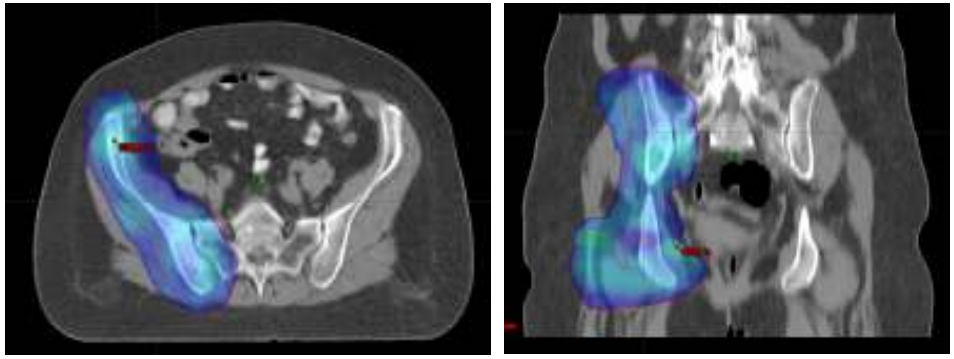
Associazione Italiana
di Radioterapia Oncologica



METASTASI OSSEE: ASSOCIAZIONE RADIOTERAPIA E FARMACI

Sara Ramella
Radioterapia Oncologica
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UNIVERSITA' CAMPUS BIO-MEDICO DI ROMA

Università Campus Bio-Medico di Roma - Via Álvaro del Portillo, 21 - 00128 Roma – Italia
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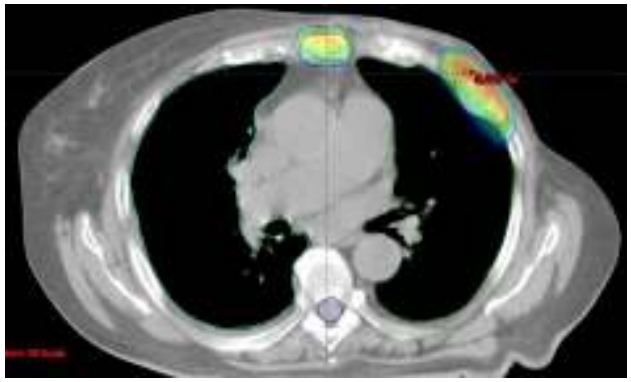
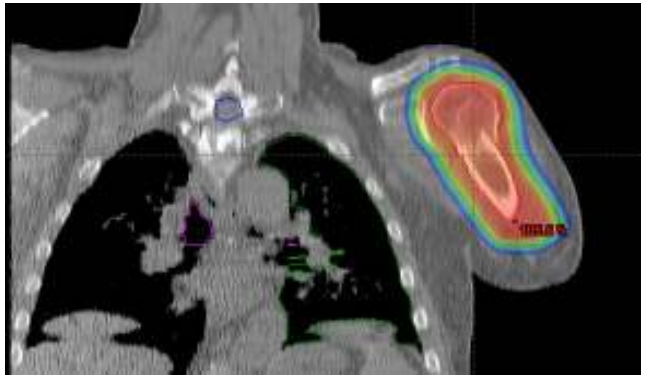
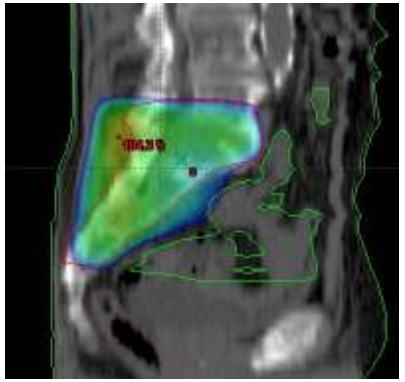


Which is the PRECISE MECHANISM OF ACTION by which RADIATION results metastatic PAIN RELIEF ?



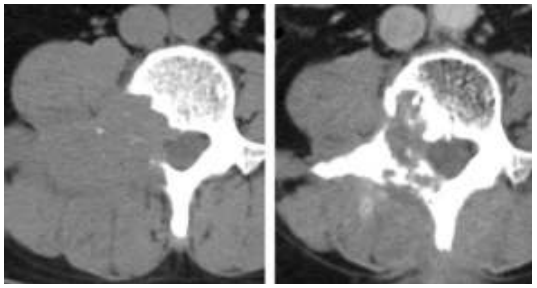


Which is the PRECISE MECHANISM OF ACTION by which Radiation results metastatic PAIN RELIEF ?

SHRINKAGE OF TUMOR BULK:

Removal of tumor from the bone enables osteoblastic repair and restored integrity of the damaged bone …..

Which is the PRECISE MECHANISM OF ACTION by which Radiation results metastatic PAIN RELIEF ?



Certain features suggest that tumor shrinkage itself *IS UNLIKELY* to account for the pain relief, such as:

- The early period of pain relief seen
- Absence of dose-response relationship
- Absence of a clear relationship to the primary tumor type

Hoskin PJ, Cancer Treat reviews 2003; 29:321-327

Which is the PRECISE MECHANISM OF ACTION by which Radiation results metastatic PAIN RELIEF ?

Meanwhile evidences from literature….

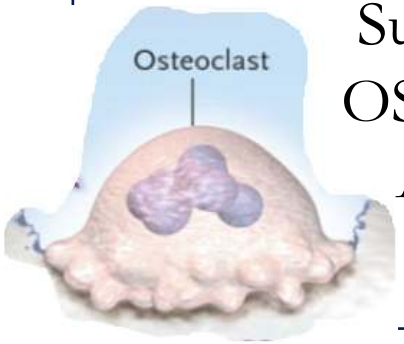
↓ URINARY MARKERS OF BONE DEGRADATION

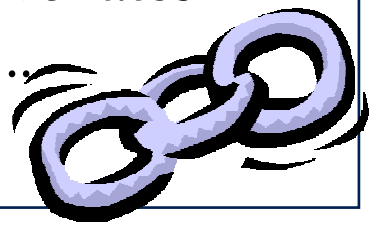
RADIOTHERAPY RESPONSE ↑

‖

Suppression of OSTEOCLAST ACTIVITY

Which provides an important link to bisphosphonates activity…..





Hoskin PJ, Lancet 2000; 355:1429-1429

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

CYTOTOXIC EFFECTS

- *IN VITRO* and *IN VIVO* EVIDENCES
- MECHANISMS OF INTERACTION
- CLINICAL EXPERIENCES

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

CYTOTOXIC EFFECTS

- *IN VITRO and IN VIVO EVIDENCES*

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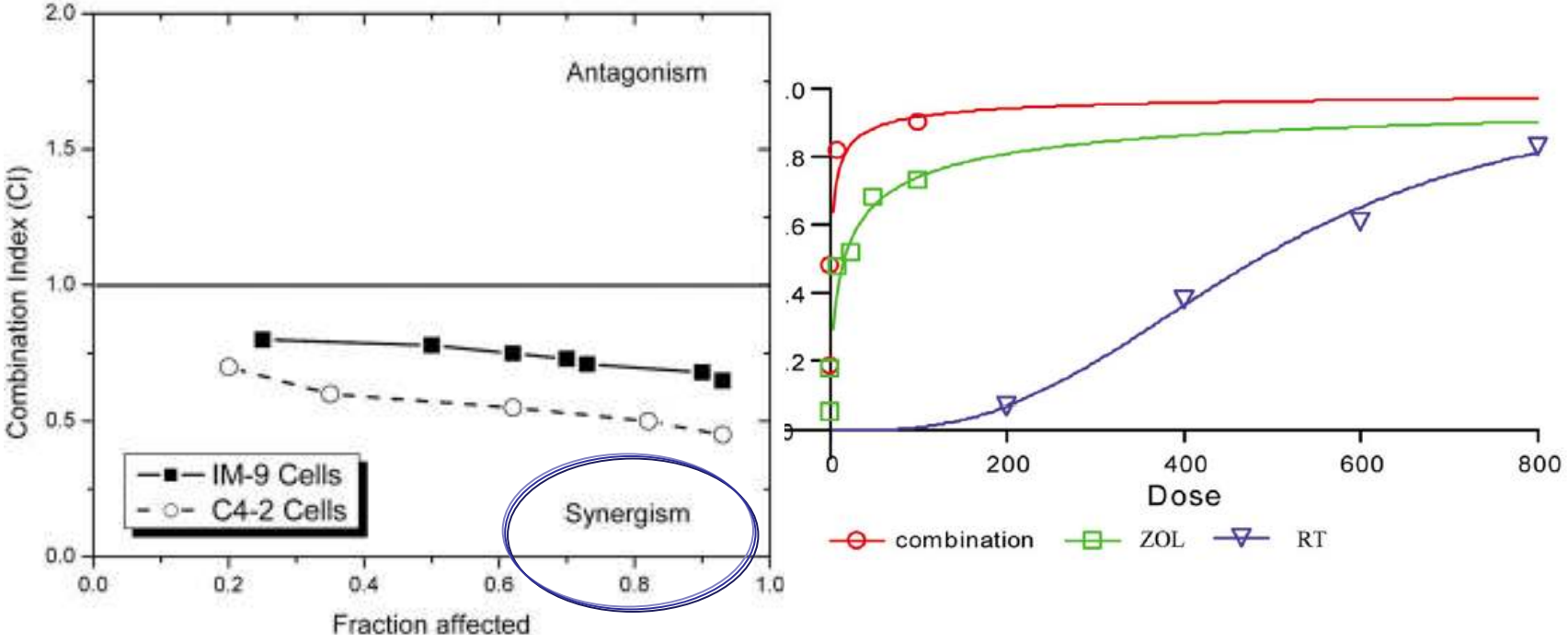
- CLINICAL EXPERIENCES

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

SINERGISTIC CYTOTOXIC EFFECTS

(In vitro evidences)



Algur E, Int J Radiat Oncol Biol Phys 2005

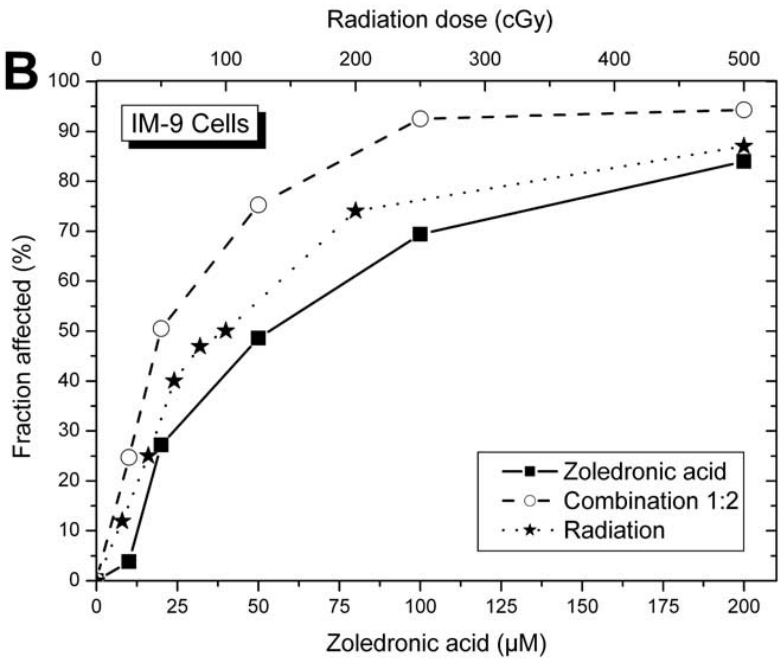
U.Ural Breast Cancer Research 2006

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

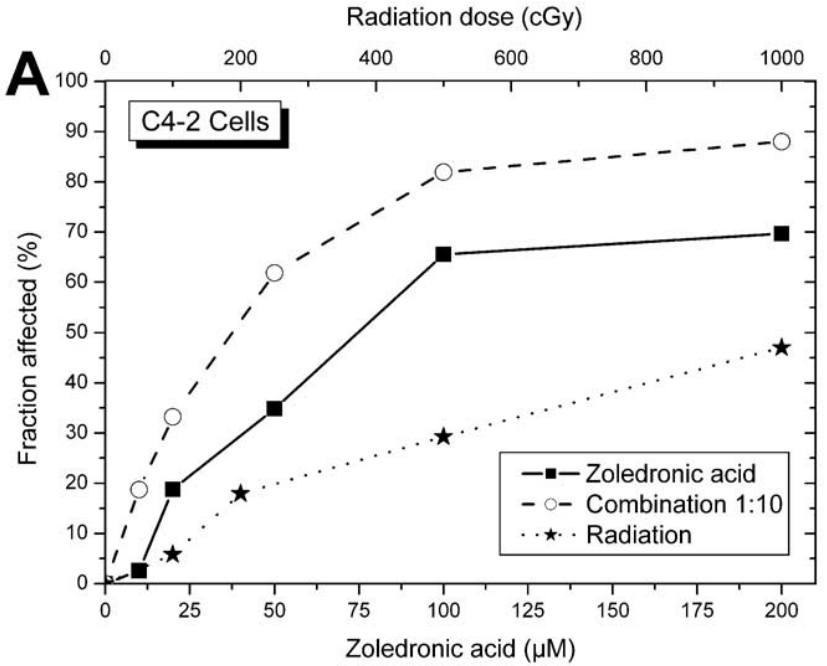
CYTOTOXIC EFFECTS

(In vitro evidences)

MIELOMA



PROSTATE

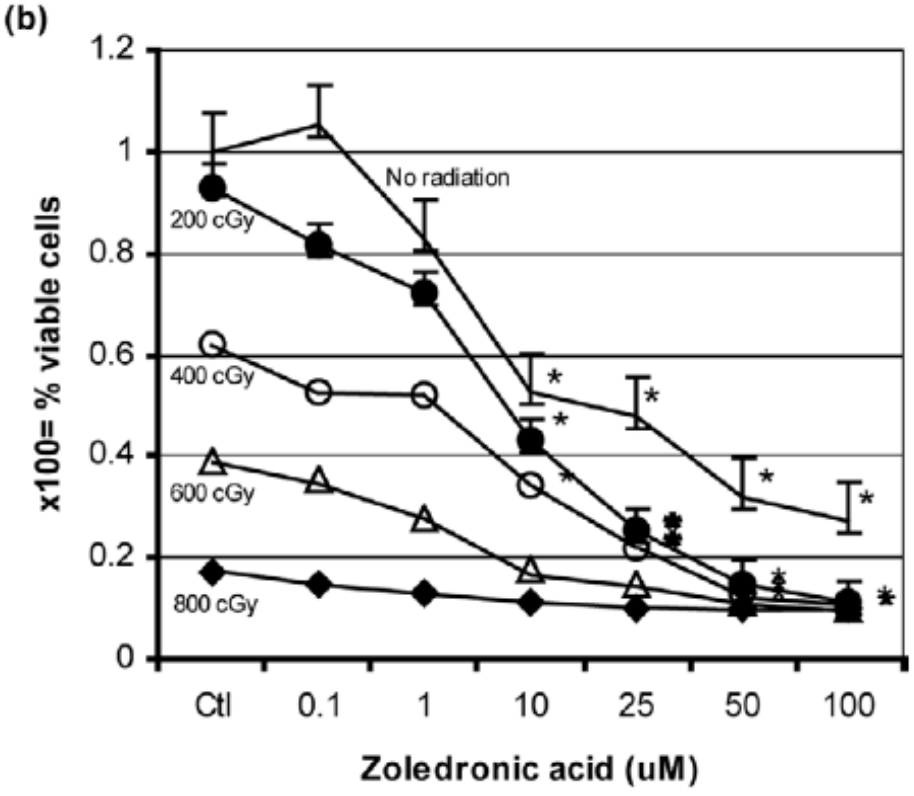


Algur E, Int J Radiat Oncol Biol Phys 2005; 61:535-542

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

CYTOTOXIC EFFECTS

(In vitro evidences)



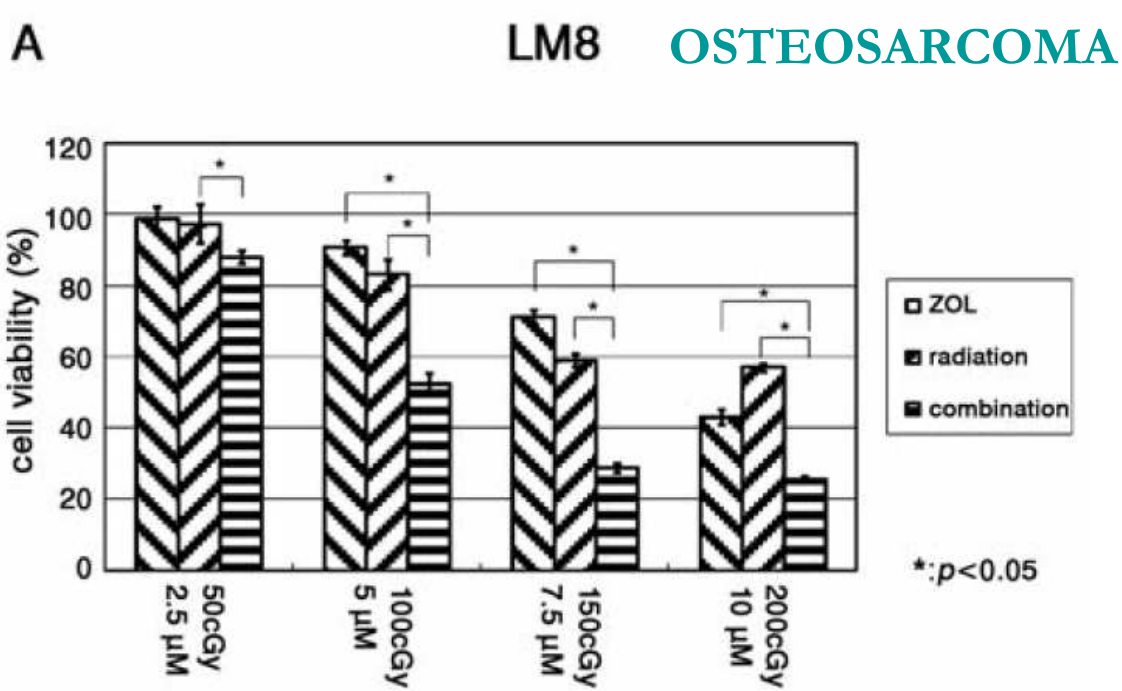
"Combination of radiation with zoledronic acid caused a greather reduction in cell viability of *BREAST CANCER* than did either treatment on its own"

U.Ural Breast Cancer Research 2006

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

CYTOTOXIC EFFECTS

(In vitro evidences)



Ryu K, Anticancer Research 2010; 30:2713-2720

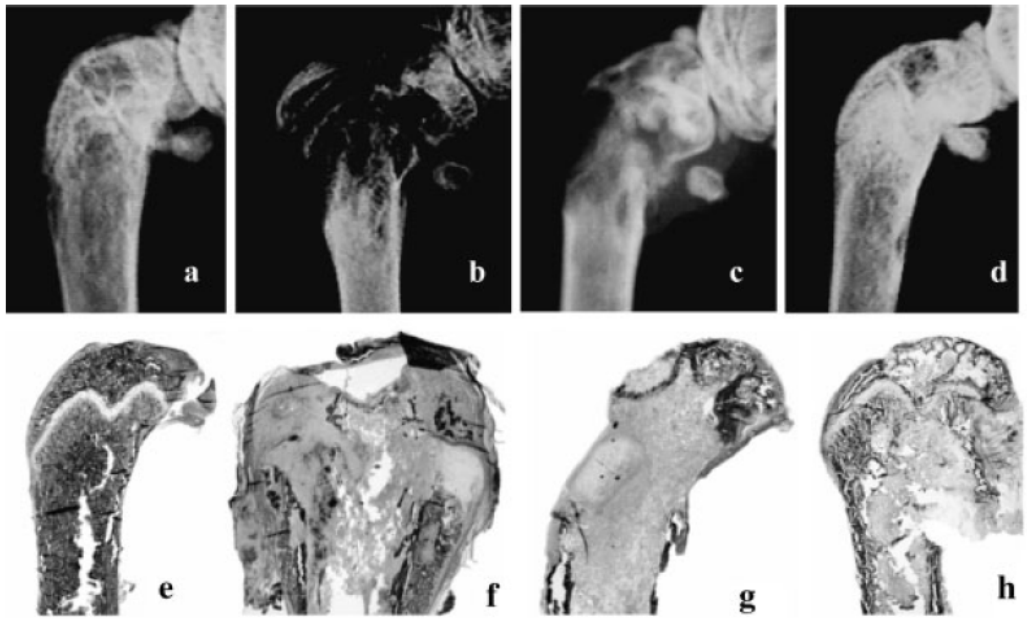
IN VIVO EXPERIENCE

Concurrent Administration of Zoledronic Acid and Irradiation Leads to Improved Bone Density, Biomechanical Strength, and Microarchitecture in a Mouse Model of Tumor-Induced Osteolysis

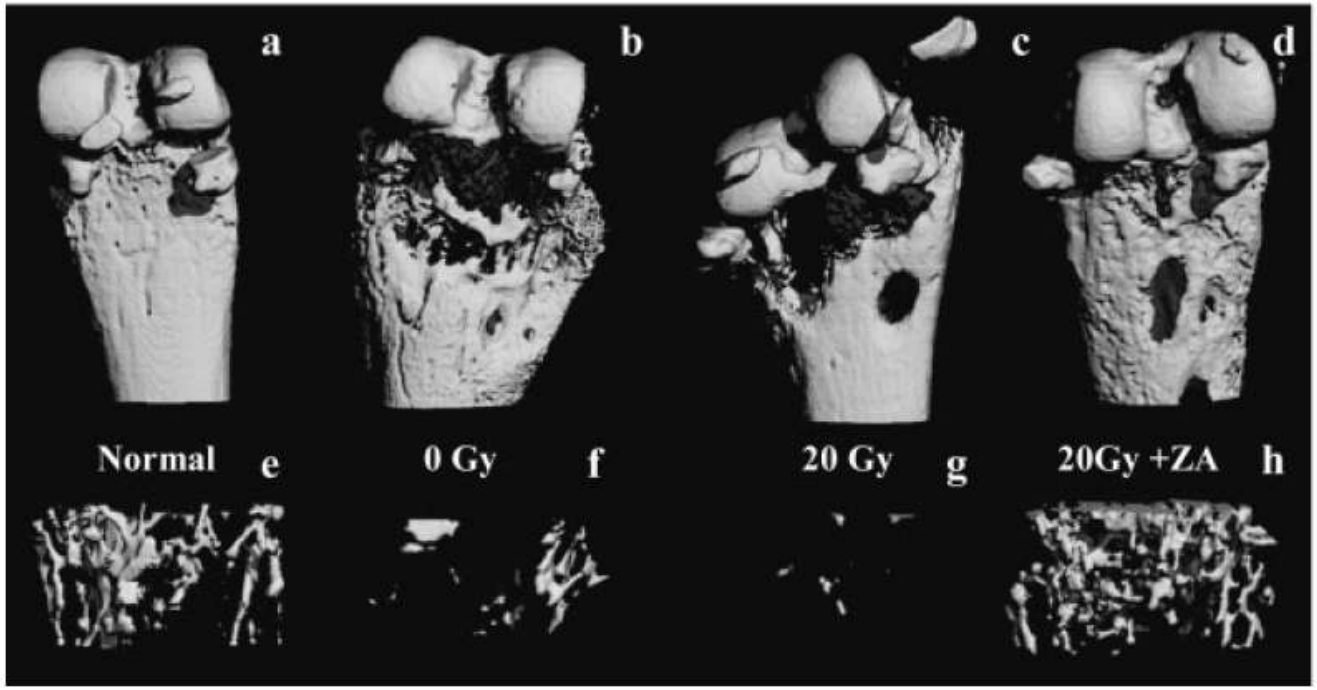
SARAH A. ARRINGTON, BS, TIMOTHY A. DAMRON, MD, KENNETH A. MANN, PhD, AND MATTHEW J. ALLEN, Vet MB, PhD*
Department of Orthopedic Surgery, SUNY Upstate Medical University, Syracuse, New York

Breast cancer cells were injected into the right femur of 30 female nude mice. Mice were divided into 3 treatment groups:

- 0 Gy + Zol
- 20 Gy
- 20 Gy + Zol



Arrington S,Journal of Surgical Oncology 2008



Mice treated with 20 Gy/ZA exhibited ***HIGHER*** bone density, bone volume, fractional trabecular bone volume, and biomechanical strength compared to mice treated with 20 Gy only ($p < 0.05$). Statistical analysis revealed that mice treated with 20 Gy/ZA were ***NOT SIGNIFICANTLY DIFFERENT*** from ***NORMAL BONES*** with respect to bone density and strength.

Arrington S,Journal of Surgical Oncology 2008

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

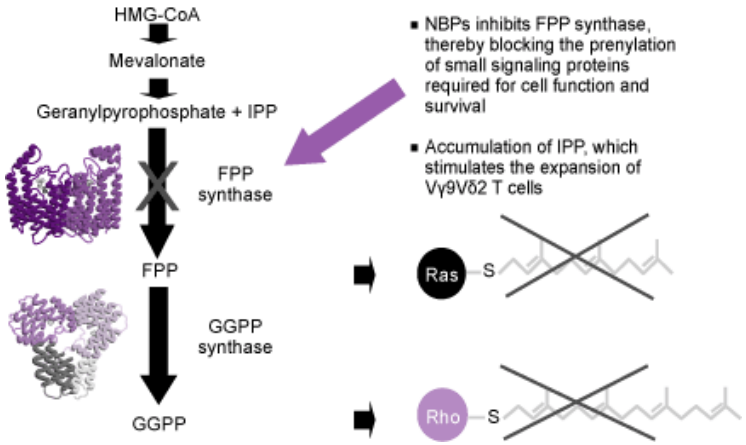
SINERGISTIC CYTOTOXIC EFFECTS

- *IN VITRO* and *IN VIVO* EVIDENCES
- *MECHANISMS OF INTERACTION*
- CLINICAL EXPERIENCES

THE INTERACTION OF RADIATION AND BISPHOSPHONATES:

1. Possible mechanisms

- BPs cause <u>Ras signaling blockade</u> by depleting cellular pools of proteins for the attachment of Ras protein to the plasma membrane

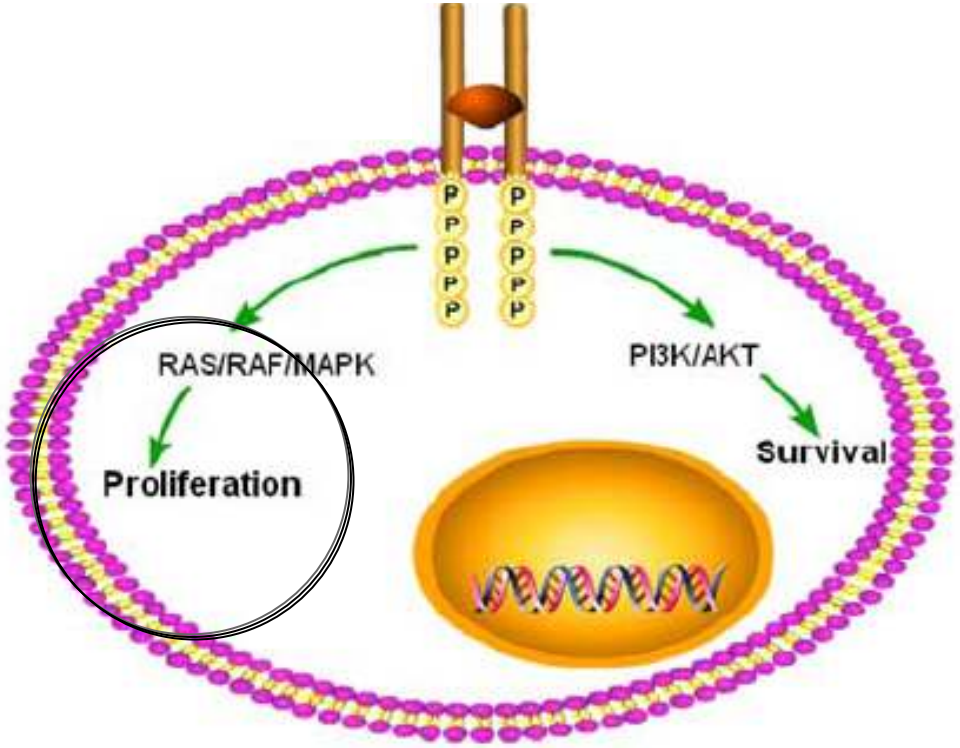


McKenna WG, Genes Chrom Cancer 2003; 38:330-338

Bernhard EJ, Cancer Research 1996; 56:1727-1730

Matsumoto S, Lung Cancer 2005;47:37-39

Cellular radiosensitation through modified signal transduction



< Apoptosis

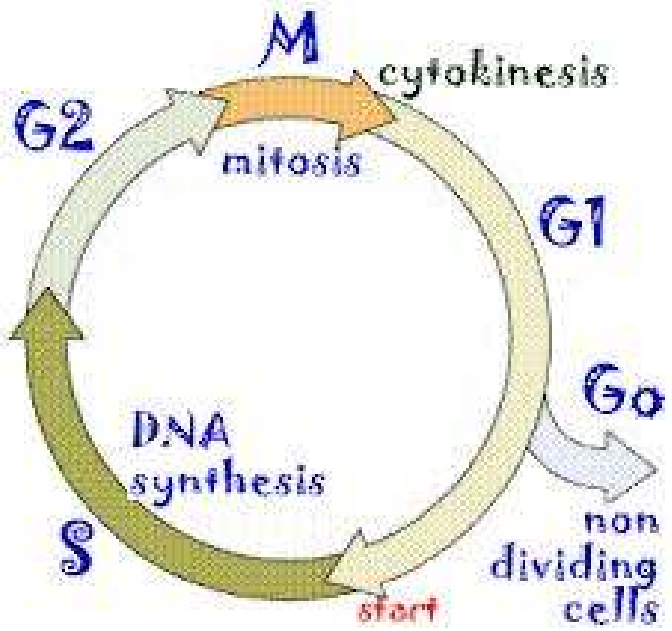
Radioresistance

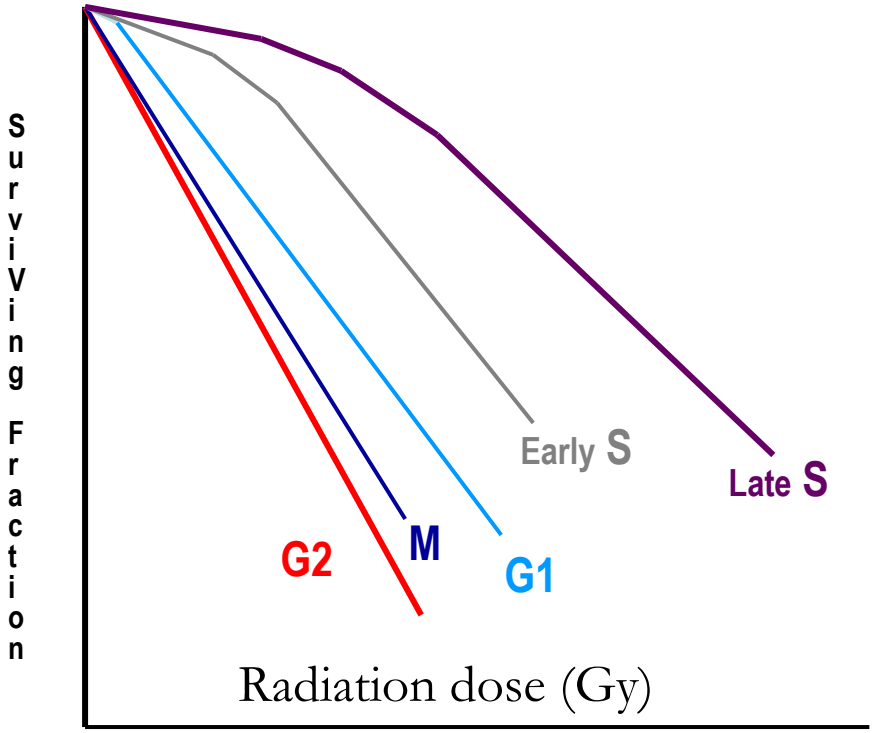
Krause, Baumann Cancer Metastasis Rev 2008

THE INTERACTION OF RADIATION AND BISPHOSPHONATES:

2. Possible mechanisms

- BPs cause cell cycle arrest in G2/M and prolongation of cell cycle progression



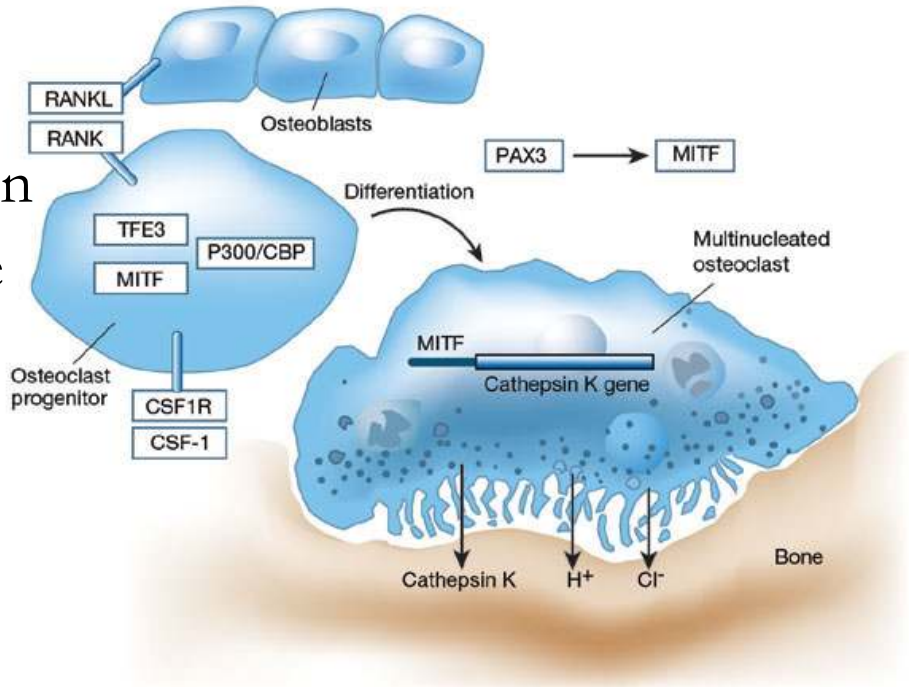


Milas L, Cancer Research 1994; 54:3506-3510
Matsumoto S, Lung Cancer 2005; 47: 31-39

THE INTERACTION OF RADIATION AND BISPHOSPHONATES:

3. Possible mechanisms

Osteoclast-forming
PROGENITORS are
radiosensitive so a combination
therapy may be more effective



Scheven BA, Bone Miner 1987; 2:291-300

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

SINERGISTIC CYTOTOXIC EFFECTS

- *IN VITRO* and *IN VIVO* EVIDENCES

- MECHANISMS OF INTERACTION

- *CLINICAL EXPERIENCES*

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

CLINICAL EXPERIENCES

1. Kouloulias, Strahlenther Onkol 2003 (33pts; phase II RT+Pamidronate)
2. Vassiliou, Int J Radiat Oncol Biol Phys 2007 (45pts; phase II RT+Ibandronate)
3. Manas A, Clin Transl Oncol 2008 (118 pts; phase III; 8Gy+Zol vs 6Gy+Zol)
4. Kijima, BJUI 2008 (23pts; retrosp. study, RT with or without Zol in RCC)
5. Cheng J, Zhonghua Zhong Liu Za zhi 2008 (45pts; random RT+Zol vs RT)
6. Atahan L, Support Cancer Care 2009 (100pts; prosp; 30Gy+Zol vs 15Gy+Zol)

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

RESULTS OF CLINICAL EXPERIENCES

- ✓ LEVELS OF RE-OSSIFICATION

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

RESULTS OF CLINICAL EXPERIENCES

- ✓ LEVELS OF RE-OSSIFICATION

- ✓ PAIN RESPONSE

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

RESULTS OF CLINICAL EXPERIENCES

- ✓ LEVELS OF RE-OSSIFICATION

- ✓ PAIN RESPONSE

- ✓ SKELETAL EVENT (pathological fractures,..)

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

RESULTS OF CLINICAL EXPERIENCES

- ✓ LEVELS OF RE-OSSIFICATION

- ✓ PAIN RESPONSE

- ✓ SKELETAL EVENT (pathological fractures,..)

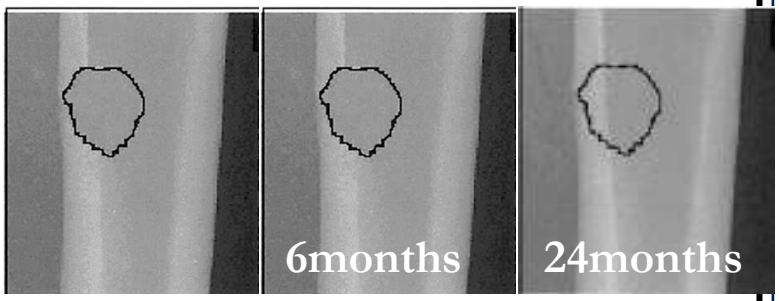
- ✓ QUALITY OF LIFE AND PS SCORE

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

LEVELS OF RE-OSSIFICATION

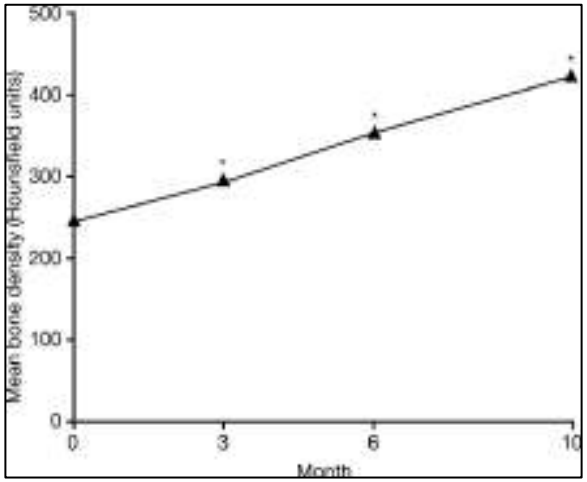
Kouloulia 2003
(33pts, RT+Pam)

Improvement in recalcification (RX)
10% 6months
43.5% 24months



Vassiliou, 2007

Bone density by CT increased by 20% at 3months, 46% 6months, 73% 10months



Cheng, 2008

RT+ZOL: 52.2%

RT: 22.7, $p<0.01$

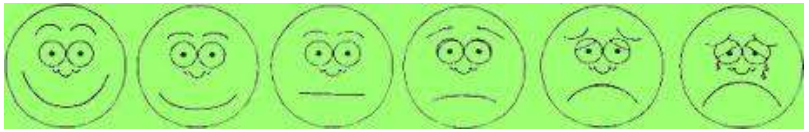
Kijima, 2008

RT+ZOL: CR and PR: 60%

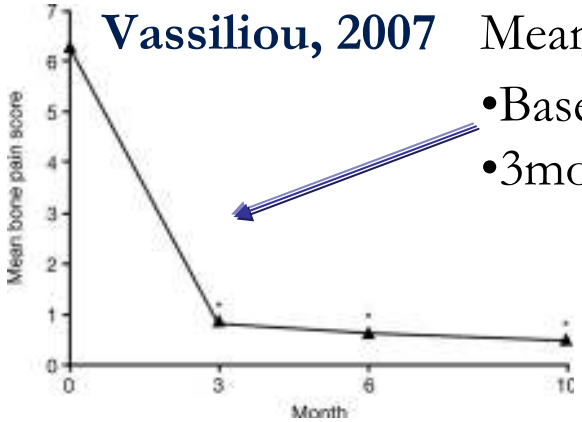
RT:CR and PR: 7%, $p=0.019$

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

PAIN RESPONSE



Vassiliou, 2007 Mean bone pain score:



- Baseline 6.3
- 3months 0.8, p<0.001

Complete pain response:
3months: 69%
10months 81%

Cheng, 2008

RT+ZOL: 91.3%

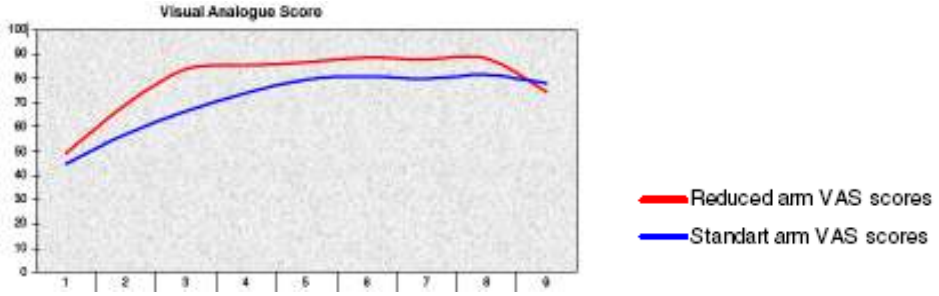
RT: 86.4, p>0.05

Atahan 2009

VAS

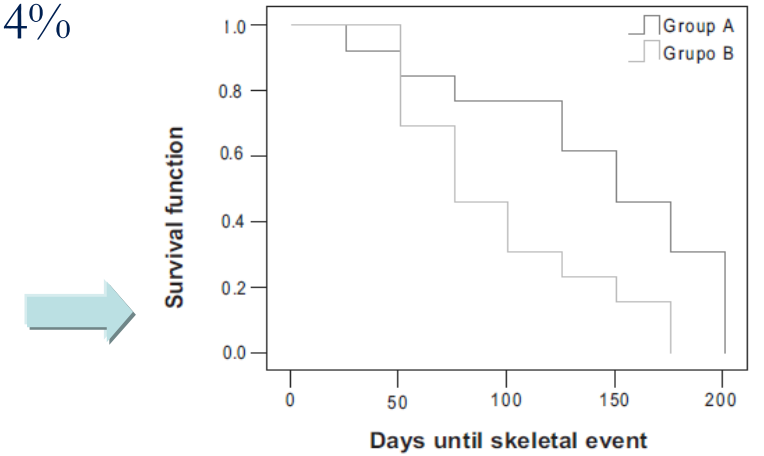
30Gy+Zol

15Gy+Zol



THE INTERACTION OF RADIATION AND BISPHOSPHONATES

SKELETAL EVENT (Pathological fractures, re-irradiation,..)

Manas A,2008 •GroupA: 8Gy+BP •GroupB: 6Gy+BP	Global incidence 4% in both groups Time to onset of skeletal event 
Kijima, 2008 RT with or without BP	

SREs	RT + Z (10)	RT (13)	*P*
Any	1	10	0.003
Additional RT to bone	1	4	
Surgery to bone	0	3	
Spinal cord compression	0	2	
Pathological fracture	0	1	

THE INTERACTION OF RADIATION AND BISPHOSPHONATES

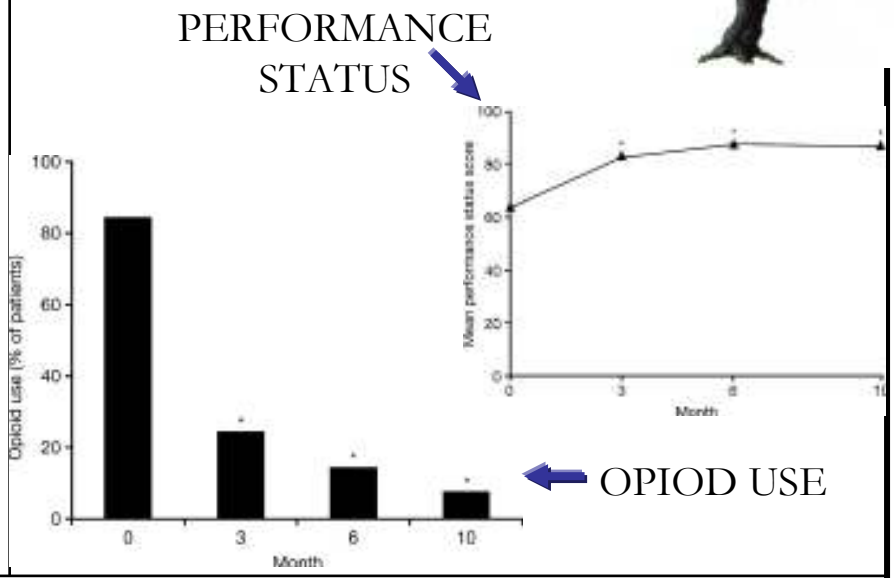
QUALITY OF LIFE AND PS SCORE

Kouloulias, 2003

Quality of Life Questionnaire

Parameter	Baseline	At 6 mo	*p**
Physical functioning	29.1 ± 11.4	85.0 ± 8.2	<0.001
Role functioning	17.2 ± 12.1	90.9 ± 13.9	<0.001
Cognitive functioning	36.4 ± 10.6	78.8 ± 11.2	<0.001
Emotional functioning	19.7 ± 15.2	81.6 ± 9.0	<0.001
Social functioning	5.1 ± 10.6	91.4 ± 11.8	<0.001
Financial difficulties	78.8 ± 27.4	40.4 ± 28.6	<0.001
Dyspnea	16.2 ± 22.2	17.2 ± 16.9	0.83
Pain	93.9 ± 12.4	8.1 ± 11.1	<0.001
Fatigue	86.2 ± 11.1	10.1 ± 9.8	<0.001
Insomnia	89.9 ± 15.5	7.1 ± 13.8	<0.001
Appetite loss	32.3 ± 5.8	29.3 ± 11.0	0.11
Nausea and vomiting	3.5 ± 9.1	7.6 ± 9.4	0.12
Constipation	4.0 ± 11.0	3.0 ± 9.7	0.68
Diarrhea	4.0 ± 11.0	6.1 ± 13.0	0.53
Global QOL	11.9 ± 9.8	83.3 ± 7.5	<0.001

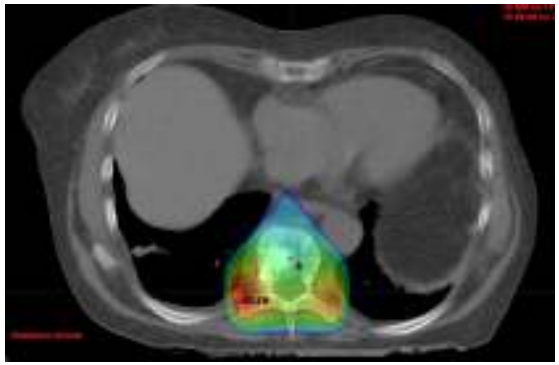
Vassiliou, 2007

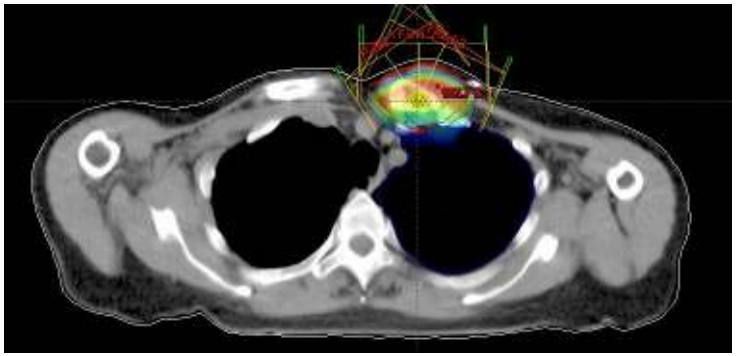


Manas A, 2008

- 8Gy+BP= KPS 78 baseline vs 85 7months, *p=0.005*
- 6Gy+BP= KPS 79 baseline vs 77 7months, ns

CONCLUSIONS:





"Quando due modalità terapeutiche vengono utilizzate in concomitanza, è fondamentale che la tossicità non venga amplificata"

Nella pratica clinica, la gestione del trattamento combinato è semplice e risulta essere privo di tossicità