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S. C. Radioterapia  
Oncologica

ASL TA/ 1 – Taranto

***METASTASI OSSEE***



# La Radioterapia: indicazioni e volumi

*Taranto 16 marzo 2007*

# Dimensioni del problema

La radioterapia delle metastasi ossee costituisce il 64% della terapia palliativa

Il paziente con metastasi ossee diventa sintomatico più precocemente e presenta una sopravvivenza più lunga rispetto il paziente con metastasi viscerali

La spettanza di vita varia da 3,5 a 30 m con *SM* variabili e inversamente correlate al grado di coinvolgimento osseo

Il dolore è presente nel 75% dei casi

La frattura patologica è frequente

### *Goals del trattamento RT*

- attenuare il sintomo più a lungo possibile
- preservare motilità e funzione ossea
- mantenere l'integrità scheletrica
- preservare la QoL

# Cosa vede il radioterapista:

## Gruppo AIRO "Palliazione in Radioterapia"

Year/ Radiotherapy Center (number)	Total n° October	Annual RT Projection	PRT October	Annual PRT Projection (%)	SBM	MBM
2001: Total 20/55 (36.4%)	2,165	~ 25,980	495	~ 5,940 (23)	83	192
% SBM / MBM					16.8	38.8
% SBM+MBM					55.6	
2000: Total 38/53 (71.7%)		33,924		10,418 (31)	2,030	3,476
% SBM / MBM					19.5	33.4
% SBM+MBM					52.8	
1998: Total 36/51 (70.6%)		32,827		9,609 (30)	5,055	
% SBM+MBM					52.6	

**Legend:** RT= all radiation therapy treatment administered; PRT= palliative radiotherapy; SBM= single bone metastases, MBM= multiple bone metastases; Total= total treatments given in the center

# Cochrane Database Syst Rev 2000

- 23 trials su 43 schemi di frazionamento
- completo *pain relief* a 1 m in 395/1580 pz (25%)
- *relief* del 50% in 788/1933 pz (41%) nel tempo
- *relief* nel 52% (759 pz) entro 4 settimane
- durata mediana del completo *relief* : 12 settimane

*Nessuna differenza in efficacia con i diversi schemi di frazionamento e in dose-risposta per dose totale erogata*

# Systematic Overview 2003

**Review sistematica su 63 lavori e 8051 pz valutati:  
*strong evidence* x la RT**

- *pain relief* completo o parziale nel 80% dei pazienti
- nel 50% dei casi si protrae  $\geq 6$  m
- grado e durata non dipendono dal tipo di frazionamento adottato
- il numero delle complicazioni tardive è basso

# Systematic Overview

Overview 1a

Skeletal metastases. Local radiotherapy of bone metastases—fractionation and dose

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results				Conclusion/comments
			OPR %	Duration	Retreatment %	SCC No. of pts	
Bone Pain Trial Working Party 1999 (27) C	A: 8 Gy/fr, 1 fr B: 4 Gy/fr, 5 fr, 20 Gy/1w or 3 Gy, 10 fr, 30 Gy/2 w (only 8 pts received 3 Gy, 10 fr, 30/Gy/2w)	761 pts A: 383 B: 378	Follow-up 1 y A 78 B+C 78	40% > 12 m No diff. between the groups	23 10 p < 0.001	6 pts 4 pts	In the trial 8 Gy single fraction was compared with a multifraction regimen (20 Gy or 30 Gy) with randomization ratio 1:1. Pain assessment: 4-grade categorized scale. SCC: reported at the index field within 12 months. Pathological fractures: 7 cases in group A, 2 cases in group B. Use of analgesic drugs did not differ between the groups at any time during the study.
Steenland 1999 (26) C	A: 8 Gy/fr, 1 fr B: 4 Gy/fr, 6 fr, 24 Gy/1 w	1 157 pts A: 578 B: 579 Mets to cervical spine excluded	Follow-up 2 y A 72 B 69 ns	20 w 24 w ns	25 7 p < 0.0001	13 pts 10 pts	Pain assessment: 11-point pain scale. Time to progression was affected by tumour histopathology (p < 0.0001), breast carcinoma > prostate carcinoma > carcinoma of the bronchi or others. Pathological fractures: 4% in group A, and 2% in group B. QoL (Rotterdam symptom checklist) not significantly different between groups. Costs including retreatment were 8% higher for group B.
Koswig 1999 (22) C	A: 8 Gy/fr, 1 fr B: 3 Gy/fr, 10 fr, 30 Gy/2 w	107 pts A 52 B 55	Follow-up 6 m A 78 B 81 ns	NR NR	NR NR	NR NR	The main endpoint was remineralization.
Jeremic 1998 (21) C	A: 4 Gy/fr, 1 fr B: 6 Gy/fr, 1 fr C: 8 Gy/fr, 1 fr	327 pts A: 109 B: 108 C: 110	Follow-up 2 m A 59* B 73* C 78*	42 w 50 w 47 w	42 44 38	4 pts 5 pts 4 pts	Only patients with their first single bone metastasis were included. Pain assessment: 4-point categorized pain scale. Pathological fractures occurred in 6, 7 and 7%, in groups A, B, and C, respectively.
Nielsen 1998 (23) C	A: 8 Gy/fr, 1 fr B: 5 Gy/fr, 4 fr, 20 Gy/4 d	239 pts A: 120 B 119	Follow-up 5 m A 62* 72** B 71* 82** ns	60% > 6 m No diff. between A and B	20 11 ns	NR NR	In both groups, 5% of the patients developed a pathological fracture.
Gaze 1997 (20) C	A: 10 Gy/fr, 1 fr B: 4.5 Gy/fr, 5 fr, 22.5 Gy/1 w	265 pts A: 134 B: 131	Follow-up 3 y A 83 B 89 ns	22.5 w 24.9 w ns	NR NR	NR NR	Re-entry of previously randomized pts was allowed. Pain assessment: 5-point categorized scale. No differences in QoL (Spitzer index) or in the prevalence of anxiety/depression (HAD scale) between groups.
Niewald 1996 (24) C	A: 4 Gy/fr, 5 fr, 20 Gy/1w B: 2 Gy/fr, 15fr, 30 Gy/3 w	97 pts A 51 B 46	Follow-up 1 y A 77 B 86 ns	35 w 35 w	2 2	NR	Pain assessment: 4-grade categorized scale. Analgesics used were not assessed. Pathological fractures: 4 pts in group A and 6 in group B.

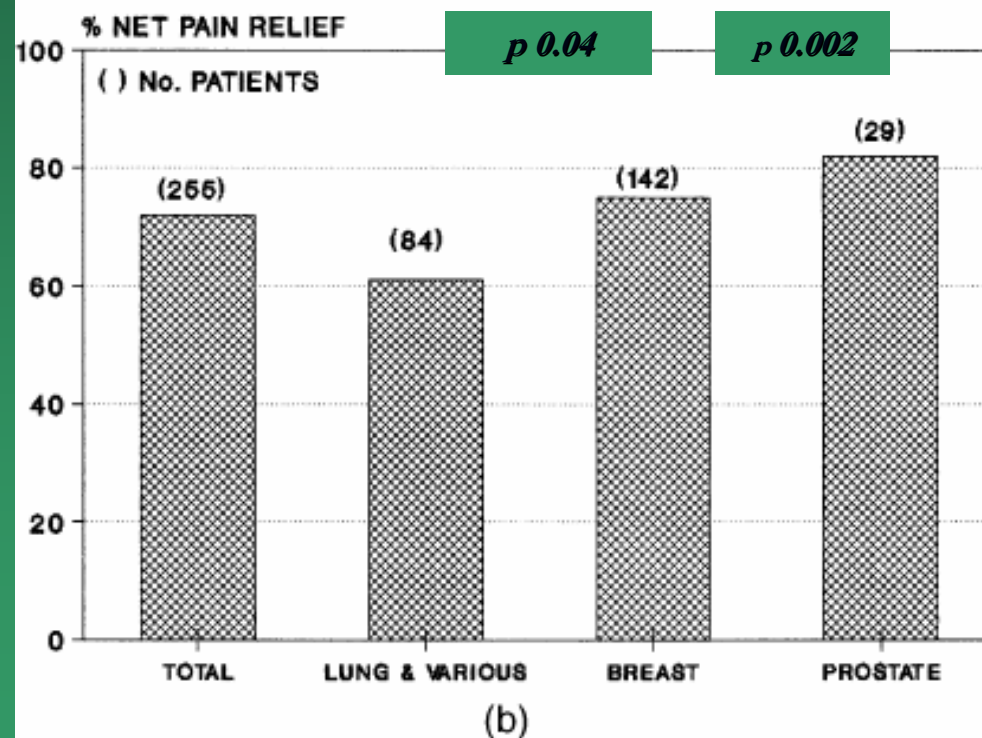
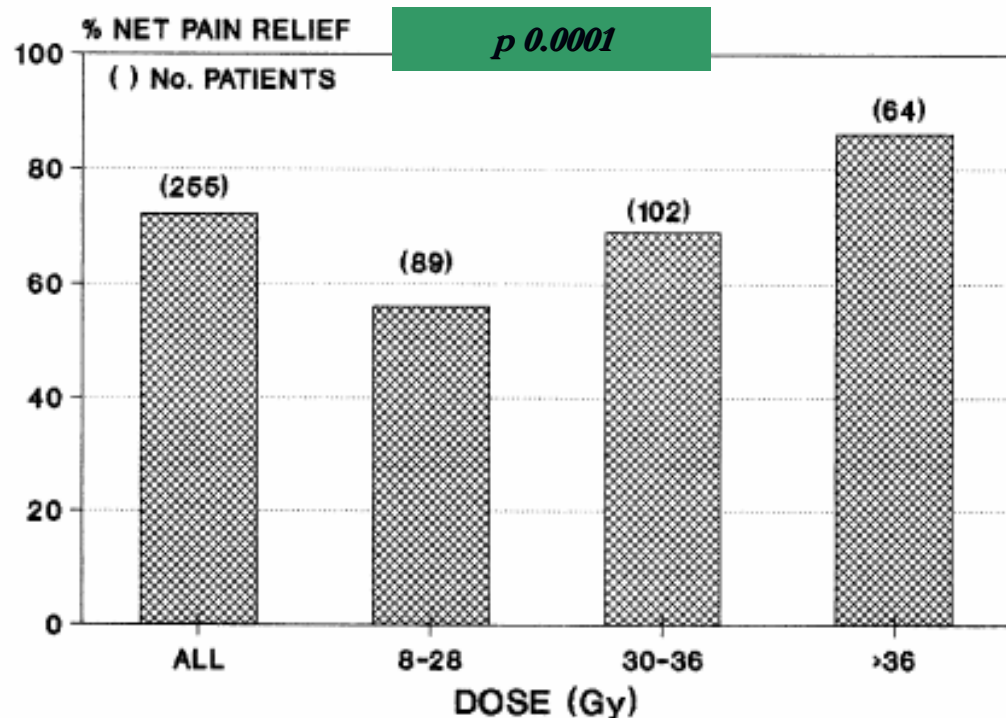
Author Year (Ref. no.) Design	Aim/study question	Patient population	Results				Conclusion/comments
			OPR %	Duration	Retreatment %	SCC No. of pts	
Rasmusson 1995 (25) C	A: 5 Gy/fr, 3 fr, 15 Gy/1 w B: 3 Gy/fr, 10 fr, 30 Gy/2 w	200 pts A 100 B 100 Only carcinoma of the breast	Follow-up 1 year A 81 B 72 ns	90% > 12 m 65% > 12 m ns	NR ns	NR	Physicians were 'blinded' as to which radiation treatment the patients had received. Pain assessment: 4-grade categorized scale. No significant changes in consumption of analgesics within the two groups.
Arcangelli 1998 (28) P	A: 1.8-2 Gy/fr, 20-23 fr, 40 Gy/4-4.5w B: 2.5-3 Gy/fr, 10-12 fr, 30 Gy/2-2.5 w C: 5-8 Gy/fr, 1-4 fr	255 pts A: 64 B: 102 C: 89	Follow-up: not clearly stated A 91 B 83 C 62 p < 0.05	Duration of pain relief sign longer for pts with CPR	NR	NR	Patient characteristics differed between the treatment groups. Pain assessment: VAS. Analgesic assessment: 5-point scale. CPR: VAS < 2 or 0 in the analgesic scale. A dose-response relationship for complete pain relief was also found.
Bremer 1999 (29) P	A: 4 Gy/fr, 1 fr B: 4 Gy/fr, 4 fr	131 pts A: 45 B: 86	Evaluated at 90 d A 55 B 80 p < 0.006	3 m 9 m p < 0.0001	NR	NR	Pts with metastases in vertebrae, or other weight-bearing bones were excluded. Pain assessment: 4-point categorized scale.
Huguenin 1998 (30) P	A: 3 Gy/fr, 10 fr, 30 Gy/2 w B: 4 Gy/fr, 5 fr, 20 Gy/1 w C: 2 Gy/fr, 10 fr, 20 Gy/2 w	40 pts Malignant melanoma and renal cell carcinoma only	All groups 63* *No. of pts and OPR in the different groups not shown	2.4 m	NR	NR	Small study.
Tombolini 1994 (31) P	A: 8 Gy/fr, 1 fr B: 5 Gy/fr, 4 fr, 20 Gy/4 d C: 4 Gy/fr, 5 fr, 20 Gy/w D: 3 Gy/fr, 10 fr, 30 Gy/2 w E: 2 Gy/fr, 20 fr, 40 Gy/4 w	103 pts A: 48 B: 7 C: 15 D: 20 E: 13 Spinal mets only	Follow-up 8 m A 82 B 85 C 85 D 80 E 80 ns	NR	4	NR	Most of the treatment was given with a 60-Co source. Analgesic assessment not performed. Pain assessment: 5-point categorized scale. Small number of patients in the different groups.
Uppelschoten 1995 (32) P	6 Gy/fr, 1 fr	211	Follow-up 4 w 88	NR	18	4 pts	Re-entry of previously randomized patients was allowed. Pain assessment: 4-point categorized scale. Analgesic assessment: 4 categories. In-field pathological fractures occurred in 5 patients (8%).

Abbreviations: CPR = complete pain relief; d = day(s); fr = fraction = m = month(s); mets = metastases; NR = not reported; ns = not significant; OPR = overall pain relief (partial and complete); pts = patient(s); SCC = spinal cord compression; w = week(s); y = year(s).

● *Clinical Investigation*

**RADIATION THERAPY IN THE MANAGEMENT OF SYMPTOMATIC BONE METASTASES: THE EFFECT OF TOTAL DOSE AND HISTOLOGY ON PAIN RELIEF AND RESPONSE DURATION**

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 LUCIANO D'ANGELO, PH.D., DIANA GIANNARELLI, PH.D.,\* GIANCARLO ARCANGELI, M.D., AND  
 ADRIANA MICHELI, M.D.



*Metastasi da polmone poco responsive rispetto a mammella e prostata (NS)*



# Fratture patologiche

EBRT è raccomandata dopo stabilizzazione di fratture patologiche e per lesioni ossee a rischio di frattura x migliore outcome funzionale

Le indicazioni a EBRT dopo posizionamento della protesi vanno meglio definite

*Report SBU 129/2, Acta Oncologica 2003*

# Systematic Overview *Acta Oncologica, 2003*

## Overview 3

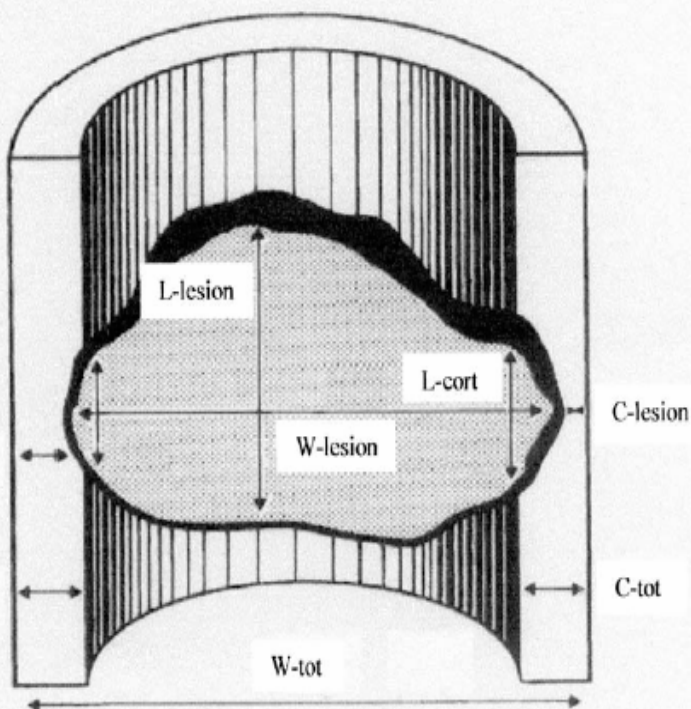
### *Skeletal metastases. Surgical treatment of pathological fractures with or without radiotherapy*

Author Year (Ref. no.) Design	Treatment	Patient population	Results	Conclusion/comments	
<u>Townsend</u> 1994 (45) R	ST only, 29 pts <u>ST+RT, 35 pts</u>  Time to postop. RT mean 14 days Median RT dose 30 Gy	Femur 26 Humerus 1 Other sites 2 Femur 32 Humerus 2 Other sites 1	64 Several types of solid tumours	Successful outcome = normal use of arm/leg: ST 4/29, 14% <u>ST+RT 19/35, 54% p &lt; 0.01</u>	Consecutive pts. Postoperative RT was the only significant predictor for a successful outcome. For a review: 25 simulation films were available. Out of these, 21 were found to have included the entire orthopaedic prosthesis. R2
<u>Haentjens</u> 1995 (44) R	ST only 19 pts ST+RT 9 pts In 2/9 pts RT given preoperatively	Femur 19 Femur 9	28 Several types of solid tumours	No difference between ST only and ST+RT; 23/28 pts achieved good function	New bone formation around the prosthesis was limited to the ST group of pts only. Small study group. R2

Abbreviations: pts = patient(s); RT = radiotherapy; ST = surgical treatment.

## Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomised trial

Yvette M. van der Linden<sup>a,\*</sup>, Herman M. Kroon<sup>b</sup>, Sander P.D.S. Dijkstra<sup>c</sup>,  
Judith J. Lok<sup>d</sup>, Ed M. Noordijk<sup>a</sup>, Jan Willem H. Leer<sup>e</sup>, Corrie A.M. Marijnen<sup>a</sup>,  
for the Dutch Bone Metastasis Study Group



La frattura femorale dipende dall'entità di coinvolgimento assiale della corticale (*ACI*)

$ACI \leq 30$  mm RT (hypo)

$ACI > 30$  mm stabilizzazione (profilassi)  
RT alte dosi (pz unfit)

# Fattori decisionali

- Performance status  $> 60\%$
- Spettanza di vita  $> 3$  mesi
- Stato metastatico di malattia
- Sede delle lesioni
- Aree coinvolte (volumi)

# Volumi

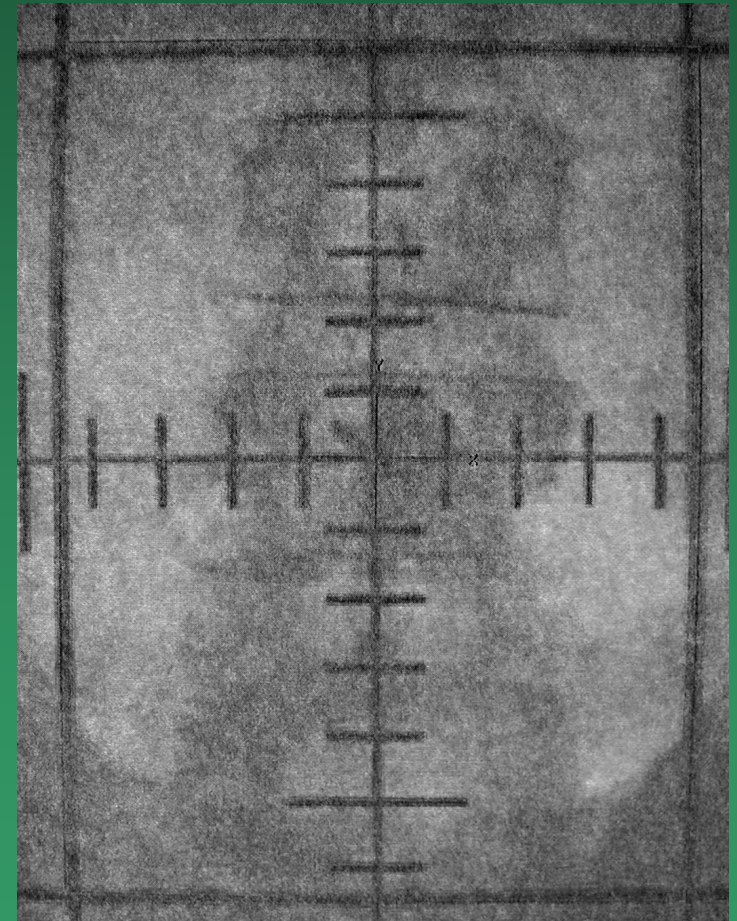
- Piccoli volumi (limited field RT)
- Ampi volumi (half body RT)
- Volumi dopo stabilizzazione
- Sedi particolari (base cranio, mandibola )

# Limited field RT

**PTV = vertebra interessata + margine**

metameri vertebrali

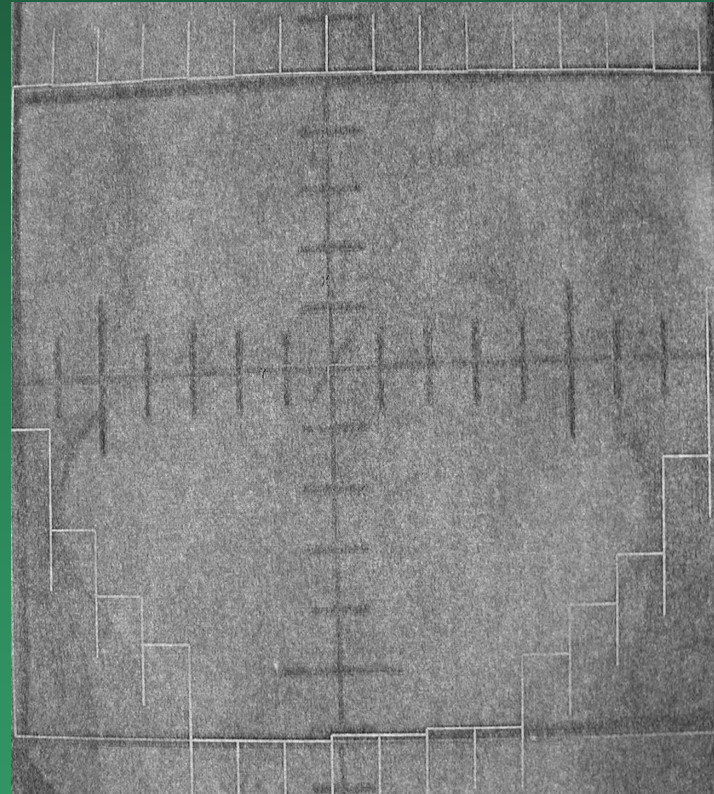
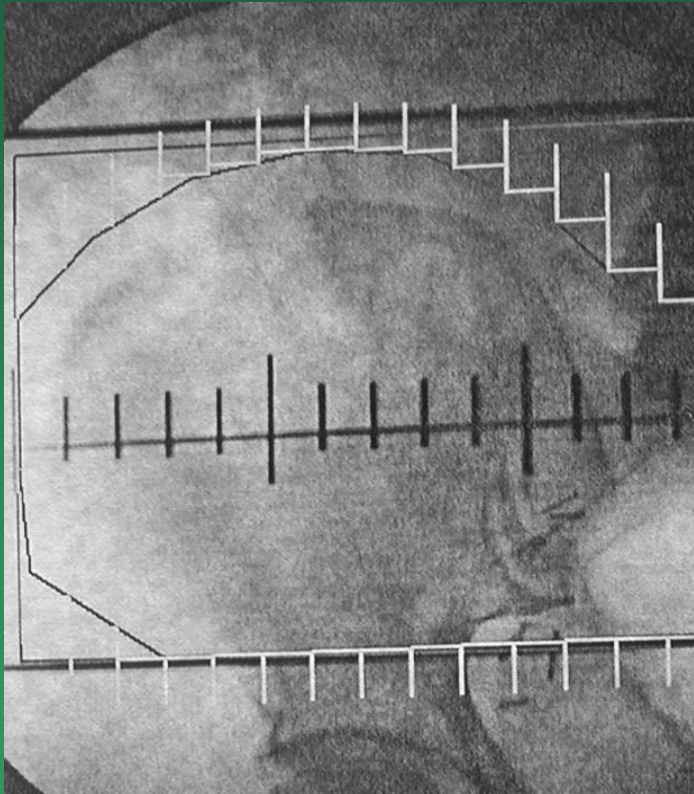
- 2 cm lateralmente
- 1 corpo vertebrale sano craniale
- 1 corpo vertebrale sano caudale



*vertebra lombare*

# Bacino

**PTV = distretto + margine con schermi**



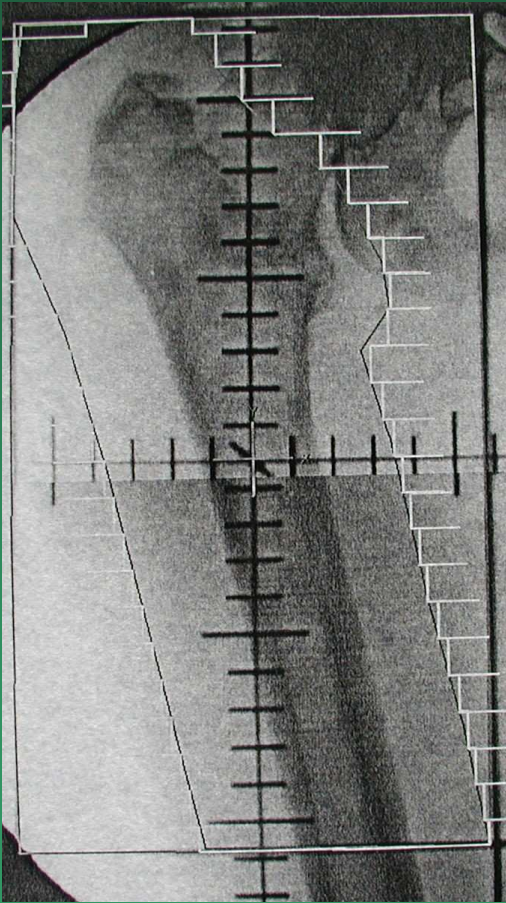
grande ala

sacro

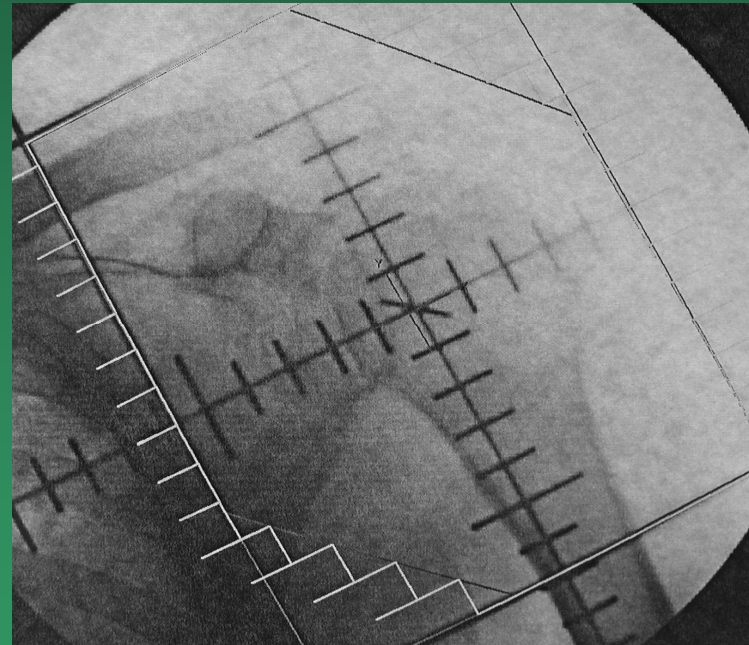
branca ileo-pubica

# Arti

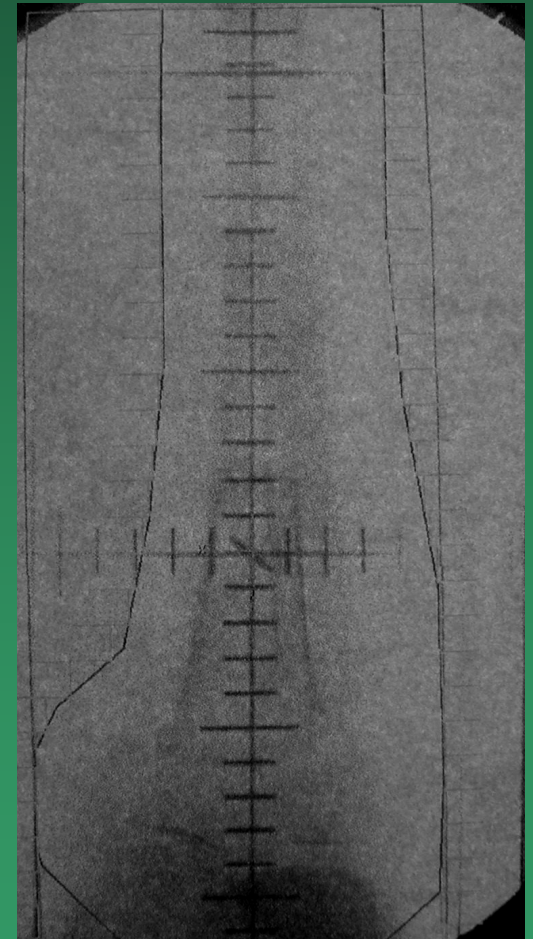
**PTV = segmento interessato + margine con schermi**



femore



scapolo-omerale



tibia



# Half Body Radiation

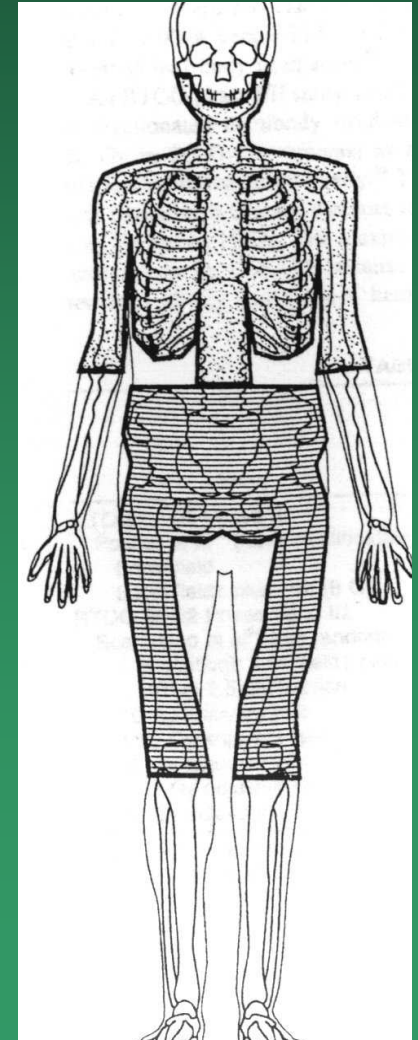
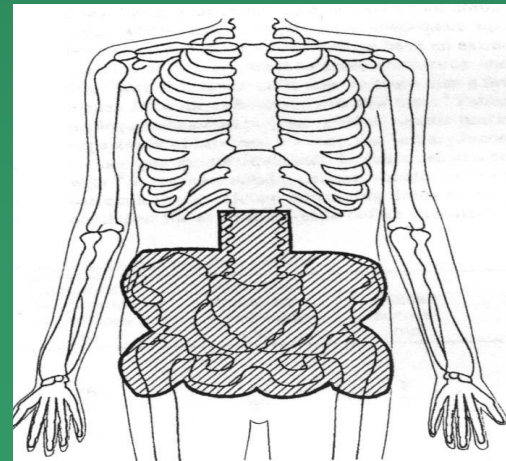
Trattamento di più lesioni incluse in un unico ampio campo con ipofrazionamento

Parte superiore (UHBI = base cranio-L4/L5)

Parte inferiore (LHBI = L4/L5 - anche)

Parte media (MBI = diaframma-forami otturatori)

*Salazar 1996*



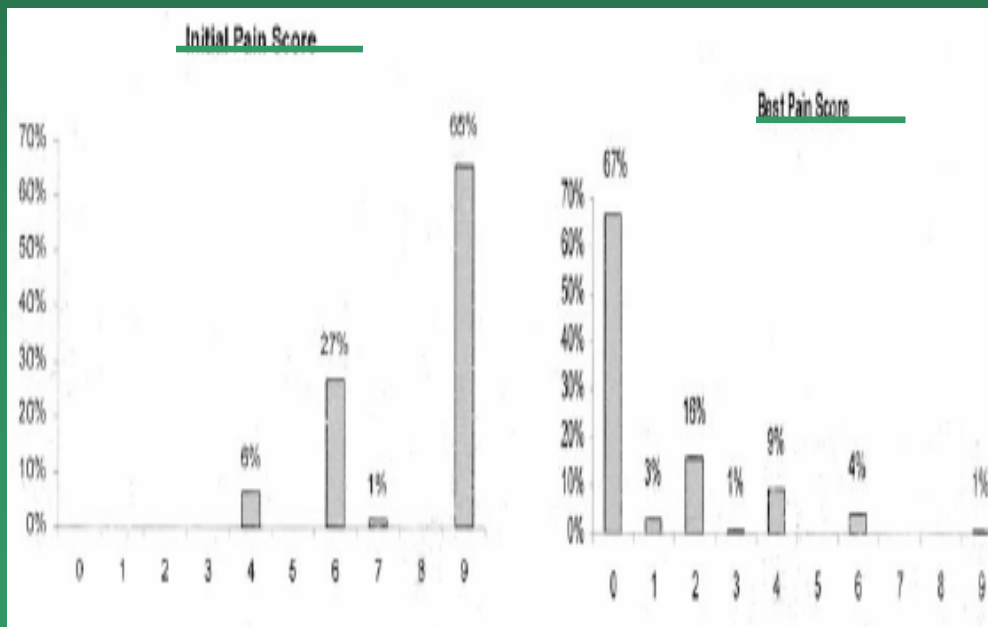
# Half body Radiation 2001

## CLINICAL INVESTIGATION

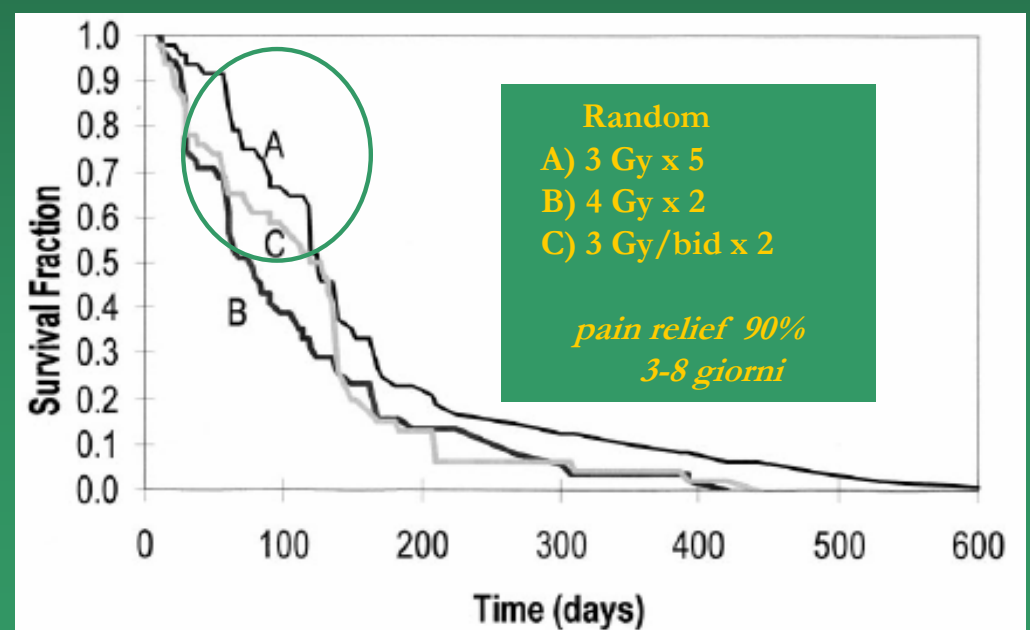
## Bone

### FRACTIONATED HALF-BODY IRRADIATION (HBI) FOR THE RAPID PALLIATION OF WIDESPREAD, SYMPTOMATIC, METASTATIC BONE DISEASE: A RANDOMIZED PHASE III TRIAL OF THE INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA)

OMAR M. SALAZAR, M.D., F.A.C.R., F.A.C.R.O.,\* TALGIT SANDHU, PH.D.,<sup>†</sup>  
NEIRO W. DA MOTTA, M.D.,<sup>‡</sup> MARÍA ÁNGELES PEREZ ESCUTIA, M.D.,<sup>§</sup>  
EDUARDO LANZÓS-GONZALES, M.D.,<sup>§</sup> A. MOUELLE-SONE, M.D.,<sup>||</sup> ALFREDO MOSCOL, M.D.,<sup>¶</sup>  
MAYER ZAHARIA, M.D., F.A.C.R., F.C.R.S.,<sup>¶</sup> AND SHAMAS ZAMAN, M.D.<sup>#</sup>



pain score



pain free survival

FRACTIONATED HALF-BODY IRRADIATION (HBI) FOR THE RAPID PALLIATION OF WIDESPREAD, SYMPTOMATIC, METASTATIC BONE DISEASE: A RANDOMIZED PHASE III TRIAL OF THE INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA)

differenza *NS*

- PS 1-2 vs 3-4
- M1<sub>oss</sub> vs M1<sub>oth</sub> (hep,pul)
- < 15 siti M1<sub>oss</sub> vs > 15 M1<sub>oss</sub>

Tossicità

G3-G4 UHBI vs LHBI *p 0.35*

- A arm = C arm
- UHBI = GI (nausea-vomito)
- LHBI = GI (diarrea-addominlgia)
- Ematologica G2-G4  
(neutropenia e piastrinopenia)

# Half body Radiation

Systematic Overview, Acta Oncologica 2003

## Overview 1b

*Skeletal metastases. Half-body irradiation*

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results OPR% Duration	Retreatment	Conclusion/comments	
Salazar 2001 (34) C	A: 3 Gy/fr, 5 fr, 15 Gy/w B: 4 Gy/fr, 2 fr/d, 8 Gy/1 d C: 3 Gy/fr, 1 fr/d, 6 Gy/2 d	156 pts A: 51 B: 56 C: 49	A 91 B 89 C 94 ns p < 0.034	155 days 101 112	NR	Lower HBI 79 pts, upper HBI 68 pts, middle HBI 9 pts. Pain relief occurred in 3 to 9 days, no difference between the groups. CPR: significantly lower in group B than in groups A and C. QoL (RTOG grading system) no difference between the groups. C1
Chua 1994 (35) R	HBI: 1.5 Gy/min Treatment fields: 35-45 cm <sup>2</sup> Source skin distance: 80 cm Total doses: 4.5-8.0 Gy Median dose of 5 Gy to the upper half body, 7.0 Gy to the lower half body	134 pts	70	Relief lasted from a few weeks to several months	NR	38% had nasopharyngeal carcinoma. Pain assessment was not shown in detail. Pain relief occurred from 24 h. Evaluation of side effects not reported. R3

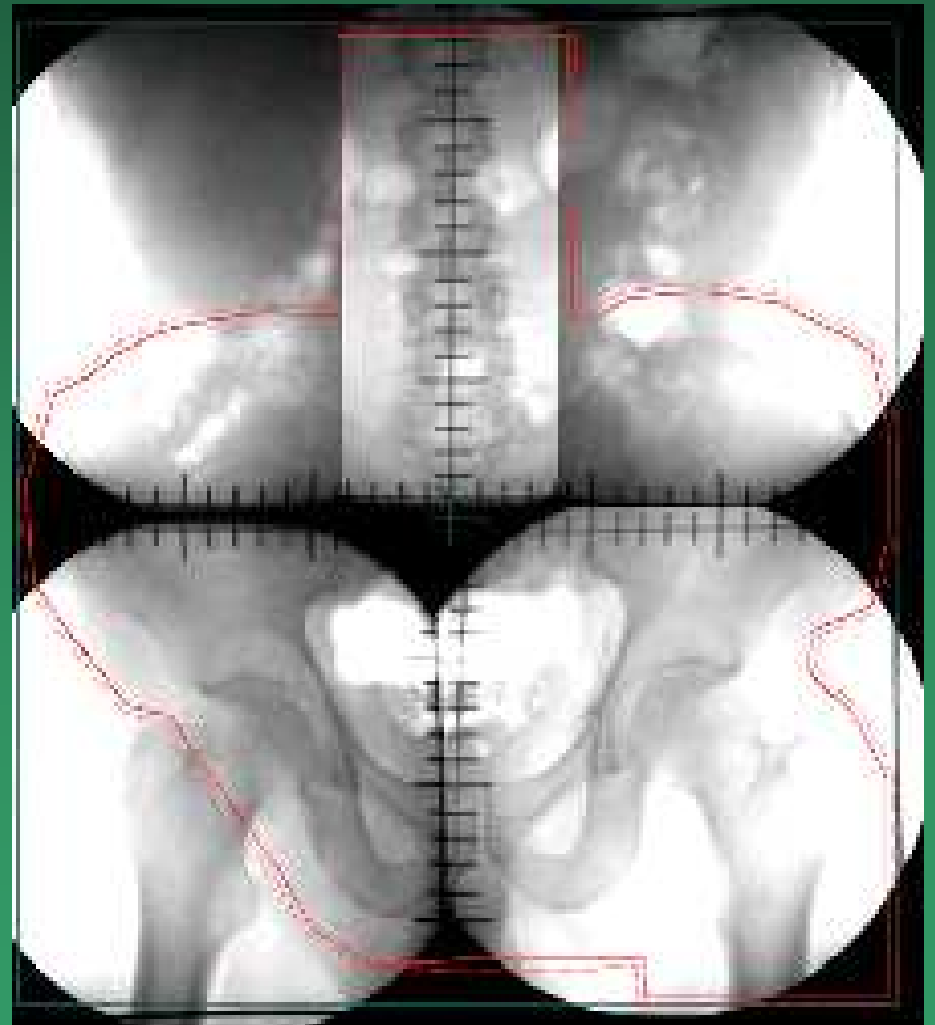
Abbreviations: CPR = complete pain relief; d = day(s); fr = fraction; HBI = half body irradiation; NR = not reported; ns = not significant; OPR = overall pain relief; QoL = quality of life; pts = patient(s); w = week(s).

## Cochrane Data base 2001

*HBI nelle lesioni ossee diffuse riduce il numero di nuovi siti algici*

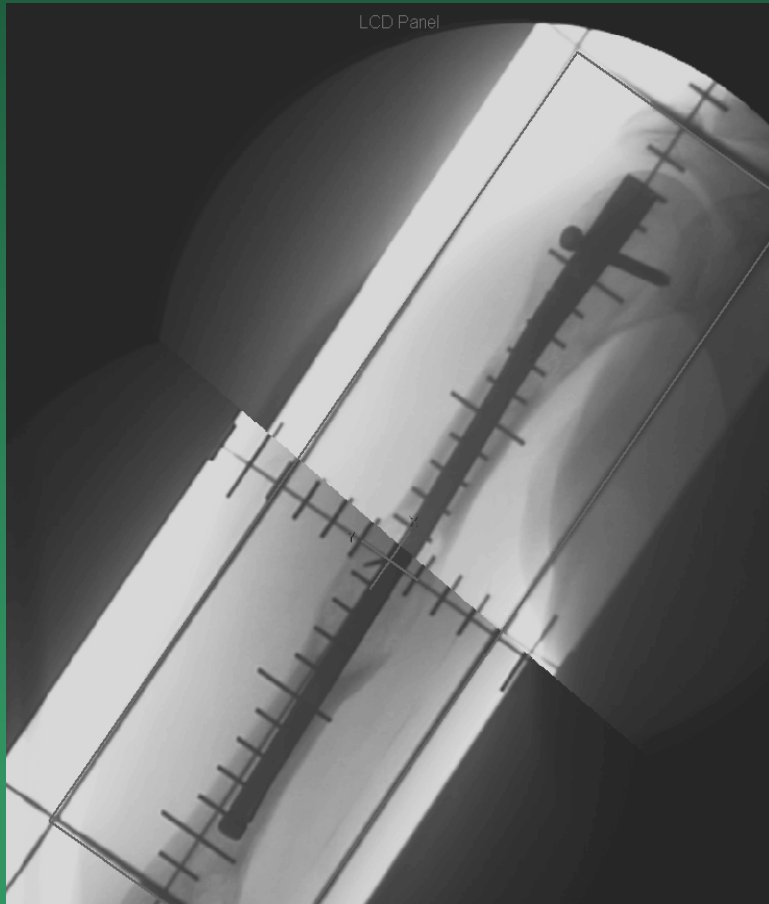
# Wide Field Radiation

pelvi ± rachide lombare ± femori

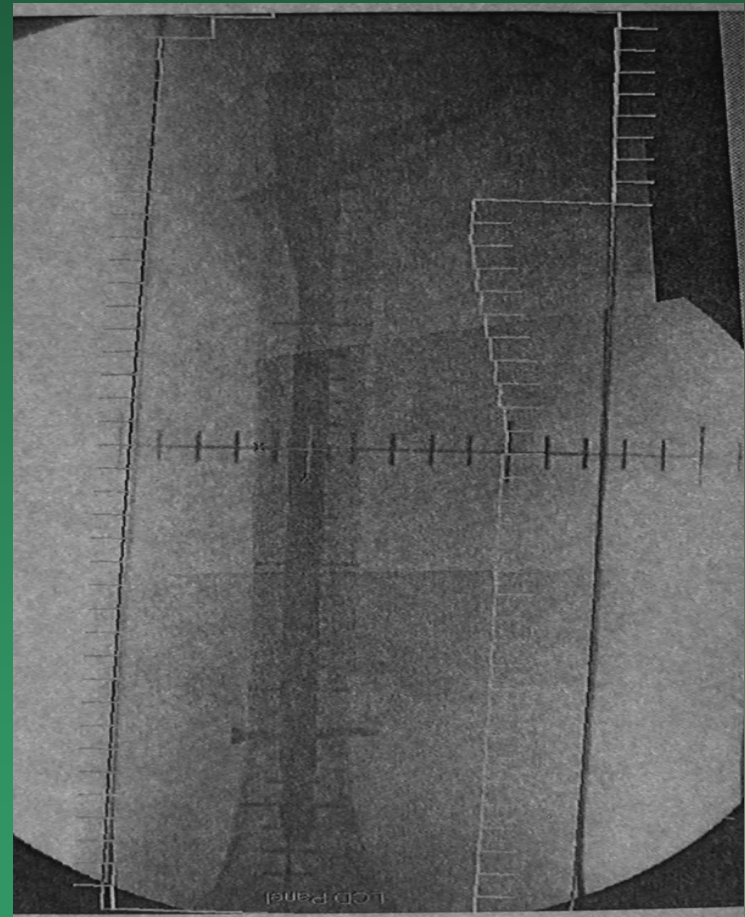


# RT post - chirurgia

**PTV = canale osseo + protesi**



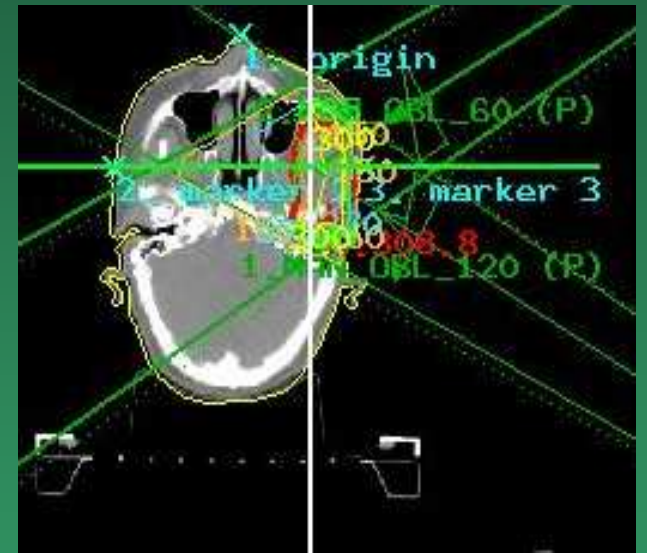
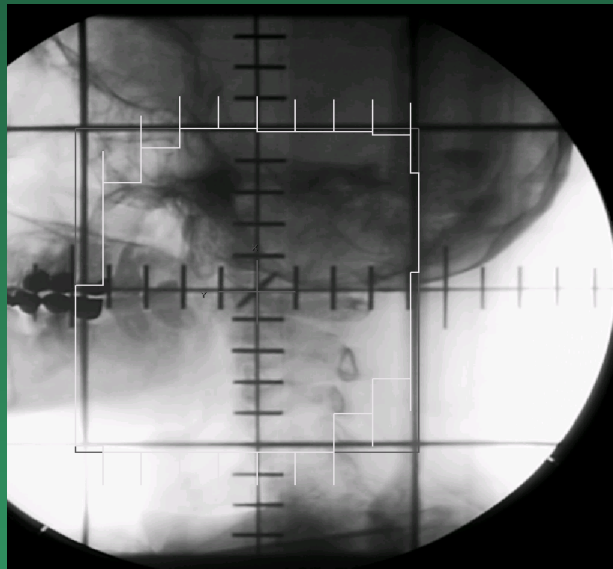
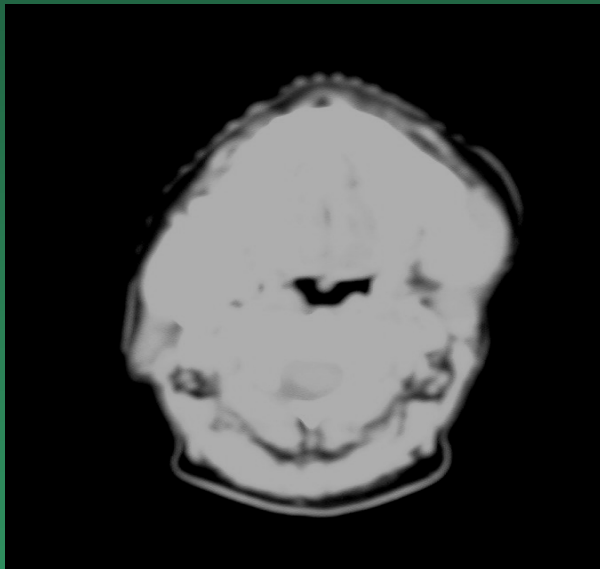
**omero**



**femore**

# RT 3D : sedi particolari

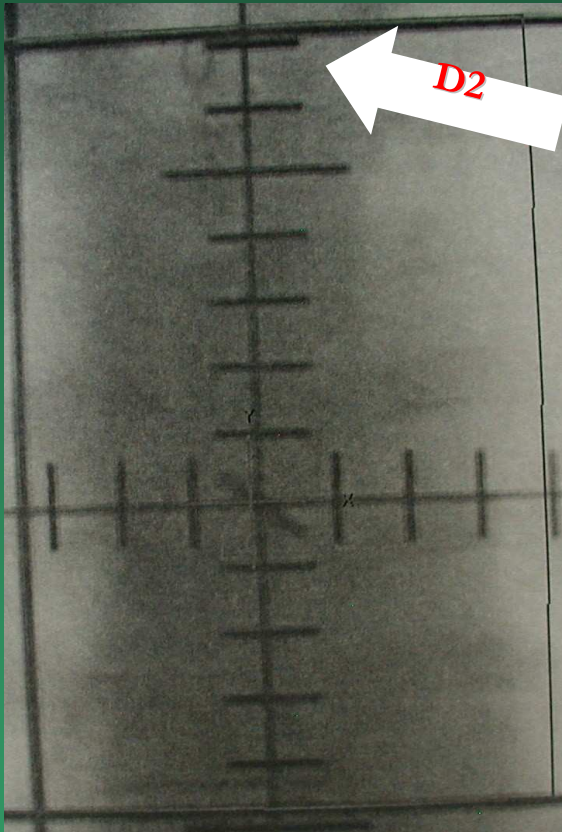
**PTV = lesione + margine in 3D**



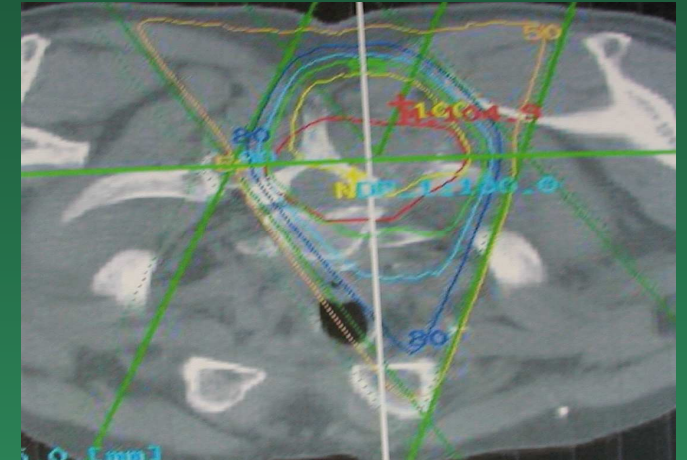
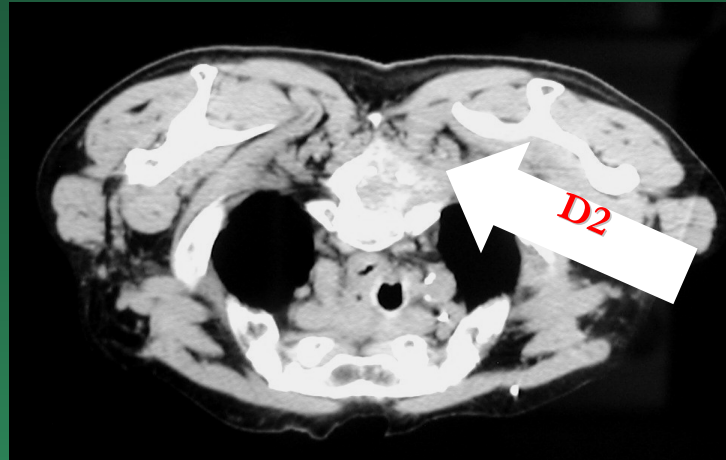
**Lesione mandibolare**

# RT 3D : ritrattamento

PTV = lesione + margine



s. mediastinica



compressione in D2



# E' cost-effective !!!

- n. pazienti trattati con RT palliativa
- media del n. campi di RT/pz
- durata media sopravvivenza
- valore di utility assegnata alla % di risposta
- costo /campo
- costo totale/totale n di mesi di risposta

Barton, 2003

Utility –adjusted cost x mese di RT palliativa

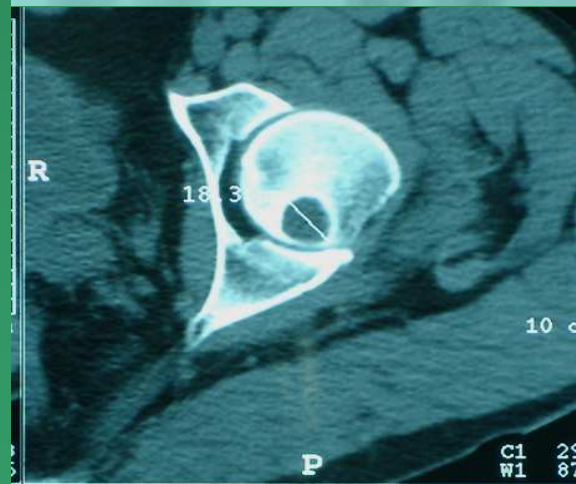
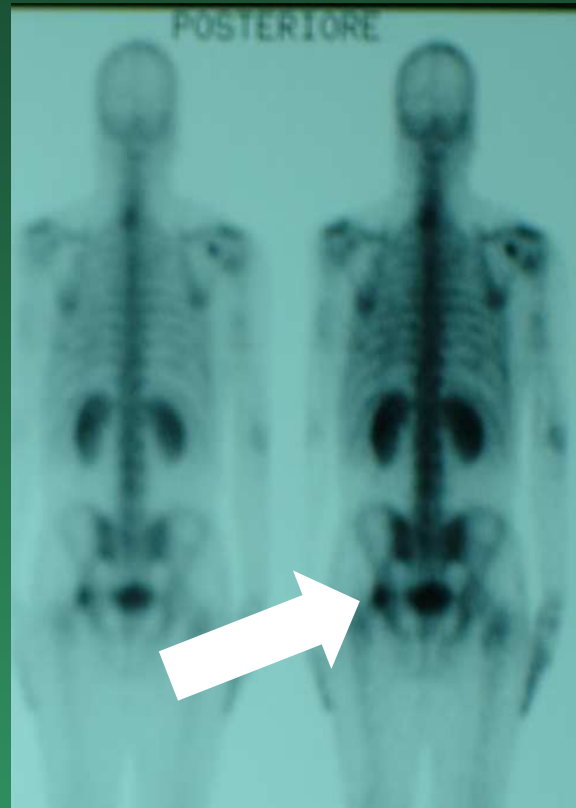
100 AUS \$ per mese

1200 AUS \$ per utility-adjusted life-anno

# Conclusioni

- pain relief
- stabilizzazione di lesioni a rischio di frattura
- fratture stabilizzate chirurgicamente
- volumi e tecniche personalizzate
- M1 oss a buona prognosi ( 3D o IMRT)
- è cost effective

# Attenzione !!!



Non sempre  
tutto ciò che  
capta e duole  
è una  
metastasi

*grazie*