:
  - Scandinavia, Cina, Giappone, India
  - Uomini/Donne = 1.8/1 – 1/1

# PAGET DISEASE IN ITALY

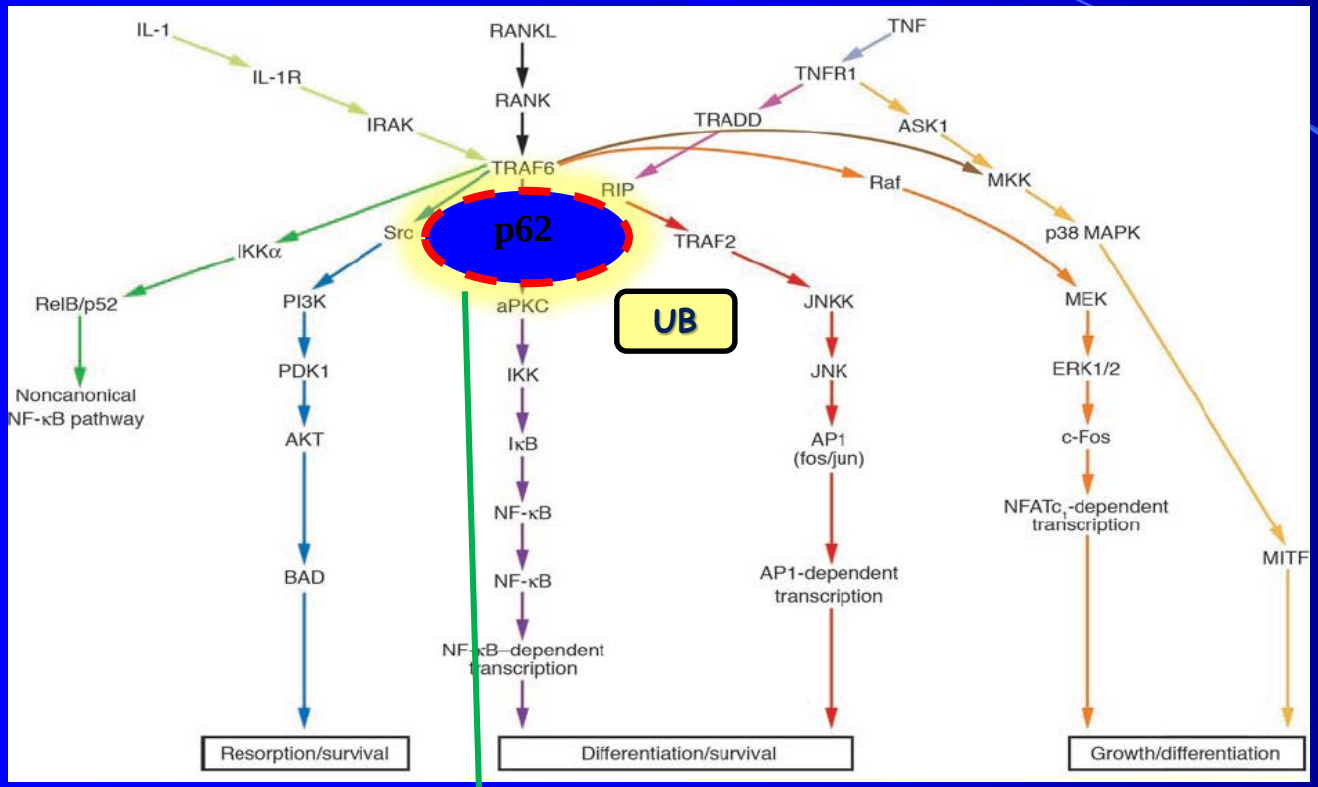
- Prevalence:
  - approximately 1 %
  - higher in males
- Secular Trends:
  - no apparent decrese in prevalence
  - probable decrease in clinical severity
- Familial Aggregation:
  - 15-28 % (SQSTM1 mutation in 5-10%)
  - probably understimated
- Environment:
  - more prevalent in rural vs. urban areas
  - association with animal-related factors
- Regional Clustering:
  - high prevalence areas detected in Toscana, Calabria and Campania
- - increased clinical severity in these areas

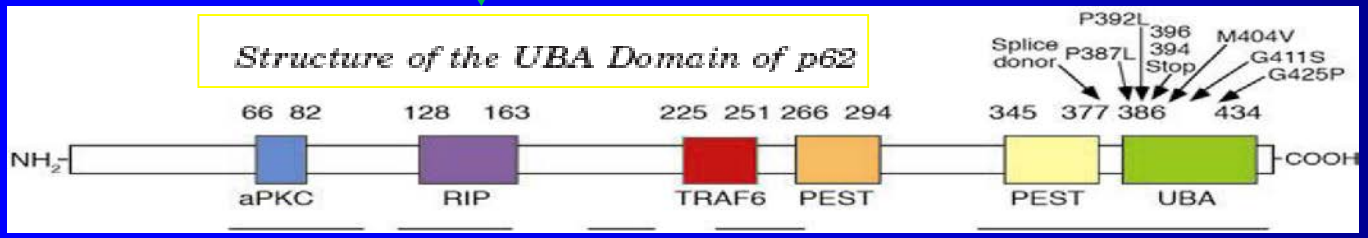
# Loci di suscettibilità per m. di Paget

| *Locus* | Cromosoma | Gene/i | Commenti |
|---|---|---|---|
| Pdb1 | 6p21.3 | Hla | Probabile falso positivo |
| Pdb2 | 18q21.1-22 | Rank | Osteodistrofia di Paget (forme rare e gravi) |
| Pdb3 | 5q35 | SQSTM1* | Il più importante gene legato all'osteodistrofia di Paget |
| Pdb4 | 5q31 | - | |
| Pdb5 | 2q36 | - | |
| Pdb6 | 10p13 | - | |
| Pdb7 | 18q23 | - | Potrebbe essere un falso positivo. Molti membri familiari che mostrano *linkage* con il Pdb7 ora mostrano mutazioni a livello del gene Sqstm1 |

*SQSTM1= Sequestosoma 1

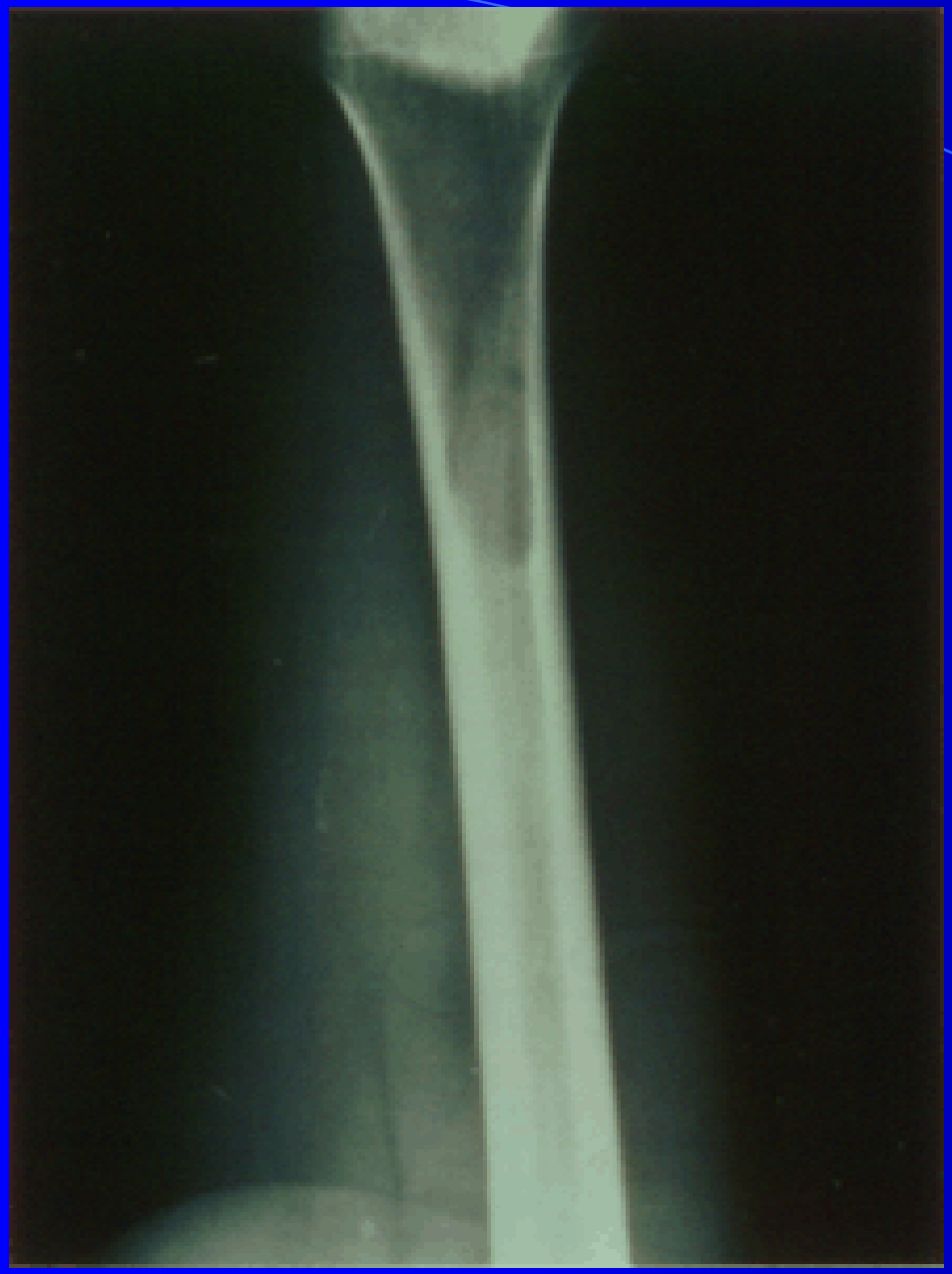
# Effetto delle mutazioni del gene del sequestosoma 1(SQSTM1)

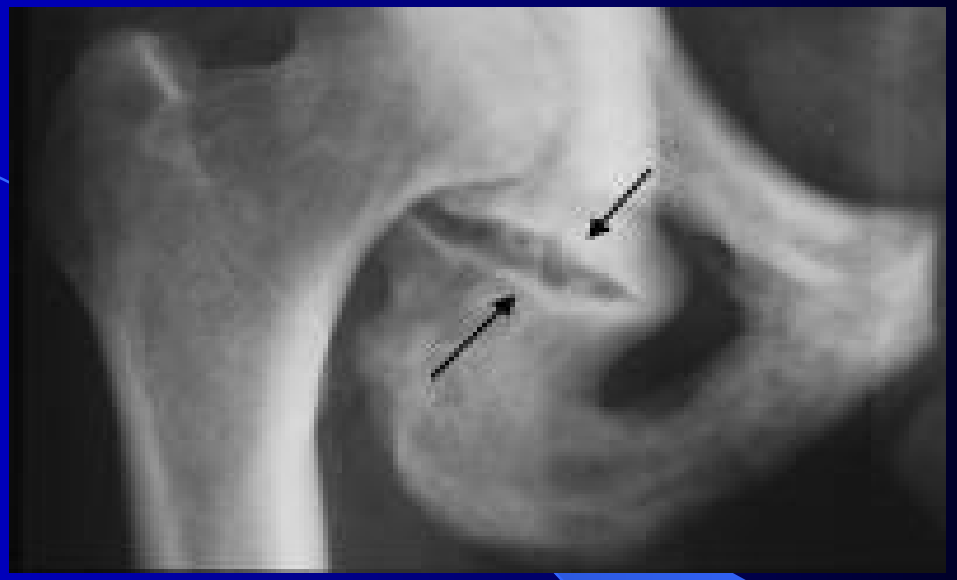


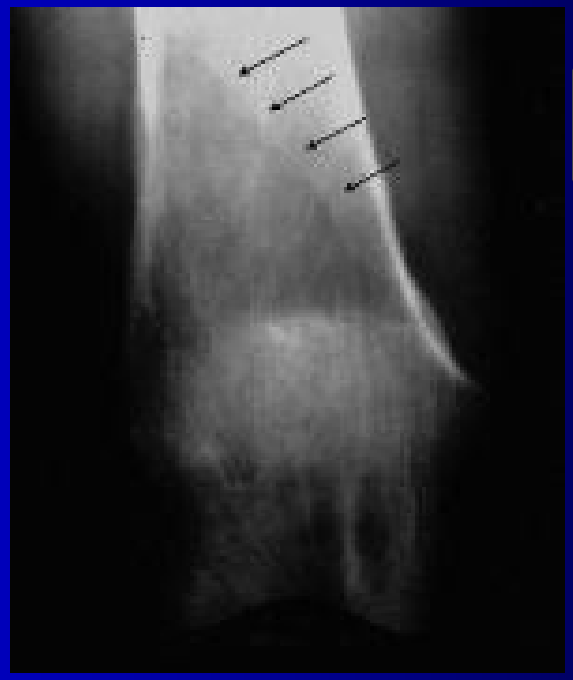




**Sono state descritte 11 differenti mutazioni tutte presenti nel dominio legante l'ubiquitina (UBA domain).**

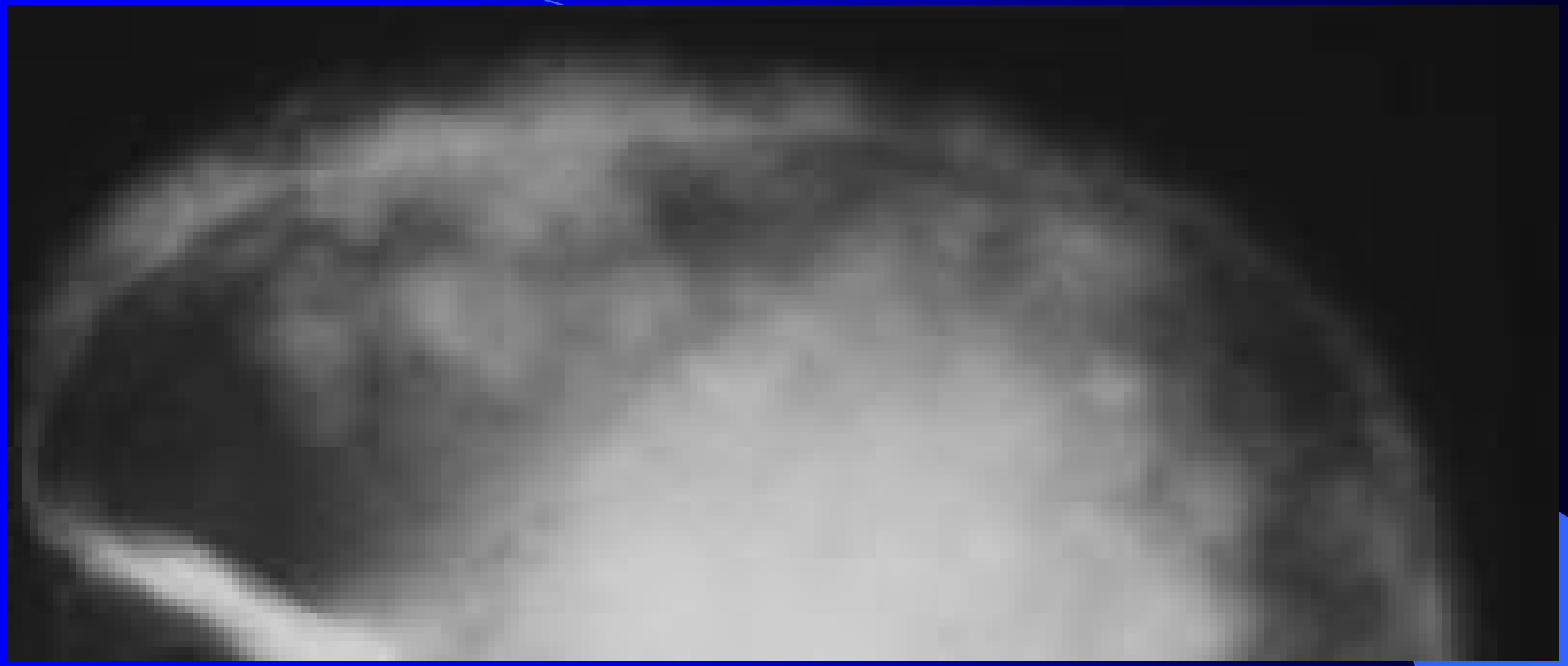
Viene danneggiata la capacità della proteina p62 di veicolare le proteine legate all'ubiquitina all'interno della via NF-kB per essere degradate, mentre resta intatta la funzione "scaffold". Questo potrebbe provocare una **prolungata attivazione della via NF-kB e quindi un'aumentata osteoclasto-genesi.**







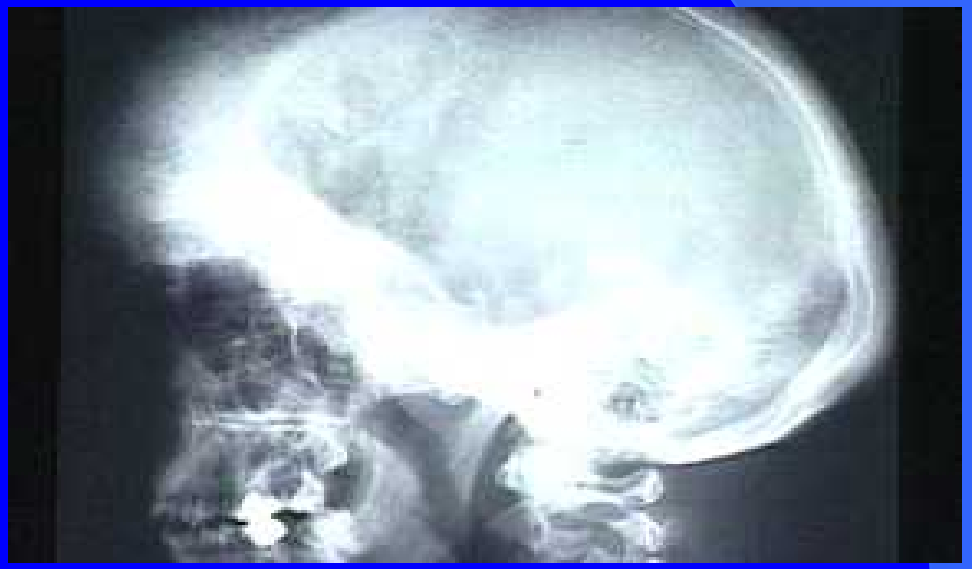
Hot phases



Mixed phase: presence of osteolytic and disorganized osteoblastic activity.
“Cotton wool” aspect of the affected bones

# Malattia ossea di Paget

Fosfatasi alcalina totale elevata



# Complications of Paget's Disease

- Deformity and joint deterioration
- Bone pain
- Hearing loss
- Neurologic impairment
- High output cardiac failure
- Sarcoma

# Complications of Paget's disease

- **Reduced quality of life**
- **Improved mortality (R.R. 1.3 after 5 years of disease)**
- **Importance of early diagnosis and treatment to prevent onset and development of complications**

# Schemi terapeutici dei BP nella MdP

| Bisfosfonato | Dose e Posologia | Indicazione approvata | Note |
|---|---|---|---|
| **Etidronato** | 2.5-20mg/Kg/die<br>max 400mg/die per 6 mesi | SI | Solo in pz. con malattia a modesta attività (ALP< 2 v.n.) |
| Clodronato | os: 800 mg/die/6 mesi<br>os: 1600 mg/die/3 mesi<br>ev: 300 mg/die x 5 gg | NO | |
| Tiludronato | os: 400 mg/die/6 mesi | NO | Non disponibile in Italia |
| Pamidronato | ev: 60- mg ogni 2 settimane x 3 | NO | |
| **Neridronato** | ev: 200 mg, dose in 1 o 2 giorni | SI | |
| Alendronato | os: 40 mg/die/6 mesi | NO | |
| Risedronato | os: 30 mg/die/3 mesi | SI | Non a carico del SSN |
| Ibandronato | ev: 2-6 mg, dose unica | NO | |
| **Zoledronato** | ev: 5 mg, dose unica | SI | |

# Complications of Paget's disease

- **Cardiovascular**
- **Osteoarticular**
- **Neurologic**
- **Neoplastic**
- **Metabolic**

# Neoplastic complication of Paget's disease

- Sarcoma (< 1%)
  - osteosarcoma
  - chondrosarcoma
  - fibrosarcoma
- Giant-cell tumor (rarely malignant)

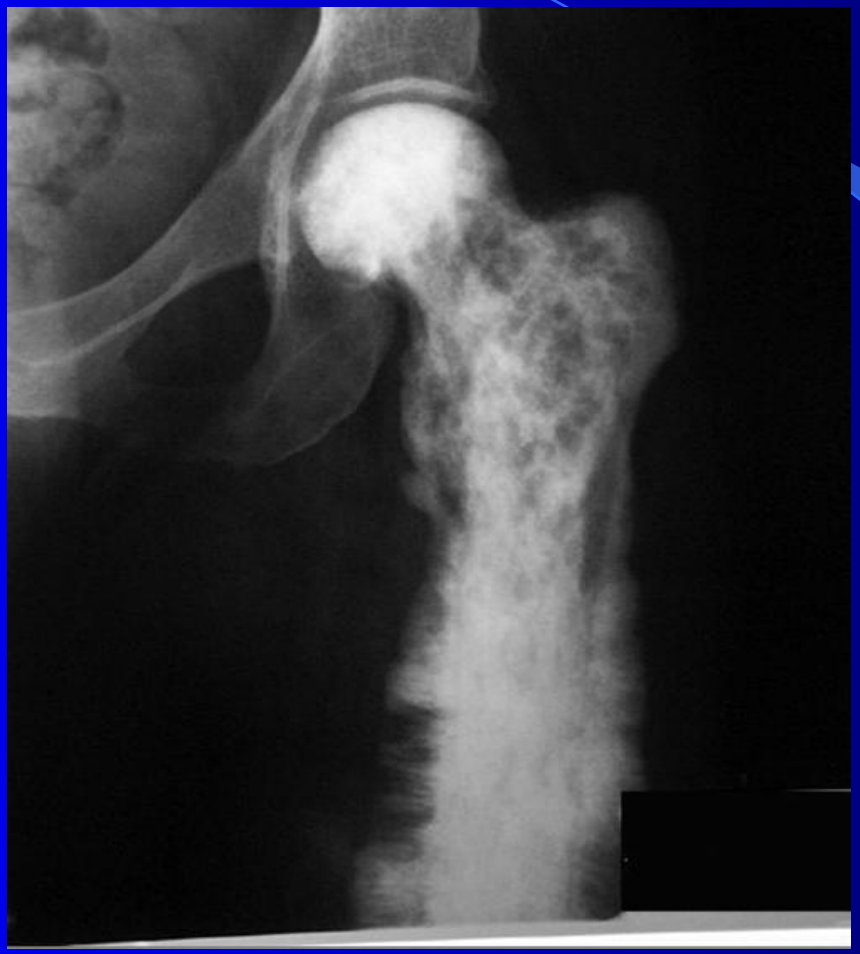
# High-risk sites for malignant transformation

- **Extremities**
- **Pelvis.**

Sarcomatous transformation should be suspected

- sudden onset of pain,
- rapid worsening of previous pain
- increased deformity
- rapid increase in the serum ALP levels

# Osteosarcoma in m. di Paget



JOURNAL OF BONE AND MINERAL RESEARCH
Volume 21, Supplement 2, 2006
Online reference number: doi: 10.1359/JBMR.06S211


# Osteosarcoma in Paget's Disease of Bone

Marc F Hansen,[1] Margaret Seton,[2] and Anand Merchant[1]

**ABSTRACT:** Paget's disease of bone (PDB) is a focal disorder of bone metabolism first described by Sir James Paget in 1876. It is presumed benign in nature and mediated by abnormal osteoclast function. The incidence of osteosarcomas complicating PDB is estimated at <1%. These cancers occur mostly in persons with long-standing, polyostotic disease and affect patients in their seventh decade or when osteosarcoma is remarkably rare in the general population. Epidemiological studies suggest that this late peak of osteosarcomas is absent in regions where Paget's is infrequently reported. Whereas PDB has a predilection for the axial skeleton, skull, femurs, and tibias, pagetic osteosarcoma tend to spare the spine, and are reported more commonly in the pelvis, femur, humerus, and skull. A molecular basis for the association of osteosarcoma with Paget's disease is unclear. These osteosarcomas are osteogenic in origin, consistently arise in sites of pagetic bone, and may present as metachronous, multifocal lesions. On histopathology, the lesions are usually osteoblastic, and the tumor phenotype is sometimes characterized as an exaggerated, chaotic form of the accelerated bone remodeling that characterizes PDB. New insights from the biology of adolescent osteosarcomas, *VCP* and *SQSTM1* mutations now defined in patients with Paget's disease, and emerging evidence that stromal lesions are present in patients with Paget's disease are changing the way we think about the pathogenesis of PDB and the rare complication of pagetic osteosarcomas.
**J Bone Miner Res 2007;21:P58–P63. Online reference number: doi: 10.1359/JBMR.06S211**

**Key words: Paget's disease of bone, osteosarcoma, bone remodeling, genetics**

TABLE 1. ANATOMIC DISTRIBUTION OF PAGETIC AND ADOLESCENT OSTEOSARCOMA[46]

| *Anatomic site* | *Adolescent osteosarcoma* | *Pagetic osteosarcoma* |
|---|---|---|
| Skull | 2% | 8% |
| Mandible | 3% | 2% |
| Humerus | 9% | 19% |
| Femur | 47% | 24% |
| Proximal tibia | 15% | 10% |
| Ilium | 7% | 26% |
| Sacrum | <1% | 3% |
| Ribs | <1% | 3% |
| Vertebrae | <1% | 3% |

**PAGETIC OSTEOSARCOMA REPRESENTS A DIVERSION FROM THE NORMAL COURSE OF PAGET'S DISEASE**

Am J Hum Genet. 2016 Feb 4; 98(2): 275–286.
Published online 2016 Feb 4. doi: 10.1016/j.ajhg.2015.12.016
PMCID: PMC4746367

# *ZNF687* Mutations in Severe Paget Disease of Bone Associated with Giant Cell Tumor

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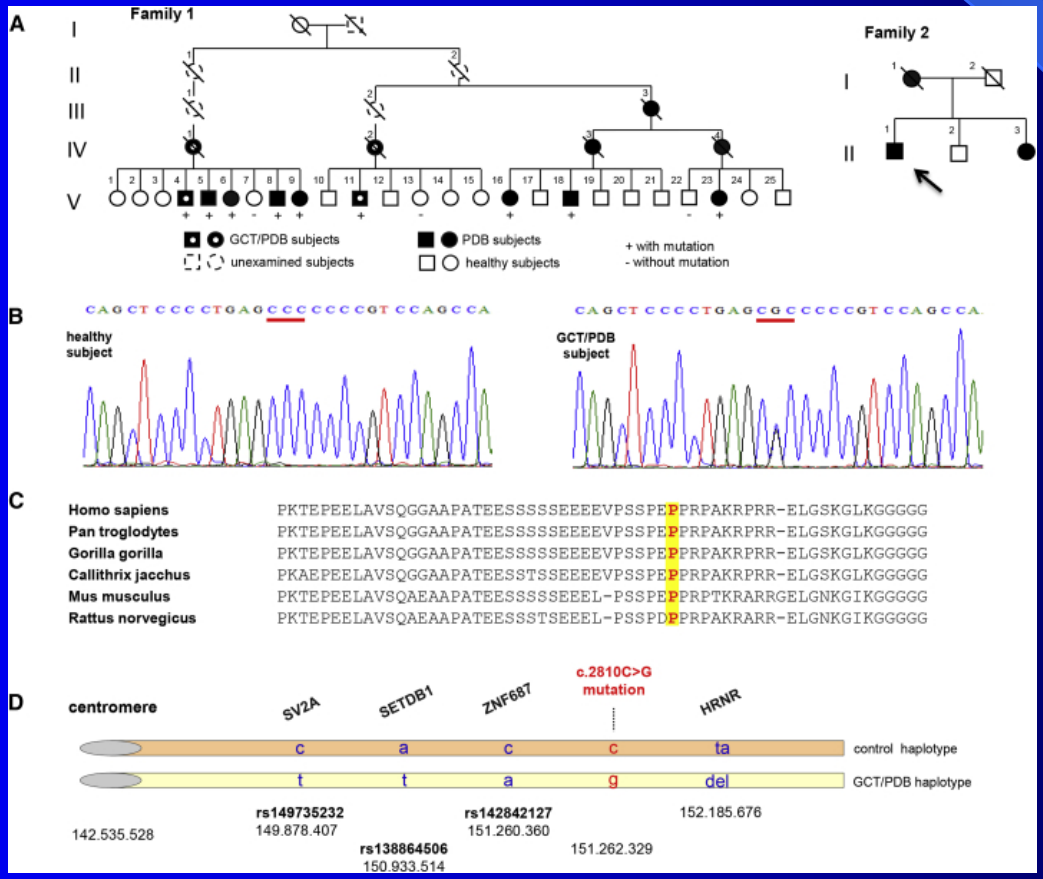

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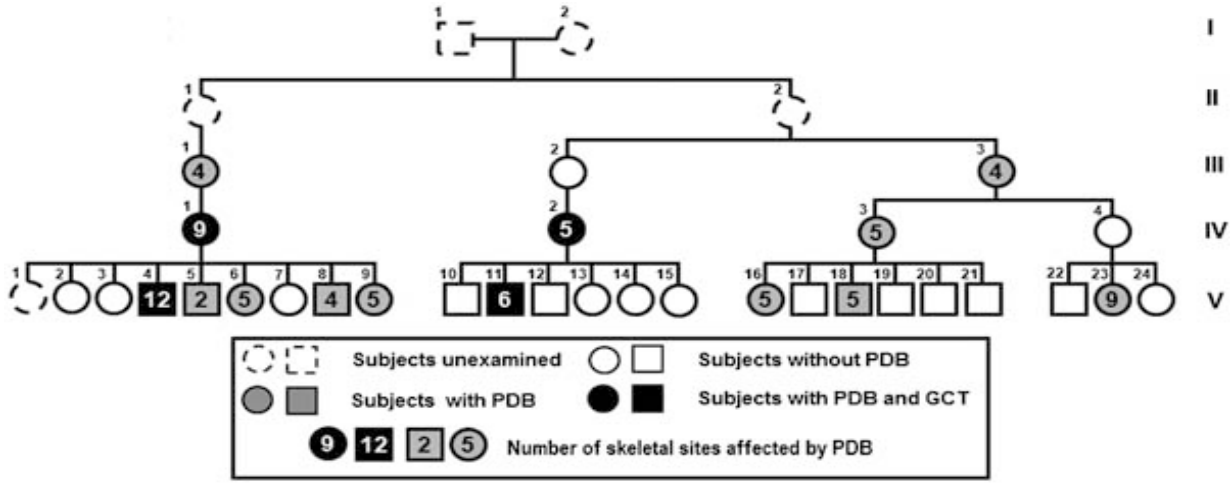


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Volume 28, Issue 2, pages 341-350, 15 JAN 2013 DOI: 10.1002/jbmr.1750
http://onlinelibrary.wiley.com/doi/10.1002/jbmr.1750/full#fig1

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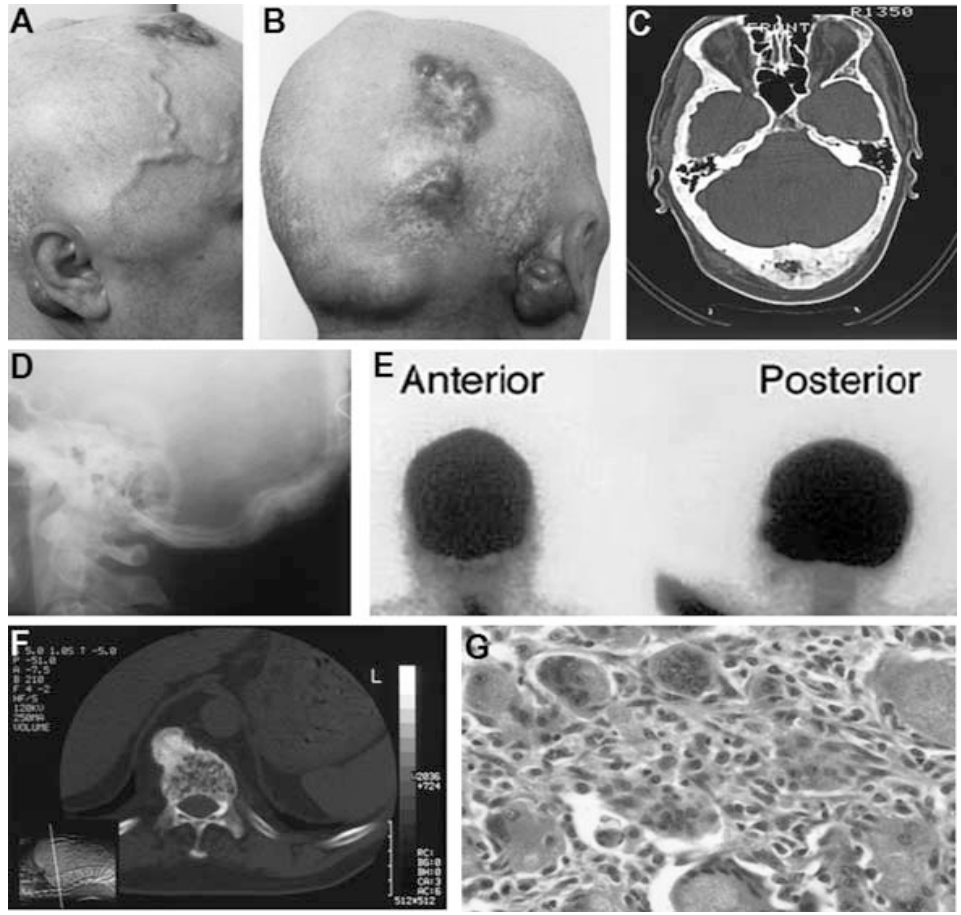


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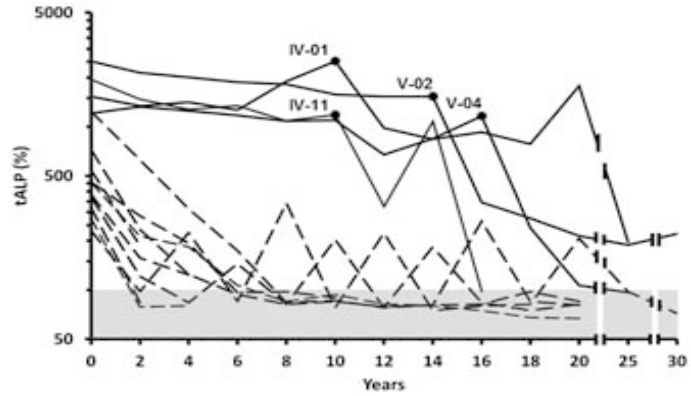


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*Reumatismo, 2007; 59(2):153-168*

LAVORO ORIGINALE

# Linee guida per la diagnosi e la terapia del morbo di Paget

## *Italian guidelines for the diagnosis and treatment of Paget's disease of bone*

S. Adami[1], P. Bartolozzi[2], M.L. Brandi[3], A. Falchetti[3], P. Filipponi[4], S. Gonnelli[5], G. Bianchi[6], G.C. Isaia[7], R. Nuti[5]


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Sono più a rischio (sino al 1-2% dei casi) i pazienti con affezioni maligne e con problemi dentari intercorrenti trattati con dosi di amino-bisfosfonati 3-5 volte superiori a quelle usate per il trattamento del MdP.

Il consenso attuale è di **non attuare misure di restrizione terapeutica in pagetici candidati al trattamento con bisfosfonati**.

È necessario raccomandare una accurata igiene dentaria o la risoluzione completa di eventuali patologie odontoiatriche prima della somministrazione del bisfosfonato.