Gestione del dolore nel paziente radioterapico. Ruolo della radioterapia nel paziente oncologico con dolore

Rosario Mazzola
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Radiol Oncol 2009; 43(4): 213-224. *doi:10.2478/v10019-009-0038-4*

review

Radiotherapy in palliative treatment of painful bone metastases

Andreja Gojkovič Horvat, Viljem Kovač, Primož Strojan

Department of Radiation Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Bone metastases are associated with considerable skeletal morbidity, including:

Severe bone pain

Spinal cord or nerve root compression

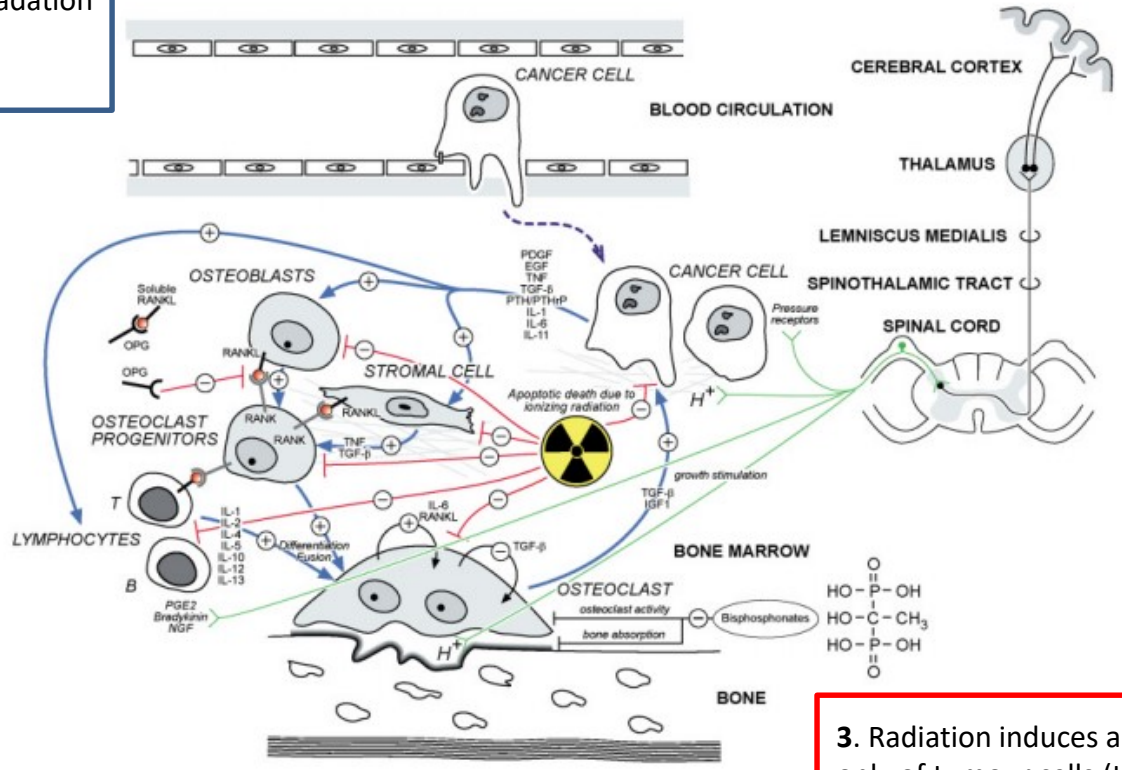
Pathological fractures

Hypercalcaemia

* In **bold** the clinical scenarios in which the role of Radiotherapy is well-known

Radiation Effects on bone metastases: Physiopathology

1. Firstly, tumor cells alter the physiological equilibrium between osteoclasts and osteoblasts, determining structural degradation of the bone **(blue arrows)**



2. Secondly tumor cells may directly invade nerve root or may increase expression of chemical mediators which stimulate nerve fibers **(in green)**

3. Radiation induces apoptotic death, not only of tumour cells (thereby reducing pressure) but also of all other cells in the cascade. Inhibitory effects of radiation are shown in **red lines**

Adapted from Mundy, 2002 and Mareel and Leroy, 2003

Int. J. Dev. Biol. 48: 599-606 (2004)

Pain control by ionizing radiation of bone metastasis

LUC A.M.-L. VAKAET* and TOM BOTERBERG

Department of Radiotherapy, Ghent University Hospital, Ghent, Belgium

Effects of irradiation on bone metastasis

1. EBRT produces ossification in 65-85% of lytic metastases in unfractured bone
2. The shrinkage of tumor bulk and osteobastic repair will restore the integrity of bone
3. Reduction by ionizing radiation of the inflammatory cells inhibits the release of chemical pain mediators and is probably responsible for the rapid reaction seen in some patients
4. Osteoclastic activity is decreased following high doses of RT

Figura 2 – La scala analgesica OMS a tre gradini nella sua formulazione originale

Figura 3 – Strategia terapeutica antalgica basata sulla scala analgesica a tre gradini dell'OMS

The control of bone pain usually begins with analgesics used in a 3-step approach:

1. NON-OPIOID ANALGESICS (**the first step - for mild to moderate pain**)
2. WEAK OPIOIDES (**the second step - persistence or increase in pain when using non-opioid analgesics)**
3. CHANGING TO HIGHER DOSES OR MORE POTENT OPIOIDS (**the third step - if the pain persists or becomes more severe**)

Severe bone pain

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review

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- ❑ To control pain in opioids poor-responsive
- ❑ To limit the dose of opioids and their side effects (constipation, nausea…)
- ❑ To prevent SRE in high-risk bone metastases

Impact of Radiotherapy on pain relief

- ".. In **up to 70% to 80%** of patients, significant pain relief can be achieved. This pain relief results in both an improved quality of life and a **significant reduction of pain medication**.."

- Complete Response in 30-50% of cases (**oppioids interruption**)

Seminars in Oncology, Vol 38, No 3, pp 443-449, June 2011

Palliative Radiotherapy—New Approaches

Birgitt van Oorschot,[a] Dirk Rades,[b] Wolfgang Schulze,[c] Gabriele Beckmann,[d] and Petra Feyer[e]

- "Pain flare" can occur after Radiotherapy, in 2–40% of patients
- It is defined as a temporary increase of bone pain at the treated site during radiation therapy or early after its cessation
- Biochemical mediators of inflammation, which are released upon the radiation therapy or transient oedema compressing nerves at the site of treatment, are suggested to contribute to this toxicity

Seminars in Oncology, Vol 38, No 3, pp 443-449, June 2011

Severe bone pain

Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial

Edward Chow, Ralph M Meyer, Keyue Ding, Abdenour Nabid, Pierre Chabot, Philip Wong, Shahida Ahmed, Joda Kuk, A Rashid Dar, Aamer Mahmud, Alysa Fairchild, Carolyn F Wilson, Jackson S Y Wu, Kristopher Dennis, Michael Brundage, Carlo DeAngelis, Rebecca K S Wong

Summary

Background Pain flare occurs after palliative radiotherapy, and dexamethasone has shown potential for prevention of such flare. We aimed to compare the efficacy of dexamethasone with that of placebo in terms of reduction of incidence of pain flare.

Lancet Oncol 2015

Published Online
October 18, 2015
http://dx.doi.org/10.1016/

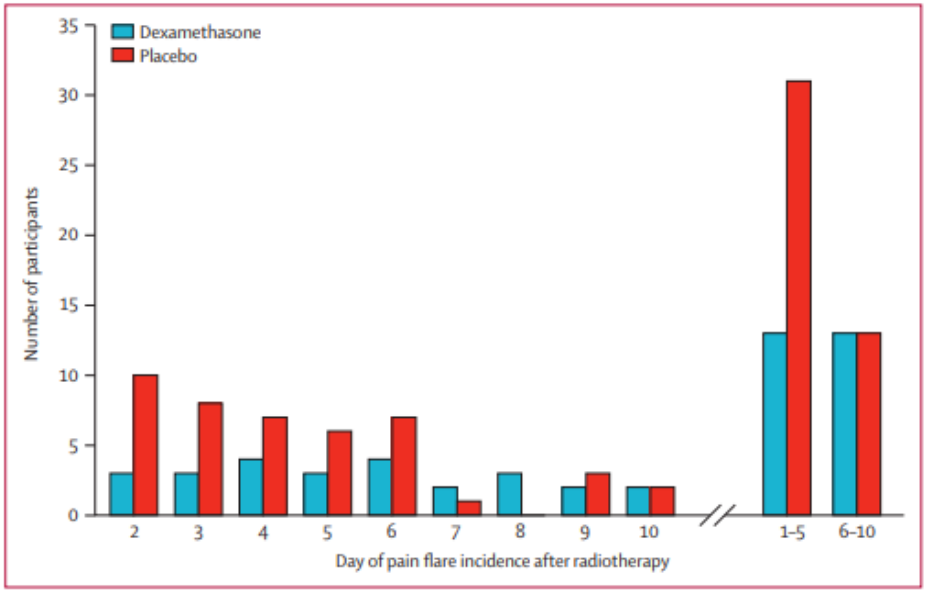

Figure 2: **Daily pain flare incidence**
For the 70 patients who experienced pain flare in the sensitivity analysis. No pain flare occurred in either group on days 0–1.

Two 4 mg dexamethasone tablets or two placebo tablets taken orally at least 1 h before the start of radiation treatment (a single 8 Gy dose to bone metastases; day 0) and then every day for 4 days after radiotherapy (days 1–4)

Severe bone pain

RT-SCHEDULING: Single Versus Multiple fractions?

Tabella.2 Randomized Trials of Single versus Multiple Fractions: Results

Study	N° of Pz (N° Eval.)	Dose (Gy/fractons)	Median Survival (mo)	Complete Response	Overall Response	Retreat Rate (%)	Path Fractures(%)	Toxicity
Gaze et al., 1997 UK (9)	265	10/1 vs 22.5/5	NA	37 47	81 76	NA	NA	21% p=NS 26% emesis
Nielsen et al., 1998, Denmark (10)	241 (239)	8/1 vs 20/5	NA	15 15	73 76	21 12	NA	No difference
Steenland et al., 1999, Netherlands (11)	1171 (1073)	8/1 vs 20/5	7	37 33	72 69	25 7	4 2	No difference
Bone Pain Working Party, 1999, UK/New Zeland (12)	765(681)	8/1 vs 20/5	NA	57 58	78 78	23 10	2 <1	No difference
Koswing & Budach, 1999, Germany (18)	107	8/1 vs 30/10	NA	33 31	81 78	NA	NA	NA
Kirkbride et al, 2000, Canada (19)	398 (287)	8/1 vs 20/5	NA	22 29	51 48	NA	NA	NA
Hartsell et al.,2005 USA/Canada (13)	949 (898)	8/1 vs 30/10	9.1 9.3	15 18	65 66	18 9	5 4	10% G 2-4 17% p=.002
Kaasa et al.,2006 Norway/Sweden (14)	376	8/1 vs 30/10	9.6 7.9	NA	No difference	16 4	4 11	NA
Arnalot et al., 2008 Spain (68)	160	8/1 vs 30/10	NA	13 11	75 86	28 2	NA	No difference
Kaasa et al., 2009 Norway/Sweden (69)	(198)180	8/1 vs 30/10	NA	NA	NA	27 9	4 5	NA

NA, not available
NS, not statistically significant.

IRCCS Sacro Cuore Don Calabria
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Negrar - Verona

Severe bone pain

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Update of the systematic review of palliative radiation therapy fractionation for bone metastases

Shayna E. Rich [a], Ronald Chow [b], Srinivas Raman [b], K. Liang Zeng [b], Stephen Lutz [c], Henry Lam [b], Maurício F. Silva [d], Edward Chow [b,*]

[a] Haven Hospice, Gainesville, OH, USA; [b] Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Canada; [c] Blanchard Valley Regional Cancer Center, Findlay, USA; [d] Radiation Oncology Unit at Santa Maria Federal University, Santa Maria, Brazil

1. **OVERALL RESPONSE RATE:** similar in patients for single fraction treatments (61%) and those for multiple fraction treatments (62%)
2. **COMPLETE RESPONSE RATE:** nearly identical in both groups (23% vs 24%, respectively)
3. **RE-TREATMENT:** significantly more frequent in the single fraction treatment arm, with 20% receiving additional treatment to the same site versus 8% in the multiple fraction treatment arm ($p < 0.01$)
4. No significant difference was seen in the risk of pathological fracture at the treatment site, rate of spinal cord compression at the index site, or in the rate of acute toxicity

Symptomatic RT:
Clinical Predictive factor of pain relief

- ❑ "Pain relief" within 2-4 weeks after Radiotherapy
- ❑ Mean duration of remission is approximately 19 weeks
- ❑ Patients with breast cancer or prostate cancer have higher response rates, as well as duration of remission, than patients with lung cancer or other primary tumors
- ❑ Beyond 6 weeks: Poor-Responsive patients

Seminars in Oncology, Vol 38, No 3, pp 443-449, June 2011

Severe bone pain

Symptomatic RT in multiple painful bone metastases.

Hemibody Irradiation (HBI)

- The upper, middle or, lower half of the skeleton may be irradiated
- Delivering 6–8 Gy in single fraction results in pain response in 70% of patients after 24–48 h
- The intensity of pain is reduced significantly, from 8 to 1, according to the visual-analogue scale, and there is a decrease in morphine consumption
- It is a very convenient treatment type for advanced cancer patients since it involves a short hospital stay and acceptable side effects

Cancers (Basel). 2019 Mar 19;11(3)

Symptomatic RT in oligometastatic painful bone metastases

Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Spinal metastases: Is stereotactic body radiation therapy supported by evidences?

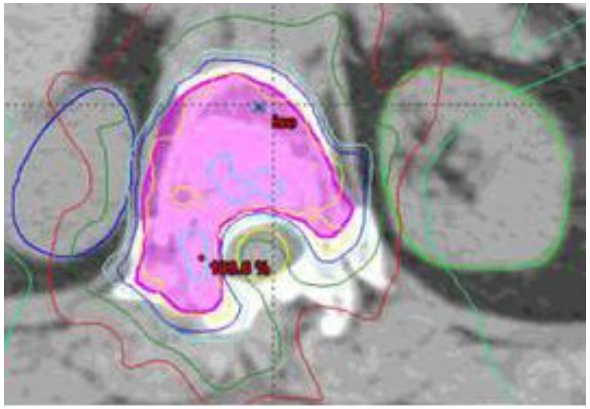
Berardino De Bari[a,*], Filippo Alongi[b], Gianluca Mortellaro[c], Rosario Mazzola[b,c], Schiappacasse Luis[a], Guckenberger Matthias[d]

[a] Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[b] Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, Negrar-Verona, Italy
[c] Radiation Oncology Department, University of Palermo, Palermo,Italy
[d] Department for Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

A B S T R A C T

Stereotactic body radiotherapy (SBRT) is becoming widely adopted in the treatment of primary and secondary tumors. Spinal bone metastases are frequently discovered in cancer patients, and in the past have been usually treated with a palliative goal. Nevertheless, in some particular clinical settings, such as oligometastatic patients and/or those with a long life expectancy, spinal SBRT could be considered a valid therapeutic option to obtain long-lasting palliation and, when possible, with a curative goal.

This review aims to summarize available clinical and dosimetric data of published studies about spinal SBRT.

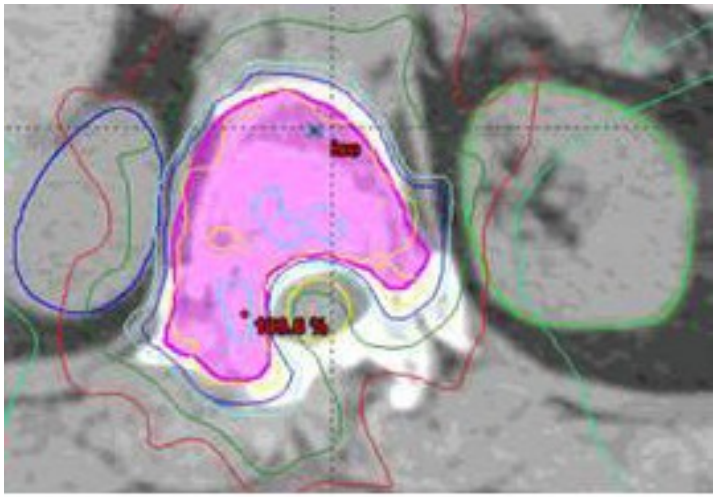


•***Spinal radiosurgery*** has been proven to be an option in the treatment of spinal metastases in properly selected patients, even though only retrospective and phase I–II studies are available.

•**Local control** based on imaging and/or **pain control** is achieved in **80%** of presentations.

•SBRT can also be safely applied in the pre-operative setting, with the intent of reducing the extent of surgery (which can be limited to epidural decompression and fixation).

Sahgal et al J of Neursurg Spine, 2011.



Severe bone pain

Original article

Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy

Tanja Sprave [a,c], Vivek Verma [b], Robert Förster [a,c,d], Ingmar Schlampp [a,c], Thomas Bruckner [e], Tilman Bostel [a], Stefan Ezechiel Welte [a], Eric Tonndorf-Martini [a], Nils Henrik Nicolay [a,c,f], Jürgen Debus [a,c], Harald Rief [a,c,*]

[a] University Hospital of Heidelberg, Department of Radiation Oncology, Germany; [b] Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, USA; [c] Heidelberg Institute of Radiation Oncology (HIRO), Germany; [d] University Hospital Zurich, Department of Radiation Oncology, Switzerland; [e] University Hospital of Heidelberg, Department of Medical Biometry; and [f] Heidelberg Institute of Radiation Oncology (HIRO), German Cancer Research Center (DKFZ), Germany

ARTICLE INFO

Article history:
Received 21 March 2018
Received in revised form 22 April 2018
Accepted 23 April 2018
Available online xxxx

Keywords:
Bone metastases
Spine
SBRT
IMRT
Palliative radiotherapy

ABSTRACT

Background: To report the primary endpoint of a randomized trial comparing pain response following palliative stereotactic body radiation therapy (SBRT) versus conventionally-fractionated 3D-conformal radiotherapy (3DCRT) for previously untreated spinal metastases.

Methods: Fifty-five patients with histologically/radiologically confirmed painful spinal metastases were analyzed in this single-institutional, non-blinded, randomized explorative trial. Participants were randomly assigned (1:1) to receive single-fraction SBRT (24 Gy) or 3DCRT (30 Gy in 10 fractions). The primary endpoint was pain relief of >2 points on the visual analog scale (VAS) measured within the irradiated region at 3 months following radiotherapy completion. Other recorded parameters included pain response (per International Bone Consensus response definitions), use of concurrent medications and opioid usage (oral morphine equivalent dose, OMED). All parameters were assessed at baseline and at three and six months after RT. Intention-to-treat analysis was applied. This trial is registered with ClinicalTrials.gov, number NCT02358720.

Findings: Despite no significant differences for VAS at 3 months between groups ($p = 0.13$), pain values decreased faster within this time period in the SBRT arm ($p = 0.01$). At 6 months following RT, significantly lower VAS values were reported in the SBRT group ($p = 0.002$). There were no differences in OMED consumption at 3 ($p = 0.761$) and 6 months ($p = 0.174$). There was a trend toward improved pain response in the SBRT arm at 3 months ($p = 0.057$), but significantly so after 6 months ($p = 0.003$). No patient in the SBRT group experienced grade ≥3 toxicities according to the Common Terminology Criteria for Adverse Events v.4.03.

Conclusions: This randomized trial demonstrates the utility of palliative SBRT for spinal metastases, which was associated with a quicker and improved pain response. Larger ongoing randomized studies will assist in further addressing these endpoints.

Spinal cord or nerve root compression

Radiol Oncol 2009; 43(4): 213-224. *doi:10.2478/v10019-009-0038-4*

review

Radiotherapy in palliative treatment of painful bone metastases

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Bone metastases are associated with considerable skeletal morbidity, including:

Severe bone pain

Spinal cord or nerve root compression

Pathological fractures

Hypercalcaemia

* In **bold** the clinical scenarios in which the role of Radiotherapy is well-known

Spinal cord or nerve root compression

ROLE of Radiotherapy

Indication for surgery of MSCC is usually limited to:

- Patients with a good performance status
- Survival prognosis of more than 3 months
- Involvement of only one spinal segment

These clinical scenarios are represented for only about 10% of all MSCC patients

Radiotherapy alone remains still an important treatment option for MSCC

Spinal cord or nerve root compression

OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical efficacy of percutaneous vertebroplasty combined with intensity-modulated radiotherapy for spinal metastases in patients with NSCLC

Percutaneous vertebroplasty (PVP) can also be performed as a complement to RT to provide immediate vertebral stabilization

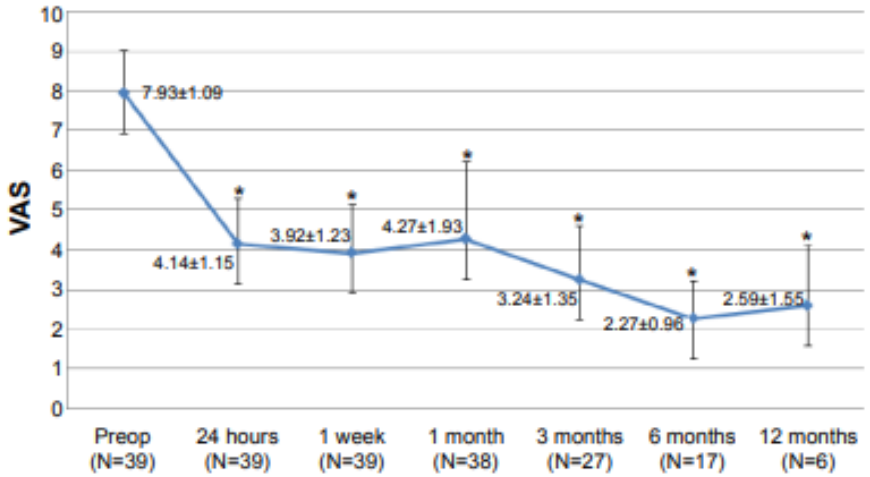

Figure 3 Visual analog scale (VAS) change of patients of at each pre- and postoperative follow-up time.
Notes: Data are expressed as mean ± standard deviation. The differences between the VAS scores prior to VP and at 1 day, 1 week, and 1, 3, 6, and 12 months, respectively, are statistically significant ($P<0.05$). *$P<0.05$ in comparison to preoperative.
Abbreviations: Preop, preoperative; VP, vertebroplasty; N, number of follow-up patients.

Spinal cord or nerve root compression

Radiotherapy alone remains still an important treatment option for MSCC…
…Association with High doses of Steroids

Table 1 – Administration of dexamethasone

Reference	Patients (*n*)	Study design	Dexamethasone dose	Results	Serious adverse effects
[22]	57	Randomised	96 mg/4 days vs no steroids	Ambulatory 81% vs 63% ($P = 0.046$)	11% vs 0% (psychoses, ulcers)
[23]	37	Randomised	100 mg + 16 mg/day vs 10 mg + 16 mg/day	Improvement 25% vs 8% ($P = 0.22$)	Not stated
[24]	66	Case–control study	96 mg/4 days vs 10 mg + 16 mg/day	Not stated	14% vs 0% (ulcers, bleeding, perforation)

Agarawal et al Clin Oncol 2006

Moderate-dose dexamethasone (16-32 mg/day) is proven to be effective and safe

Short-course vs Long-course RT: Metastatic Spinal Cord Compression (MSCC)

Table 3 – Functional outcome at 1 month after radiotherapy related to different primary tumours [34–38]

	Improvement (*n* (%))	No change (*n* (%))	Deterioration (*n* (%))	*P*
Breast cancer ($n = 335$)				
Short-course radiotherapy	44 (34)	74 (57)	12 (9)	
Long-course radiotherapy	61 (30)	118 (58)	26 (12)	0.81
Prostate cancer ($n = 281$)				
Short-course radiotherapy	52 (34)	78 (50)	25 (16)	
Long-course radiotherapy	40 (32)	72 (57)	14 (11)	0.83
Non-small cell lung cancer ($n = 252$)				
Short-course radiotherapy	16 (15)	58 (55)	31 (30)	
Long-course radiotherapy	19 (13)	78 (53)	50 (34)	0.87
Myeloma ($n = 172$)				
Short-course radiotherapy	24 (39)	35 (58)	2 (3)	
Long-course radiotherapy	66 (59)	43 (39)	2 (2)	0.10
Renal cell carcinoma ($n = 87$)				
Short-course radiotherapy	10 (27)	24 (65)	3 (8)	
Long-course radiotherapy	15 (30)	28 (56)	7 (14)	0.91

- **Short- (1 x 8Gy) and long-course radiotherapy (5 x 4Gy)** resulted in **comparable functional outcome** in breast cancer, prostate cancer, lung cancer and renal cell carcinoma patients

- In **Myeloma Patients**, **long-course radiotherapy** seems to be associated with a **better functional outcome** than short-course radiotherapy at 6 months (67% vs 43% improvement of motor function, P 0.043) and at 12 months (76% vs 40%, P 0.003)

Rades et al J Urol 2006
Rades et al Eur Urol 2006
Rades et al IJROBP 2006

Pathological fractures

Radiol Oncol 2009; 43(4): 213-224. *doi:10.2478/v10019-009-0038-4*

review

Radiotherapy in palliative treatment of painful bone metastases

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Bone metastases are associated with considerable skeletal morbidity, including:

Severe bone pain

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Pathological fractures

Hypercalcaemia

* In **bold** the clinical scenarios in which the role of Radiotherapy is well-known

Short-course vs Long-course RT: Pathological Fractures

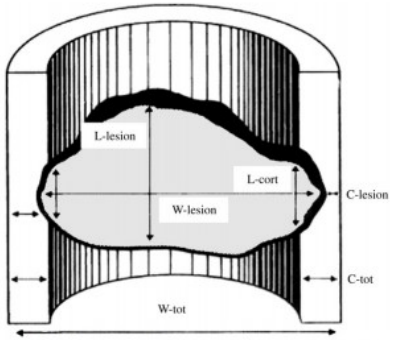


Fig. 1 — Measurements of metastatic lesions in the femur. (reproduced from ref 41, with permission)

Table 5 — Sensitivity, specificity and predictive values of risk factors for impending fracturing in femoral metastases in patients treated within the Dutch Bone Metastasis Study

	Fracture no ($n = 96$)	Fracture yes ($n = 14$)	P value*	SE (%)	SP (%)	PPV (%)	NPV (%)
Axial cortical involvement							
≤30 mm	56	2	0.01	86	58	23	97
>30 mm	40	12					
Circumferential cortical involvement							
≤50%	79	8	0.03	43	82	26	91
>50%	17	6					
Scoring system of Mirels†							
Score 6–8	12	0	0.36	100	13	14	100
Score 9–12	84	14					

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value. *Univariate analysis, using a Cox proportional hazards model. †To differentiate between high- and low-risk lesions a cut-off point between 8 and 9 was chosen as proposed by Mirels [61].

Agarawal et al Clin Oncol 2006

- An axial cortical involvement of 30 mm or more will give a 25% chance of fracturing
- Radiotherapy is usually given afterwards to induce remineralisation of the fractured bone and to stabilise the osteosynthetic prosthesis (e.g. 24 Gy/6 fractions or 30 Gy/10 fractions)
- If the patient is inoperable because of co-morbidity, deteriorating condition, or because the fracture is too complicated, palliative radiotherapy may reduce pain and enable healing in a considerable percentage of patients (e.g. 1-2 x 8 Gy or 5 x 4 Gy)

METASTASI OSSEE Litiche:
Combinazione con farmaci?

ne disease-

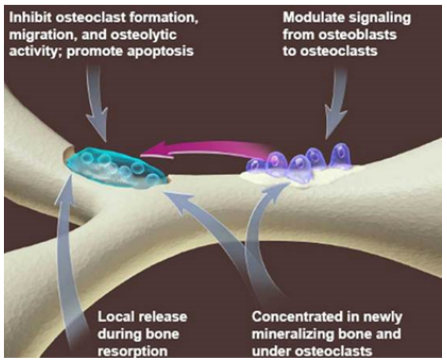
METASTASI OSSEE:
RAZIONALE DELLA COMBINAZIONE

- L'interazione tra radioterapia e bifosfonati, si esplicherebbe attraverso un effetto additivo/ super-additivo e di cooperazione spaziale

✓ ***L'effetto additivo/superadditivo*** *è dovuto all'azione non selettiva RT con danno sulle cellule tumorali e osteoclastiche a livello loco-regionale, a cui si aggiunge l'azione "selettiva" sull'attività degli osteoclasti espletata dai bifosfonati, con conseguente inibizione del riassorbimento osseo, stimolazione del processo di ricalcificazione e controllo del dolore.*

✓ **Cooperazione spaziale:** RT Locale, bifosfonati sistemici

✓ Studi in vitro hanno inoltre dimostrato *un'azione antitumorale (non chiara)* ***di tipo sinergico*** *e non semplicemente additiva della radioterapia e dell'acido zoledronico su cellule di carcinoma mammario,* prostatico e su cellule di mieloma(*radiosensibilizzazione tramite disattivazione di RAS?)*



METASTASI OSSEE:
RAZIONALE DELLA COMBINAZIONE

LINEE GUIDA TRATTAMENTO DELLE METASTASI OSSEE

In generale la radioterapia non determina tossicità severe e, inoltre, gli effetti collaterali dei bifosfonati, rappresentati da astenia, mialgie, febbre e disturbi gastroenterici, sono in genere di lieve entità, che non si sovrappongono a quelli della radioterapia stessa.

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Allo stato attuale delle conoscenze, la combinazione di radioterapia e bisfosfonati in pazienti con metastasi ossee sembra prolungare la sopravvivenza libera da eventi scheletrici e la durata della risposta al dolore rispetto alla sola radioterapia.	**Positiva debole**

TAKE HOME MESSAGES

- Radiotherapy allowed to obtain high-rate of pain relief
- To control Pain Flare administer Two 4 mg dexamethasone tablets
- Overall response rates are similar in patients for single fraction treatments and those for multiple fraction treatments
- Short- (1 x 8Gy) and long-course radiotherapy (5 x 4Gy) resulted in comparable functional outcome in MSCC
- Combining RT – Bifosfonates in lytic bone mts seems to prolong the SRE-free survival