

**ONJ : COSA C'E' DI NUOVO  
IN EPIDEMIOLOGIA,  
ETIOPATOGENESI,  
STAGING, IMAGING :  
dati della letteratura e reports da congressi**

**Alessandria  
ONJ UPDATE 2011  
19 novembre 2011**

**Vittorio Fusco**                      **SC Oncologia**  
**Az. Ospedaliera di Alessandria**



**Gruppo di Studio ONJ**



**Dipartimento Onco-Ematologico**

## **CENTRO di DOCUMENTAZIONE sulla OSTEONECROSI**

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**Tel 0131- 206753 o 0131- 206155**

# OSTEONECROSI DA DIFOSFONATI

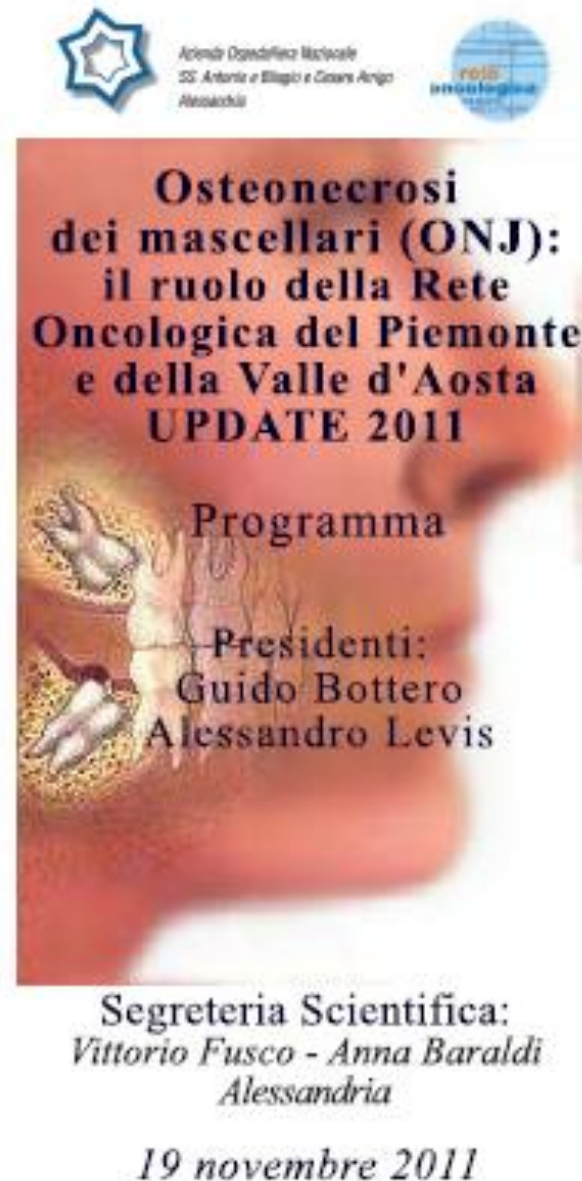
## WORKSHOP ALESSANDRIA

**22 NOVEMBRE 2005**

Coordinato da

dott. Vittorio Fusco  
(SOC Oncologia)

dott.ssa Anna Baraldi  
(SOC Ematologia)



ONJ (osteonecrosis of jaws)

" GRANDE

E' IL DISORDINE

SOTTO IL CIELO... "

# ONJ

- **Definizione** ???
- **Quadro e decorso clinico** ! (ma variabile)
- **Epidemiologia** ??
- **Diagnostica e Staging** ??
- **Fattori di rischio** ??
- **Prevenzione** !!?
- **Trattamento** !??
- **Etiopatogenesi** !??



**FIGURE 1.** Exposed necrotic bone in the mandible in a patient who was taking pamidronate (Aredia). Exposed bone initiated by a tooth removal.



**FIGURE 2.** Exposed necrotic bone in the maxilla in a patient who was taking pamidronate (Aredia). Exposed bone occurred spontaneously.

## Marx (Miami University) J Oral Max Surg Sept 2003

36 cases (24 Pam, 6 Zometa, 6 both)(86% mandib)



**Fig 1.** Bone necrosis of the mandible on a female patient with metastatic breast cancer to bone under treatment with zoledronic acid.



**FIGURE 1.** Exposed necrotic maxillary bone in a patient receiving zoledronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr Jay Neugarten, New Hyde Park, NY.)



nic radiograph of the mandible following extrac-  
teeth in a patient receiving pamidronate. The  
led bone in the region of the nonhealing extrac-

## Migliorati, JCO 2003

5 cases

## Ruggiero et al (Long Island) JOMS May'04

63 cases

# **Etio patogenesi della ONJ : MULTIFATTORIALE ?**

*Bisphosphonates and osteomyelitis of the jaw: a pathogenic puzzle.*

**Bertoldo F, Santini D, Lo Cascio V.**

**Nat Clin Pract Oncol. 2007 Dec;4(12):711-21. Review.**

*Pathophysiology, risk factors and management of bisphosphonate-associated osteonecrosis of the jaw: Is there a diverse relationship of amino- and non-aminobisphosphonates?*

**Diel IJ, et al**

**Crit Rev Oncol Hematol. 2007 Dec;64(3):198-207. Epub 2007 Sep 12. Review.**

*Bisphosphonates and osteonecrosis of the jaw: moving from the bedside to the bench.*

**Allen MR.**

**Cells Tissues Organs. 2009;189(1-4):289-94.**

**Epub 2008 Aug 13. Review.**

*Osteonecrosis of the jaw: who gets it, and why?*

**Reid IR.**

**Bone. 2009 Jan;44(1):4-10.**

**Epub 2008 Oct 7. Review.**

# ONJ : IPOTESI ETIOPATOGENETICHE

**3 fattori  
principali  
ipotizzati  
(sec. Allen)**

**BP-INDUCED  
REMODELING  
SUPPRESSION**

(“low bone  
turnover”)

**DISRUPTED  
ANGIOGENESIS**

(“avascular  
bone necrosis”)

**INFECTION**

(“chronic  
osteomyelitis”)



# Allen MR, Cells Tissues Organs 2009

**The most commonly proposed mechanisms for ONJ ...**

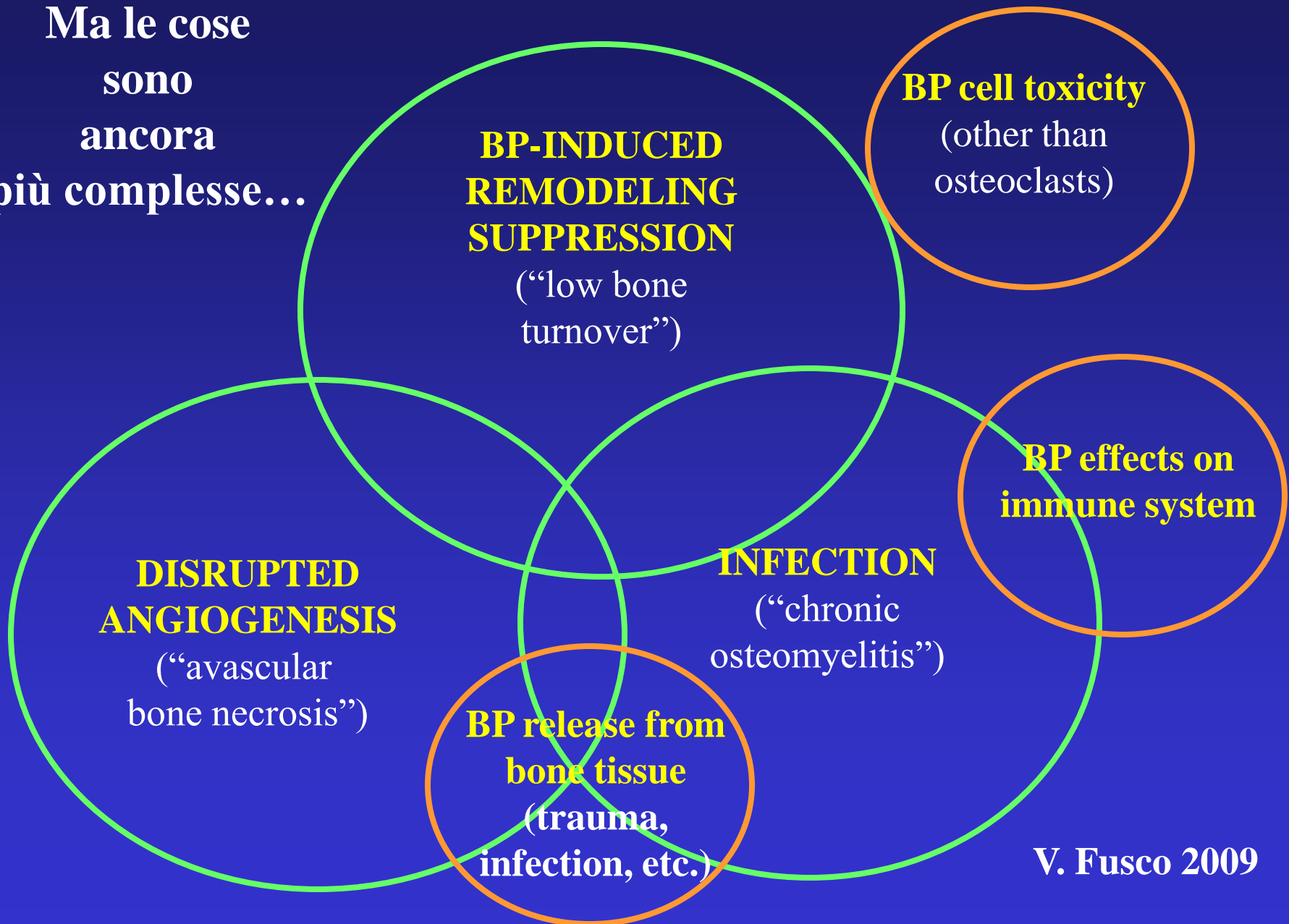
- Remodelling suppression,**
- Disrupted angiogenesis, and**
- Infection**

**Most supportive data for each of these are  
either indirect or nonexistent**

**→ *Necessità di studi ulteriori e di modelli animali !!***

# ONJ : IPOTESI ETIOPATOGENETICHE

Ma le cose  
sono  
ancora  
più complesse...



# ONJ : MODELLI ANIMALI - 1

Autore	Articolo	Rivista
<b>Marino KL et al.</b>	Development of a <u>Rat Model</u> of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ).	J Oral Implantol. 2011
<b>López-Jornet P et al.</b>	<u>Perioperative Antibiotic Regimen</u> in Rats Treated With Pamidronate Plus Dexamethasone and Subjected to Dental Extraction: A Study of the Changes in the Jaws.	JOMS 2011
<b>López-Jornet P et al.</b>	An experimental study of bisphosphonate-induced jaws osteonecrosis in Sprague–Dawley rats.	J Oral Pathol Med 2010
<b>Basi DL et al.</b>	Matrix Metalloproteinase-9 Expression in Alveolar Extraction Sockets of Zoledronic Acid Treated Rats.	JOMS 2011
<b>Kuiper JW et al.</b>	Zoledronate and Pamidronate <u>negatively affect neutrophil effector functions and survival</u> in a murine model.	Br J Pharmacol. 2011
<b>Ali-Erdem M et al.</b>	Extraction socket healing in rats treated with bisphosphonate: Animal model for bisphosphonate related osteonecrosis of jaws in multiple myeloma. patients	Med Oral Patol Oral Cir Bucal 2011
<b>Aghaloo TL et al.</b>	<u>Periodontal disease and bisphosphonates</u> induce osteonecrosis of the jaws in the rat.	J Bone Miner Res 2011
<b>Yamashita J et al.</b>	Effect of zoledronate on <u>oral wound healing</u> in rats.	Clin Cancer Res 2011
<b>Huja SS et al.</b>	Zoledronic acid decreases bone formation without causing osteocyte death in mice.	Arch Oral Biol. 2009

# ONJ : MODELLI ANIMALI - 2

Autore	Articolo	Rivista
Wen D et al.	Anatomic site variability in rat skeletal uptake and desorption of fluorescently labeled bisphosphonate.	Oral Dis. 2011
Kubek DJ et al.	Ovariectomy stimulates and bisphosphonates inhibit intracortical remodeling in the mouse mandible.	Orthod Craniofac Res 2010
Maahs MP et al.	Association between Bisphosphonates and Jaw Osteonecrosis: a study in wistar rats.	Head Neck 2010
Aguirre JI et al	Effects of alendronate on bone healing after tooth extraction in rats.	Oral Diseases 2010
Bi Y et al.	Bisphosphonates cause osteonecrosis of the jaw-like disease in mice.	Am J Pathol. 2010
Allen MR et al.	<u>Compromised osseous healing of dental extraction sites</u> in zoledronic acid-treated dogs.	Osteoporos Int 2010
Biasotto M et al.	A novel animal model to study non spontaneous bisphosphonates osteonecrosis of jaw.	Oral Pathol Med 2010
Hokugo A et al.	Increased prevalence of bisphosphonate-related osteonecrosis of the jaw with <u>vitamin D deficiency</u> in rats.	J Bone Miner Res. 2010
Senel FC et al.	Jaw bone changes in rats after treatment with zoledronate and pamidronate.	OOOE 2010
Bigi MM et al.	Experimental model of distraction osteogenesis in <u>edentulous</u> rats	Braz Oral Res. 2011
Kobayashi Y et al.	Zoledronic acid delays wound healing of the tooth extraction socket, inhibits oral epithelial cell migration, and promotes proliferation and adhesion to hydroxyapatite of oral bacteria, without causing osteonecrosis of the jaw, in mice.	J Bone Miner Metab 2009

## **ONJ : MODELLI ANIMALI - 3**

- **BP: inibizione di guarigione dopo estrazione**
- **BP: tossicità sui tessuti molli**
- **BP: effetto antiangiogenetico**
- **BP: effetto immunodepressivo e favorente infezioni**
- **diversità tra i diversi BP**
- **possibile ruolo del deficit di vitamina D**

# ONJ : studi genetici, endocrinologici, immunologici

Autore	Articolo	Rivista
<b>Such E et al.</b>	CYP2C8 gene polymorphism and bisphosphonate-related osteonecrosis of the jaw in patients with multiple myeloma	Haematologica 2011
<b>Di Martino MT et al.</b>	A peroxisome proliferator-activated receptor gamma (PPARG) polymorphism is associated with zoledronic acid-related osteonecrosis of the jaw in multiple myeloma patients:analysis by DMET microarray profiling.	British Journal of Haematology 2011
<b>Katz J et al.</b>	Bisphosphonate-Induced Osteonecrosis of the Jaw: Long-Term Outcomes.	Supportive Oncology 2009
<b>Arduino PG et al.</b>	Vascular endothelial growth factor genetic polymorphisms and haplotypes in female patients with bisphosphonate-related osteonecrosis of the jaws.	Journal of Oral Pathology & Medicine 2011
<b>Marini F et al.</b>	Pharmacogenetics of bisphosphonate-associated osteonecrosis of the jaw.	Front Biosci 2011
<b>Cornish J et al.</b>	Bone-bound bisphosphonate inhibits growth of adjacent non-bone cells.	JOMS 2011
<b>Ravosa MJ et al.</b>	Bisphosphonate effects on the behaviour of oral epithelial cells and oral fibroblasts.	Arch Oral Biol. 2011
<b>Shikama Y et al.</b>	Pro-IL-1 <sub>α</sub> accumulation in macrophages by alendronate and its prevention by clodronate.	Toxicology Letters 2010
<b>Saia G et al.</b>	Occurrence of Bisphosphonate-Related Osteonecrosis of the Jaw After Surgical Tooth Extraction.	JOMS 2010
<b>Kikuri T et al.</b>	Cell-based immunotherapy with mesenchymal stem cells cures bisphosphonate-related osteonecrosis of the jaw-like disease in mice.	J Bone Miner Res. 2010
<b>Pozzi S et al</b>	The Role of Bisphosphonates in Multiple Myeloma: Mechanisms, Side Effects, and the Future.	The Oncologist 2011
<b>Scheper M et al.</b>	A novel soft-tissue in vitro model for bisphosphonate-associated osteonecrosis.	Fibrogenesis & Tissue Repair 2010

# Journal of Oral Pathology and Medicine 2011

## Vascular endothelial growth factor genetic polymorphisms and haplotypes in female patients with bisphosphonate-related osteonecrosis of the jaws

P. G. Arduino<sup>1</sup>, E. Menegatti<sup>2</sup>, M. Scoletta<sup>3</sup>, C. Battaglio<sup>1</sup>, M. Mozzati<sup>3</sup>, A. Chiecchio<sup>4</sup>, D. Berardi<sup>2</sup>, A. M. Vandone<sup>5</sup>, M. Donadio<sup>5</sup>, S. Gandolfo<sup>6</sup>, C. Scully<sup>7</sup>, R. Broccoletti<sup>1</sup>

<sup>1</sup>Department of Biomedical Sciences and Human Oncology, Oral Medicine Section, University of Turin, Turin, Italy; <sup>2</sup>Department of Medicine and Experimental Oncology, Clinical Pathology Section University of Turin, Italy; <sup>3</sup>Oral Surgery Unit, Dentistry Section, S. Giovanni Hospital of Turin, Department of Clinical Physiopathology, School of Medicine and Dentistry, University of Turin, Turin, Italy; <sup>4</sup>Faculty of Math. Phys. Nat. Sc., University of Turin, Turin, Italy; <sup>5</sup>Medical Oncology 1 – COES, S. Giovanni Hospital of Turin, Turin, Italy; <sup>6</sup>Department of Clinical and Biological Sciences, Oral Medicine and Oral Oncology Section, University of Turin, Orbassano (TO), Italy; <sup>7</sup>University College London, London, UK

**METHODS:** Test subjects were 30 Italian female patients with BRONJ (Group A). Control subjects were 30 female patients with a history of intravenous bisphosphonate use without any evidence of osteonecrosis (Group B) and 125 unrelated healthy volunteers (Group C). Three single-nucleotide polymorphisms were investigated: -634 G>C, occurring in 5' untranslated region (UTR); +936 C>T, occurring in 3' UTR; and -2578 C>A of the promoter region.

**RESULTS:** The frequency of the VEGF CAC (+936/-2578/-634) haplotype was increased in patients with BRONJ, compared with female disease-negative controls [odds ratio (OR) = 2.76, 95% CI = 1.09–4.94,  $P = 0.039$ ; corrected  $P$  value:  $P_c = 0.117$ ], and was also increased compared with female healthy controls (OR = 2.11, 95% CI = 1.14–3.89,  $P = 0.024$ ; corrected  $P$  value:  $P_c = 0.072$ ). The CC homozygotes of -634G>C of VEGF gene and AA homozygotes of -2578C>A have also been significantly correlated in female patients who developed BRONJ compared with healthy controls (OR = 2.04, 95% CI = 1.12–3.70,  $P = 0.008$ ; corrected  $P$  value:  $P_c = 0.024$ ).

# ONJ : ETIOPATOGENESI – reviews e modelli

Autore	Articolo	Rivista
<b>Pazianas M</b>	Osteonecrosis of the Jaw and the Role of Macrophages.	J Natl Cancer Inst 2011
<b>Allen MR</b>	The effects of bisphosphonates on jaw bone remodeling, tissue properties, and extraction healing.	Odontology 2011
<b>Li D</b>	Effects of antiresorptive agents on osteomyelitis: novel insights into the pathogenesis of osteonecrosis of the jaw.	Ann N Y Acad Sci. 2010
<b>Mawardi H et al.</b>	A Role of Oral Bacteria in Bisphosphonate-induced Osteonecrosis of the Jaw.	J Dent Res 2011
<b>Subramanian G et al.</b>	A model for the pathogenesis of bisphosphonate-associated osteonecrosis of the jaw and teriparatide's potential role in its resolution.	OOOOE 2011
<b>Handschel J et al.</b>	Infection, vascularization, remodelling - are stem cells the answers for bonediseases of the jaws?	Head & Face Medicine 2011
<b>Allen MR</b>	The effects of bisphosphonates on jaw bone remodeling, tissue properties, and extraction healing.	Odontology 2011
<b>Otto S</b>	Osteonecrosis or metastases of the jaw or both? Case report and review of the literature.	J Oral Maxillofac Surg. 2010



# DENOSUMAB

- Meccanismo alternativo (RANK-L)
- Somministrazione sottocutanea (non DH)
- Minore tossicità ?
- Maggiore efficacia ?

# DENOSUMAB



Stopeck, JCO 2010

ONJ :  
2% (DEN) vs 1.4% (ZA)

## Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Fizazi, Lancet 2011

ONJ :  
2% (DEN) vs 1% (ZA)



Henry, JCO 2011

ONJ :  
1.1% (DEN) vs 1.3% (ZA)

# ONJ da Bevacizumab da solo (senza BP)

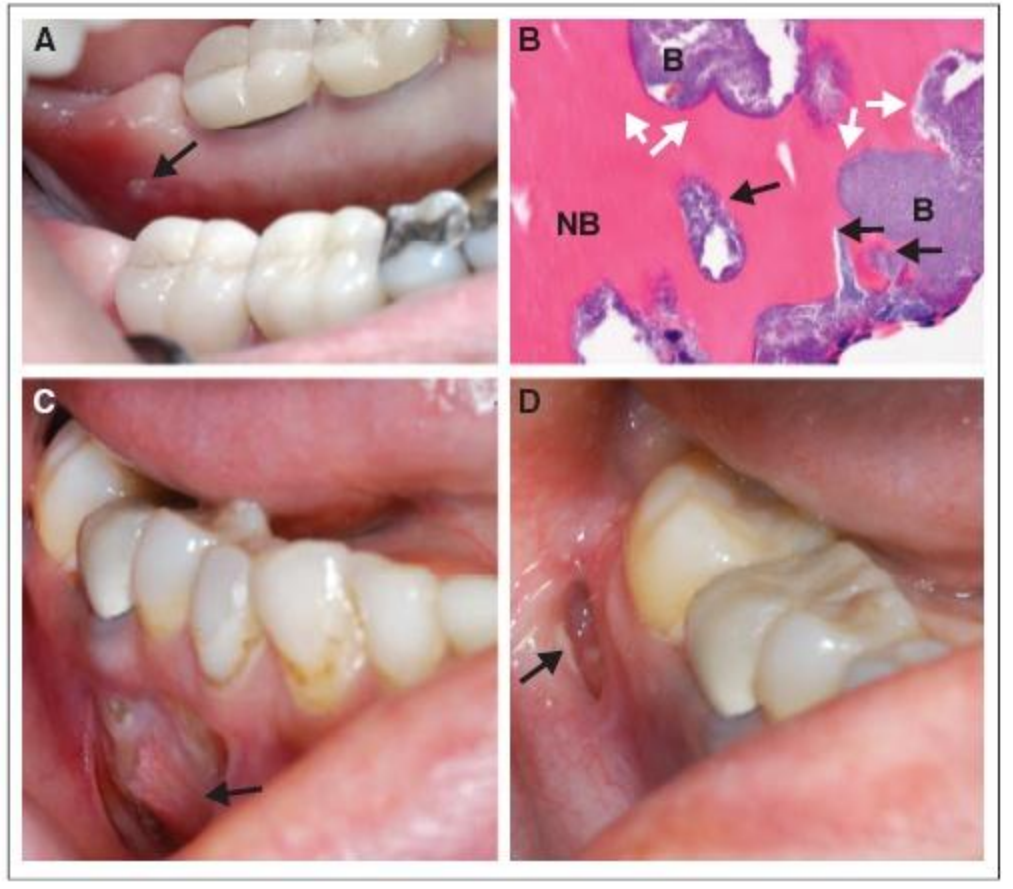
VOLUME 26 • NUMBER 24 • AUGUST 20 2008

JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

Osteonecrosis of the Jaw Related  
to Bevacizumab

**2 casi di ONJ in pazienti  
Trattati con Avastin  
(Bevacizumab)  
e NON con BPs  
  
(1 tumore mammario,  
1 glioblastoma m.)**



## ONJ : ANTIANGIOGENETICI (bevacizumab, sunitinib)

Autore	Articolo	Rivista
Van Poznak C et al.	Osteonecrosis of the jaw and bevacizumab therapy.	Breast Cancer Res Treat 2010
Guarneri V et al.	Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer.	Breast Cancer Res Treat 2010
Fusco V et al.	ONJ in patients with renal cancer treated with bisphosphonates (BPs) and sunitinib or other targeted therapy (TT) agents: a multicenter survey.	ASCO 2011 (abstract 84652)

**Novembre - Dicembre 2010: Alert di EMEA e AIFA per Sunitinib (27 casi in 101.400 pazienti) e Bevacizumab (55 casi in 800.000 pazienti).**

**Survey in 3 unità di Oncologia Medica e 4 unità di Patologia Orale (Alessandria, Pavia, Verona-Padova, Pordenone, Roma, Torino, Palermo): 19 casi di ONJ in pazienti con carcinoma renale.**

**V. Fusco 2011**

## ONJ : quanto è frequente ?

**INCIDENZA : ?**

**PREVALENZA : ?**

**“FREQUENZA” : ?**

**tra  
<0.5%  
e >12%**

**Numeri assoluti : ?**

(epidemiologia; carichi di lavoro...)

**Rischio individuale : ?**

(rischio nel tempo...; costi-benefici)

**NUMERATORE : numero di casi osservati  
(osteonecrosi)**

**DENOMINATORE : popolazione di provenienza  
(esposti)**

**MA**

- con quale patologia di base ?
- per quanto tempo trattata (esposta) ?
- con quali farmaci ? uno o diversi (switch) ?
- per quanto tempo seguita (follow-up) ?
- con quali possibili fattori predisponenti ?

# I nuovi casi di ONJ stanno diminuendo? Diminuiranno?

**Forse SI perché :**

- screening / prevenzione nei pazienti già in trattamento  
(valutazione odontoiatrica; non terapie aggressive)
- attenta valutazione dei pazienti candidati a bifosfonati...
- bifosfonati non prolungati oltre i 24 mesi...
- new switch (es Zoledronico → Pamidronato, Ibandronato, ecc)...

**Forse NO perché :**

- *apparente* “picco” di osservazioni nel 2004-2005 (“*harvesting*”)
- maggiore lunghezza di sopravvivenza (e follow-up)  
(nuovi farmaci, nuove tecnologie, terapie di supporto, ecc.)
- nuovi cofattori? (es thalidomide ed antiangiogenetici)....
- maggiore attenzione e consapevolezza  
(→ diagnosi in fase clinica iniziale)
- possibilità di diagnosi preclinica ? (scintigrafia ossea, RM,...)
- nuovi utilizzi dell’ac. zoledronico (CTIBL, osteoporosi)(adjuv ?)

# ONJ - EPIDEMIOLOGIA : studi su BP orali

Autore	Articolo	Rivista
<b>Malden N et al.</b>	An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence	J Bone Miner Metab 2011
<b>Barrier A et al.</b>	Jaw osteonecrosis induced by oral biphosphonates: 12 cases.	STOMAX-371 2010
<b>Otto S et al.</b>	Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: Not just a sporadic coincidence-a multi-centre study.	Journal of Cranio-Maxillo-Facial Surgery 2010
<b>Lo JC et al.</b>	Oral Health Considerations in Older Women Receiving Oral Bisphosphonate Therapy.	J. Am Geriatr. Soc. 2011
<b>Favia G et al.</b>	Osteonecrosis of the Jaw Correlated to Bisphosphonate Therapy in Non-oncologic Patients: Clinicopathological Features of 24 Patients.	J. Rheumatol. 2009
<b>Manfredi M et al.</b>	Bisphosphonate-related osteonecrosis of the jaws: a case series of 25 patients affected by osteoporosis.	J. Oral Maxillofac. Surg. 2010



# ONJ - EPIDEMIOLOGIA : surveys

**A survey of consultant members of the British Association of Oral and Maxillofacial Surgeons regarding bisphosphonate-induced osteonecrosis of the jaws**

S.N. Rogers<sup>a,b,\*</sup>, J. Hung<sup>a</sup>, A.J. Barber<sup>a</sup>, D. Lowe<sup>a,b</sup>

British Journal of Oral and Maxillofacial Surgery 2009

124/168 (74%) dei consultants avevano visto casi di ONJ

**Bisphosphonate-associated Osteonecrosis of the Jaw in Ontario: A Survey of Oral and Maxillofacial Surgeons**

ALIYA A. KHAN, LORENA P. RIOS, GEORGE K.B. SÁNDOR, NAZIR KHAN, EDMUND PETERS, MOHAMMED O. RAHMAN, CAMERON M.L. CLOKIE, EDWARD DORE, and SACHA DUBOIS

J Rheumatol 2011

2004-2006 : 32 casi (19 ev, 13 orali)

Ontario: 13 milioni di abitanti ....

V. Fusco 2011

# ONJ - EPIDEMIOLOGIA :

## dati di incidenza da studi randomizzati

Autore	Articolo	Rivista
<b>Stopeck AT</b>	Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study.	Journal Of Clinical Oncology 2010
<b>Henry DH</b>	Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma.	Journal Of Clinical Oncology 2011
<b>Fizazi K</b>	Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study.	Lancet 2011
<b>Saad F</b>	Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases.	Annals of Oncology 2011
<b>Fusco V</b>	Osteonecrosis of the Jaw After Zoledronic Acid and Denosumab Treatment.	Journal Of Clinical Oncology 2011
<b>Coleman RE</b>	Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01–04) for women with stage II/III breast cancer.	Breast Cancer Res Treat 2011
<b>Morgan</b>	First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial.	Lancet 2010

# ONJ - EPIDEMIOLOGIA : reports di singoli centri

**Monaco di Baviera : 126 casi** Journal of Cranio-Maxillo-Facial Surgery 2011

Bisphosphonate-related osteonecrosis of the jaws – Characteristics, risk factors, clinical features, localization and impact on oncological treatment<sup>☆</sup>

Sven Otto <sup>a,\*</sup>, Christian Schreyer <sup>a</sup>, Sigurd Hafner <sup>a</sup>, Gerson Mast <sup>a</sup>, Michael Ehrenfeld <sup>a</sup>,  
Stephen Stürzenbaum <sup>b</sup>, Christoph Pautke <sup>a</sup>

**Parma : 151 casi**  
Journal of Oral  
Pathology & Medicine  
2011

**Bisphosphonates-related osteonecrosis of the jaws: a concise review of the literature and a report of a single-centre experience with 151 patients**

**Treatment of bisphosphonate-related osteonecrosis of the jaws: presentation of a protocol and an observational longitudinal study of an Italian series of cases**

Sebastiano Ferlito <sup>a</sup>, Sergio Puzzo <sup>a,\*</sup>, Filippo Palermo <sup>b</sup>, Placido Verzì <sup>a</sup>

British Journal of Oral and Maxillofacial Surgery 2011

**Catania : 94 casi**  
(solo stadi I-II)

V. Fusco 2011

# ONJ - EPIDEMIOLOGIA : mieloma

**Gimsing**

Lancet Oncol 2010

2/156 (1.2% )

Vs 8/157 (5.1%)

**Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial**

*Peter Gimsing, Kristina Carlson, Ingemar Turesson, Peter Fayers, Anders Waage, Annette Vangsted, Anne Mylin, Christian Gluud, Gunnar Juliusson, Henrik Gregersen, Henrik Hjorth-Hansen, Ingerid Nesthus, Inger Marie S Dahl, Jan Westin, Johan Lannig Nielsen, Lene Meldgaard Knudsen, Lucia Ahlberg, Martin Hjorth, Niels Abildgaard, Niels Frost Andersen, Olie Linder, Finn Wisloff*

**Walter**

Head Face Medicine 2010

Retr : 4/81 (4.9%)

Pr : 16/78 (20%)

**Prevalence of bisphosphonate associated osteonecrosis of the jaws in multiple myeloma patients**

*Head & Face Medicine 2010, 6:11 doi:10.1186/1746-160X-6-11*

**Morgan**

Lancet 2010

**First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial**

*Gareth J Morgan, Faith E Davies, Walter M Gregory, Kim Cocks, Sue E Bell, Alex J Szubert, Nuria Navarro-Coy, Mark T Drayson, Roger G Owen, Sylvia Feyler, A John Ashcroft, Fiona Ross, Jennifer Byrne, Huw Roddie, Claudius Rudin, Gordon Cook, Graham H Jackson, J Anthony Child, on behalf of the National Cancer Research Institute Haematological Oncology Clinical Study Group*

**ZOL 4% (35/983)**

**vs CLO <1% (3/979)**

**V. Fusco 2011**

# Bisphosphonate-Related Osteonecrosis of the Jaw: Tip of the Iceberg

*Robert John W. Knight, MB BCh, MRCS,\*† Chaithan Reddy, BDS, MBBS, MS,\*†  
Michael A. Rtshiladze, MA, MBBS, BSc,\*† Gregory Lvoff, BDS, MBBS, FRACS (ENT), FRACDS,†‡  
David Sherring, BDS, MBBS, FRACS (Maxfax), FRACDS,†  
and Damian Marucci, MBBS, FRACS (Plast), PhD\*†*

*The Journal of Craniofacial Surgery* • Volume 21, Number 1, January 2010

# **ONJ - EPIDEMIOLOGIA : position papers e guidelines -1**

**J Bone Miner  
Metab 2010**

**Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons**

Toshiyuki Yoneda • Hiroshi Hagino • Toshitsugu Sugimoto • Hiroaki Ohta •  
Shunji Takahashi • Satoshi Soen • Akira Taguchi • Satoru Toyosawa •  
Toshihiko Nagata • Masahiro Urade

**Bisphosphonate osteonecrosis of the jaw—a literature review of UK policies versus international policies on bisphosphonates, risk factors and prevention**

Vinod Patel<sup>a</sup>, Niall M.H. McLeod<sup>b,\*</sup>, Simon N. Rogers<sup>c</sup>, Peter A. Brennan<sup>b</sup>

**British Journal  
of Oral and  
Maxillofacial  
Surgery 2010**

**MASCC-ISOO  
Support Care Cancer  
2010**

**Systematic reviews of oral complications from cancer therapies, Oral Care Study Group, MASCC/ISOO: methodology and quality of the literature**

Michael T. Brennan • Linda S. Elting •  
Fred K. L. Spijkervet



# ONJ - EPIDEMIOLOGIA : position papers e guidelines -2

**Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: Executive summary of recommendations from the American Dental Association Council on Scientific Affairs.**

Hellstein JW, Adler RA, Edwards B, Jacobsen PL, Kalmar JR, Koka S, Migliorati CA, Ristic H; for the American Dental Association Council on Scientific Affairs Expert Panel on Antiresorptive Agents.

**J Am Dent Assoc. 2011**

## **Guidelines for supportive care in multiple myeloma 2011**

John A. Snowden,<sup>1</sup> Sam H. Ahmedzai,<sup>2</sup> John Ashcroft,<sup>3</sup> Shirley D'Sa,<sup>4</sup> Timothy Littlewood,<sup>5</sup> Eric Low,<sup>6</sup> Helen Lucraft,<sup>7</sup> Rhona Maclean,<sup>1</sup> Sylvia Feyler,<sup>8</sup> Guy Pratt<sup>9</sup> and Jennifer M. Bird<sup>10</sup> On behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and UK Myeloma Forum

**British Journal of Haematology 2011**

## **American Society of Clinical Oncology Executive Summary of the Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer**

*Catherine H. Van Poznak, Sarah Temin, Gary C. Yee, Nora A. Janjan, William E. Barlow, J. Sybil Biermann, Linda D. Bosserman, Cindy Geoghegan, Bruce E. Hillner, Richard L. Theriault, Dan S. Zuckerman, and Jamie H. Von Roenn*

**Journal of Clinical Oncology 2011**

**V. Fusco 2011**

# Tecniche di IMAGING

**-Rx OPT**      **Poco sensibile e specifica, ma ineludibile (1° livello)**

**-Scintigrafia ossea**      **Molto sensibile, poco specifica ?**

(Chiandussi 2006, Zanglis 2008)

**-TC**      **Quadri nosografici variabili**

(Bianchi 2007, Raje 2008, Maksimovic 2008, ecc.)

**-“Cone beam CT”**      **??? (in USA)**

(Kumar 2007)

**-Risonanza Magnetica**

**Utile per programmare terapia chirurgica maggiore ?**

(Bedogni 2007, Bisdas 2008, Wutzl 2006, ecc.)

**Capace di individuare lesioni pre-cliniche ?**

(Garcia-Ferrer 2008)

**-Med.Nucleare (sestamibi; FDG-PET; NaF-PET, ecc) ??**

(Catalano 2007, Raje 2008, Ho 2008)



# ONJ - IMAGING

Autore	Articolo	Rivista
<b>Torres S et al.</b>	Fractal dimension evaluation of cone beam computed tomography in patients with bisphosphonate-associated osteonecrosis.	Dentomaxillofac Radiol. 2011
<b>Fatterpekar GM et al.</b>	Bone-within-bone appearance: a red flag for biphosphonate-associated osteonecrosis of the jaw.	J Comput Assist Tomogr. 2011
<b>Van den Wyngaert T et al.</b>	Prognostic Value of Bone Scintigraphy in Cancer Patients With Osteonecrosis of the Jaw.	Clin Nucl Med 2011
<b>Morris PG et al.</b>	Bone Scans, Bisphosphonates, and a Lack of Acute Changes Within the Mandible.	JOMS 2010
<b>Hutchinson M et al.</b>	Radiographic Findings in Bisphosphonate- Treated Patients With Stage 0 Disease in the Absence of Bone Exposure.	JOMS 2010
<b>Yamazaki Y et al.</b>	Use of FDG PET to Evaluate Hyperbaric Oxygen Therapy for Bisphosphonate-Related Osteonecrosis of the Jaw.	Clinical Nuclear Medicine 2010
<b>Vassiliou V</b>	Osteonecrosis of the jaws: clinicopathologic and radiologic characteristics, preventive and therapeutic strategies.	Strahlenther Onkol. 2010
<b>Treister NS et al.</b>	Use of cone-beam computerized tomography for evaluation of bisphosphonate-associated osteonecrosis of the jaws.	Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010

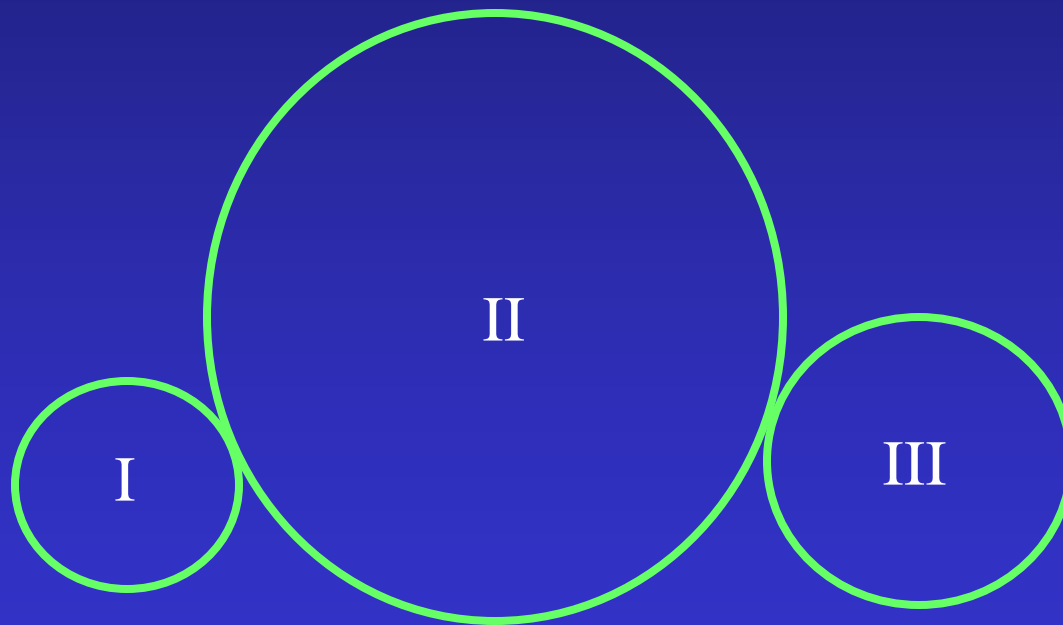
# Staging and Treatment Strategies (See Table 1)

## Staging

In order to direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either IV or oral bisphosphonates, the AAOMS proposes use of the following staging categories:

1. Patients at risk: No apparent exposed/necrotic bone in patients who have been treated with either IV or oral bisphosphonates.
2. Patients with BRONJ
  - Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.
  - Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection.
  - Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border

**Sarà sufficiente questo tipo di stadiazione ?**



# AAOMS 2009 : compare lo Stadio 0 ...

Alterazioni ossee senza (ancora)  
osso esposto

o allargamento della definizione ?

Colella G, Campisi G, Fusco V

AAOMS position paper : BP-related ONJ 2009 update:  
The need to refine the BRONJ definition

JOMS (J Oral Max Surg) may 2009

V. Fusco

# SICMF-SIPMO panel : POSITION PAPER BRONJ

## Stadiazione BRONJ- AAOMS 2009

### Criticità analizzate dalla Commissione:

- Criterio clinico esclusivo è insufficiente  
*(Segni radiologici -TC- di malattia precedono l'esposizione ossea)*
- Stadio 0 non è necessariamente uno stadio precoce  
*(pazienti in stadio 0 presentano quadri radiologici sovrapponibili a quelli di pazienti con esposizione ossea)*
- Continuo passaggio di stadio 1-2 di pazienti con BRONJ, come conseguenza delle cicliche riacutizzazioni del **processo infettivo** e del **dolore** ad esso associato.

# Conclusioni

!!!! ???? ?

# INTERDISCIPLINARIETA' !!!

Oncologia

25 centri

Ematologia

15 centri



Chir. Maxillo Facciale

Odontoiatria

19 centri

**Se vuoi arrivare presto,  
corri da solo.**

**Se vuoi arrivare lontano,  
corri assieme agli altri.**

**Proverbio africano**