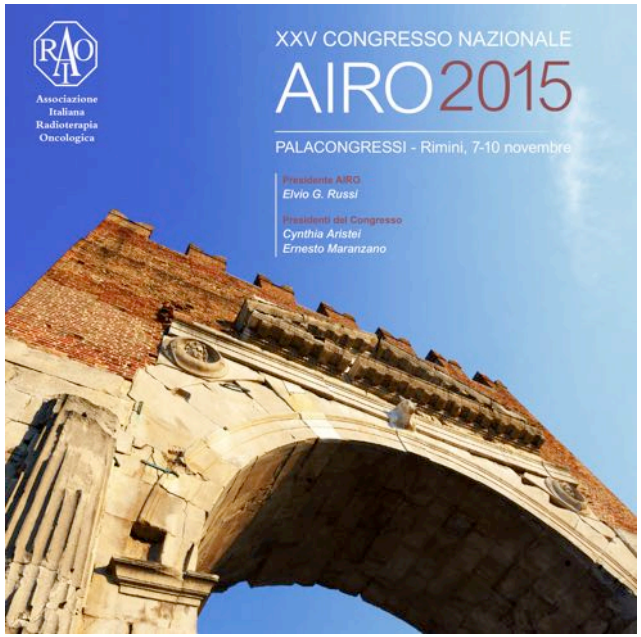
DICHIARAZIONE

Relatore: Dr. F. Trippa

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro



SIMPOSIO AIRO-AINM

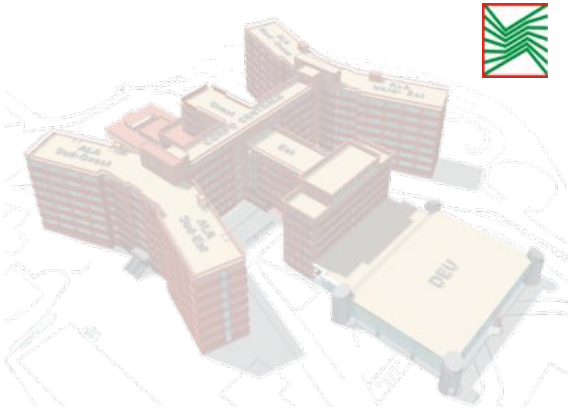
Trattamento delle metastasi ossee nel paziente con tumore della prostata resistente alla castrazione

La radioterapia esterna nelle metastasi ossee complicate

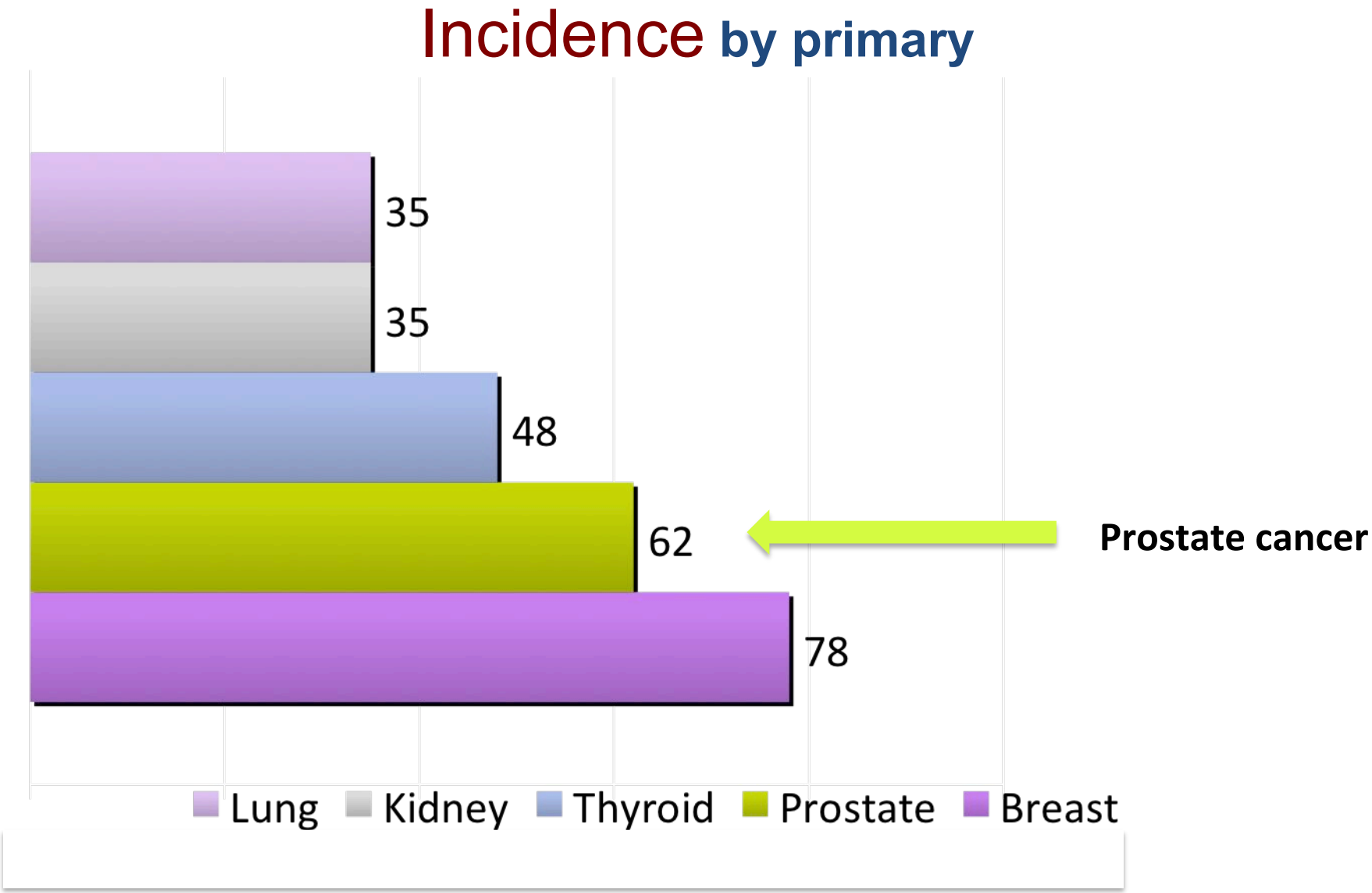
Fabio Trippa

S.C. DI RADIOTERAPIA ONCOLOGICA

AZIENDA OSPEDALIERA "S.MARIA" - TERNI



Bone metastases



Coleman RE. Clin Cancer Res 2006

Prognostic factors in patients with hormone-refractory metastatic prostate cancer

The **BONE SCAN INDEX (BSI)**
is a **quantitative expression of tumor burden** seen on bone scintigraphy.

Bone Scan Index	Median survival (months)
<1.4%	18.3
1.4-5%	15.5
>5%	8.1

Kalderstam et al. BMC Med Imaging 2014
Anand et al. J Nucl Med 2015

Results of pain relief with RT on uncomplicated bone metastases

- After first time RT only **60-70%** of patients with bone metastases obtain a pain relief.
- Only **one-third** of responders achieve a complete response.
- Approximately **50%** of initial responders show pain relapse **within 1 year** after first RT.

Lutz S, ASTRO evidence–based guidelines. Int J Radiat Oncol Biol Phys 2011;79:965-976

Clinical Oncology

Volume 24, Issue 2, March 2012, Pages 112–124

2012

Update on the Systematic Review of Palliative Radiotherapy Trials for Bone Metastases

E. Chow[I], L. Zeng[I], N. Salvo[I], K. Dennis[I], M. Tsao[I], S. Lutz[†]

8 Gy single fraction as effective as multifraction RT

- **25** randomized trials
- **5617** patients
- Overall response rate:
  - **60%** (1696/2818) in single fraction arms
  - **61%** (1711/2799) in multiple fraction arms
- Complete response rate:
  - **23%** (620/2641) in single fraction arms
  - **24%** (634/2622) in multiple fraction arms

Complicated bone metastases

*In about **50-70%** of patients, bone mets produce signs and symptoms, such **skeletal** or **neuropathic pain**, **pathological fractures**, **nerve-root damage** and/or **spinal cord compression***

- Worsening quality of life
- Decrease of survival

Falkmer et al. Acta Oncologica 2003; 42(6):620-633

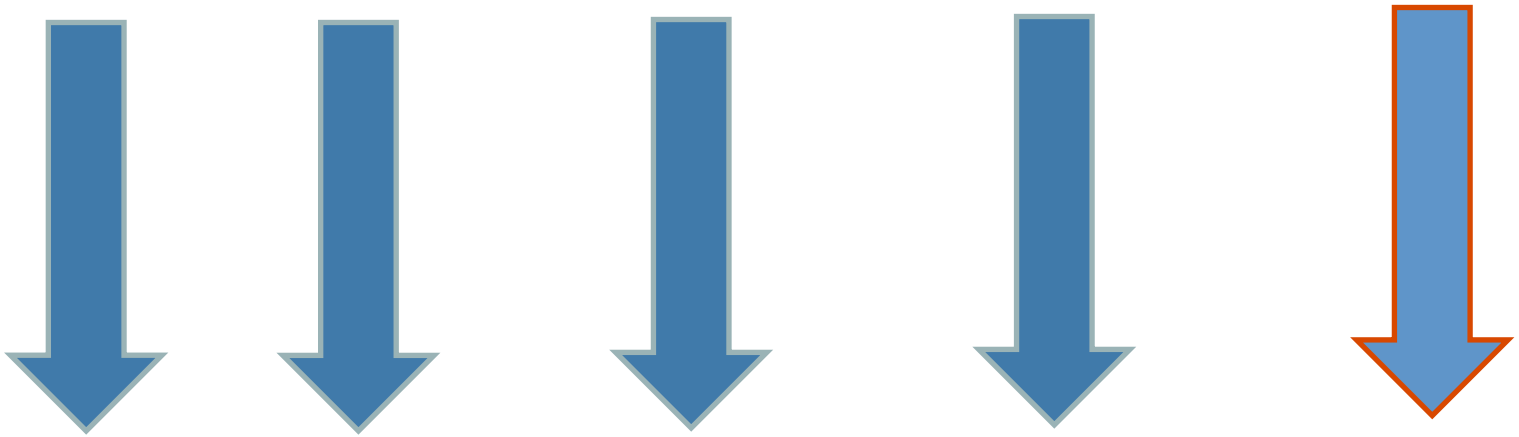
Complicated bone metastases

- **associated pathologic fracture or high fracture risk**
- **soft tissue or extraosseous component penetrating the normal cortical boundary**
- **neuropathic pain**
- **associated spinal cord/cauda equina compression**

Complicated bone metastases

- **associated pathologic fracture or high fracture risk**
- **soft tissue or extraosseous component penetrating the normal cortical boundary**
- **neuropathic pain**
- **associated spinal cord/cauda equina compression**

PATHOLOGICAL FRACTURE can have consequence on



Clinic **Social status** **Economic status** **QoL** **Prognosis**

Impact on survival:
Fractures negatively affect survival

Pathologic fractures correlate with a significantly increased relative risk of death

• Breast cancer	1.52 (1.28-1.81) p< 0.0001
• Multiple myeloma	1.44 (1.06-1.95) p= 0.02
• Prostate cancer	1.29 (1.01-1.65) p= 0.04
• Lung cancer	1.08 (0.87-1.34) p= 0.49

Hei Y et al. 28° Annual SABSC 2005
Saad F et al. ECCO 2005

Bone metastases

Incidence by site & primary

	Breast	Lung	Prostate
Theca	28%	16%	14%
Ribs	59%	65%	50%
Spine	60%	65%	60%
Limbs	32%	27%	38%
Pelvis	38%	25%	57%

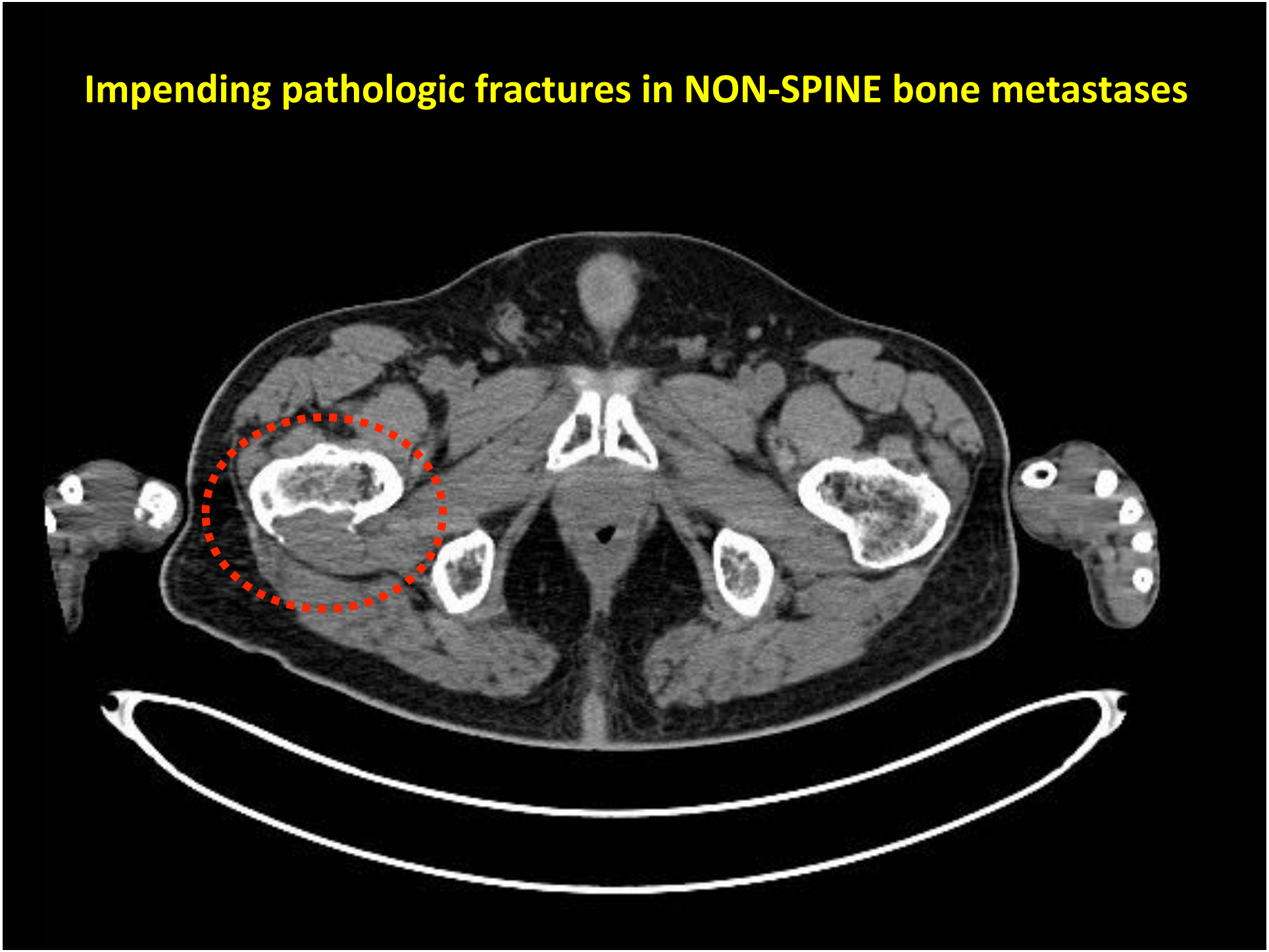
Impending pathologic fractures in NON-SPINE bone metastases

Risk criteria

- Both lytic and blastic long bone metastases >50% of the circumferential cortical bone;
- pain with weight-bearing stresses persists, increases, or recurs despite adequate local irradiation;
- lesions of the proximal femur > 2.5 cm in any dimension or
- if they are associated with avulsion of the lesser trochanter.

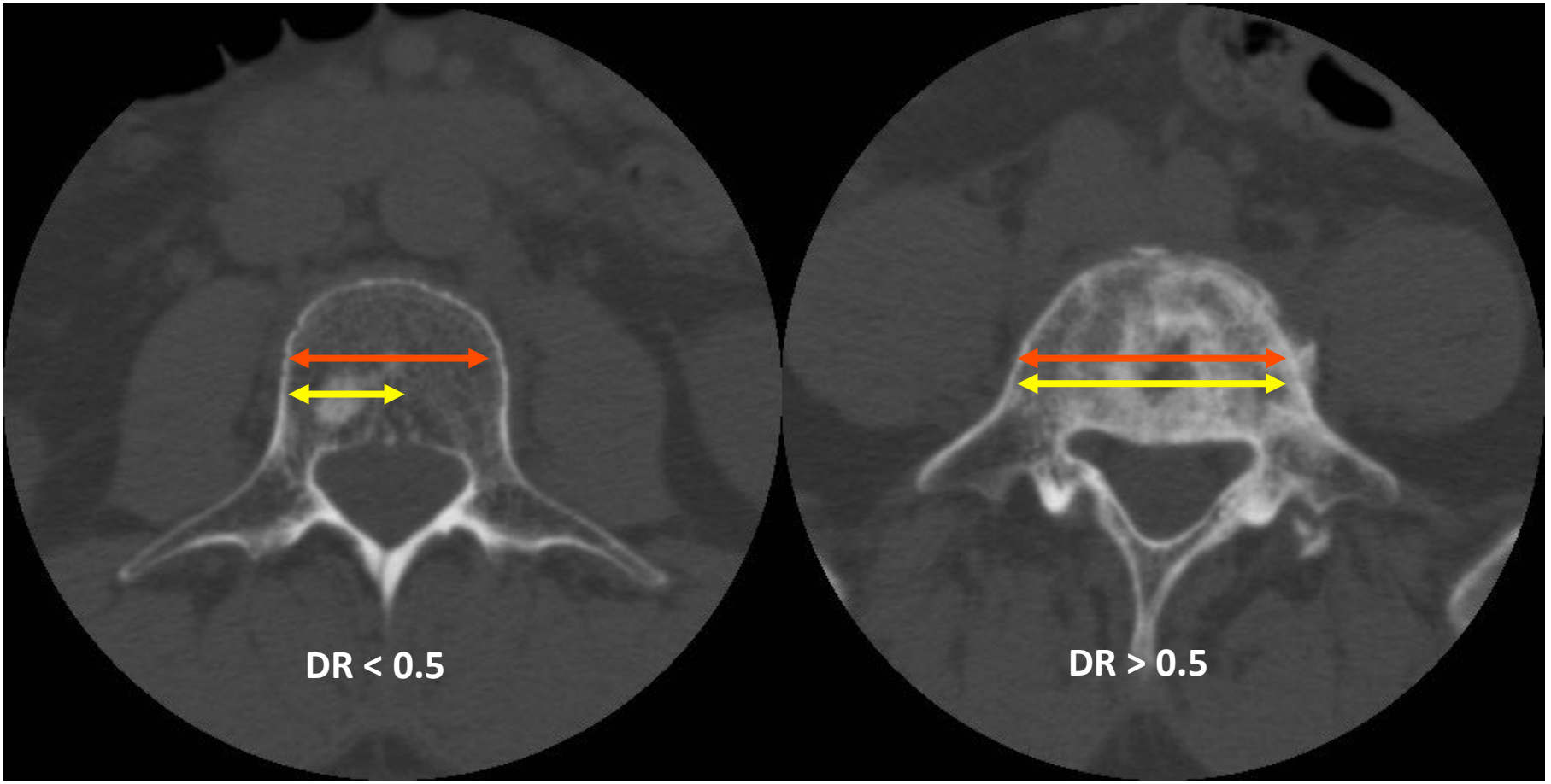
Hurrington KD. Instr Course Lect. 1986;35:357-81

Impending pathologic fractures in NON-SPINE bone metastases



Impending pathologic fractures in SPINE bone metastases

Defect Ratio -DR



- DR= Ø max of lesion (lytic or blastic) / Ø max of vertebral body
- DR ≥ 0.5 → high risk of patological fracture

Ebihara et al Spine 2004;29(9):994-999

SPINAL INSTABILITY NEOPLASTIC SCORE (SINS)

JOURNAL OF CLINICAL ONCOLOGY

Fourney et al 2011;29(22):3072-3077

Score:

0-6 ***stable***

7-12 ***potentially unstable***

13-18 ***unstable***

Spine Location

Pain

Type of bone lesion

Rx alignment

Body collapse

Posterolateral body involvement

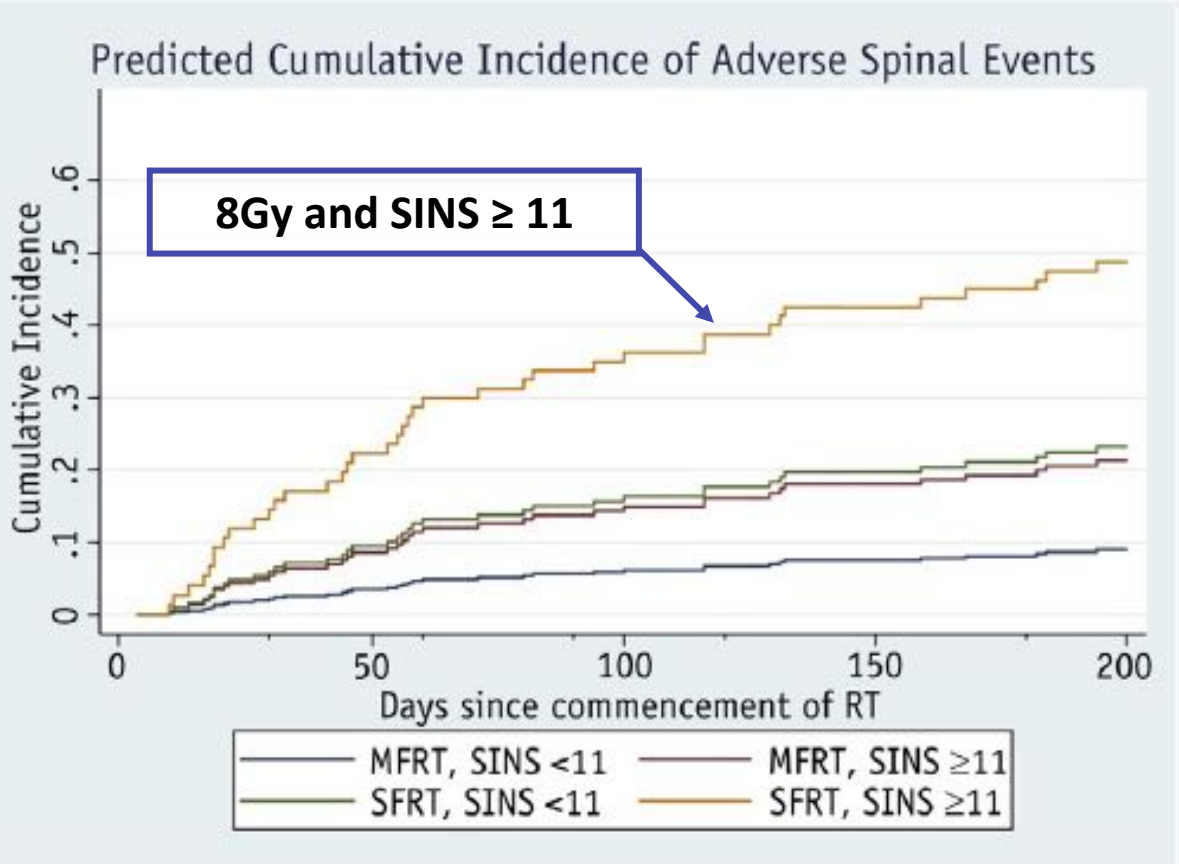
The sensitivity and specificity of SINS for **potentially unstable** or **unstable** lesions were **95.7%** and **79.5%,** respectively.

Adverse Outcomes After Palliative Radiation Therapy for Uncomplicated Spine Metastases: Role of Spinal Instability and Single-Fraction Radiation Therapy

International Journal of Radiation Oncology biology • physics
www.redjournal.org
Int J Radiation Oncol Biol Phys, Vol. 93, No. 2, pp. 373–381, 2015

Tai-Chung Lam, MBBS, FRCR,* Hajime Uno, PhD,†

Competing risk regression analysis found that pretreatment spinal instability and single-fraction RT (8 Gy) was associated with a higher hazard of SAE. Propensity score matched analysis comparing single-fraction versus multifraction RT confirmed the finding (hazard ratio = 3.9, 95% confidence interval 1.6-9.6, $P = .003$).



Treatment of choice

for pathologic fracture or high fracture risk

- **Surgical stabilization**

if the patient has adequate PSK and a good life expectancy (?)

- **External Beam Radiotherapy**

post operative *or* ***alone*** *in patients ineligible for surgery*

- **Bisphosphonates**

the use of bisphosphonates does not obviate the need of radiotherapy for patients with painful bone mets

Radiotherapy after surgery
for pathologic fracture or high fracture risk

Postoperative radiotherapy is associated to:

- ✓ Increase of functional status;
- ✓ Decrease of subsequent surgical procedures at 12 months (*3% vs. 15%*);
- ✓ A possible increase in overall survival;

however……

- ✓ It is not evident a relation between radiotherapy regimen and patient functional status;
- ✓ generally **multiple hypofractionated regimens** (*e.g., 5 x 4Gy; 10 x 3Gy*) are preferred.

Towsend et al. Int J Radiat Oncol Biol Phys 1996; 31:43-49

Radiotherapy alone
for high fracture risk
Single *vs.* multiple fractions?

- Systematic review of 5 randomized trials, 2476 patients:
- Overall pain-response rates: single fraction RT *vs.* multifraction RT were **60%** and **59%** (1060/1807), respectively.
- Risk of pathologic fracture is **1.82 times** greater in single fraction respect multiple fractions.
- Pathologic fracture most commonly occur in **weight-bearing bones** (e.g., femur).

Sze et al. Clin Oncol (R Coll Radiol). ***2003*** *15(6):345-52.*

Radiotherapy alone
for high fracture risk
Single *vs.* multiple fractions?

Results of randomized Trial RTOG 97-14

8Gy vs. 10x3Gy in spine mets

- Single fraction produced **less** acute toxicity and a **higher** rate of **retreatment** than Multifraction RT.
- Single and Multifraction RT resulted in ***comparable*** pain relief and **narcotic use** at 3 months.
- There was **no difference** in long-term **risk of pathologic fracture** between two regimen of RT.

Howell et al. Cancer 2013;119(4):888-96

Radiotherapy alone
for high fracture risk

- In clinical practice **multifraction RT** regimen ***is preferred*** to **single fraction**.

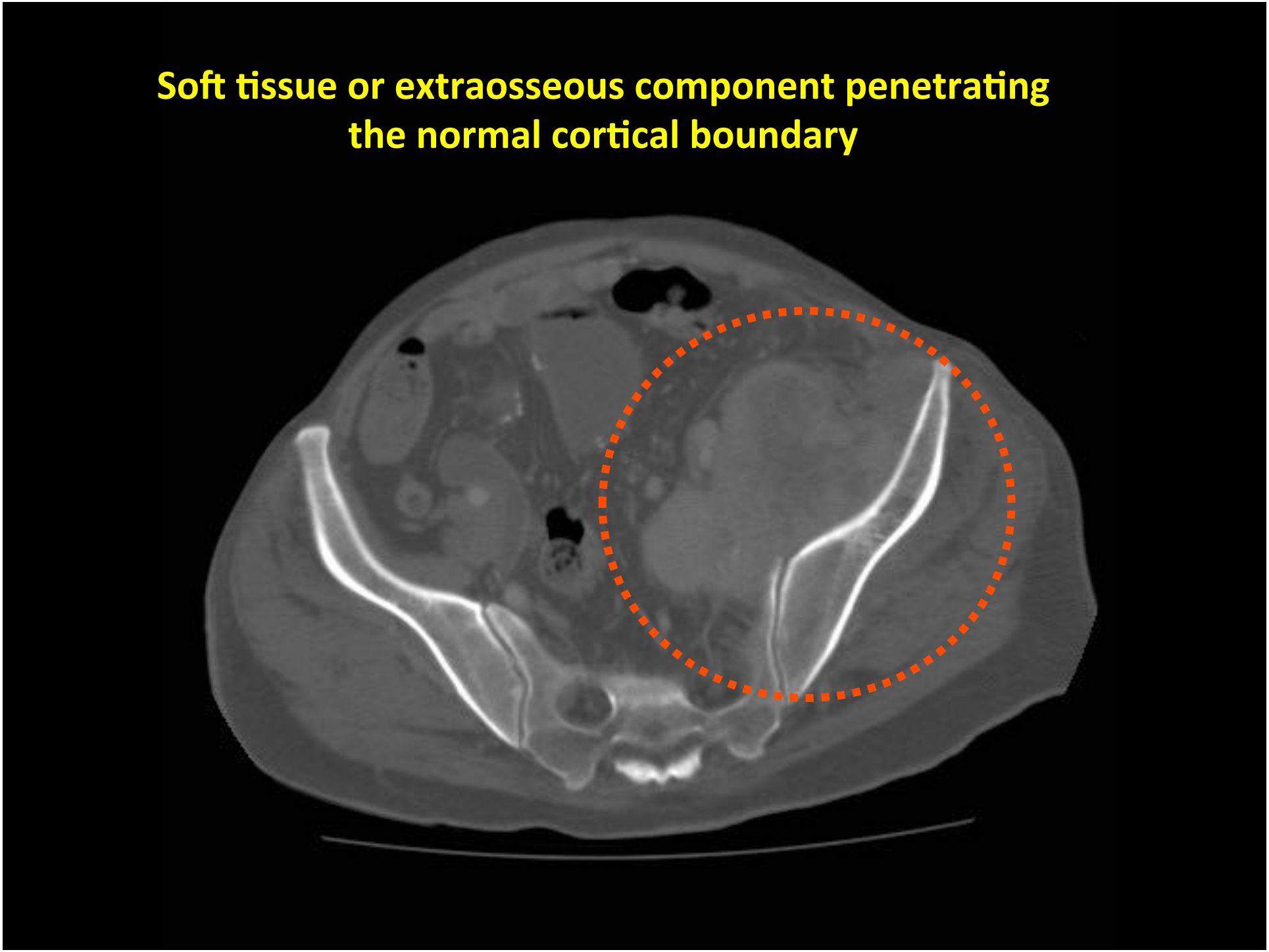
- There was **not evidence** on optimal multifraction RT schedule.

- Generally **5x4Gy** or **10x3Gy** is adopted.

Complicated bone metastases

- associated pathologic fracture or high fracture risk
- **soft tissue or extraosseous component penetrating the normal cortical boundary**
- neuropathic pain
- associated spinal cord/cauda equina compression

Soft tissue or extraosseous component penetrating the normal cortical boundary



Soft tissue or extraosseous component penetrating the normal cortical boundary

- Traditionally this subset of patients have a good response to RT.
- However there are few data regarding the optimal RT regimen.
- Generally, **multifraction RT** schedules are preferred.

Complicated bone metastases

- associated pathologic fracture or high fracture risk
- soft tissue or extraosseous component penetrating the normal cortical boundary
- **neuropathic pain**
- associated spinal cord/cauda equina compression

CLINICAL EVALUATION

Neuropathic pain

superficial burning, searing, shooting, stabbing or electric shock-like sensation

plus

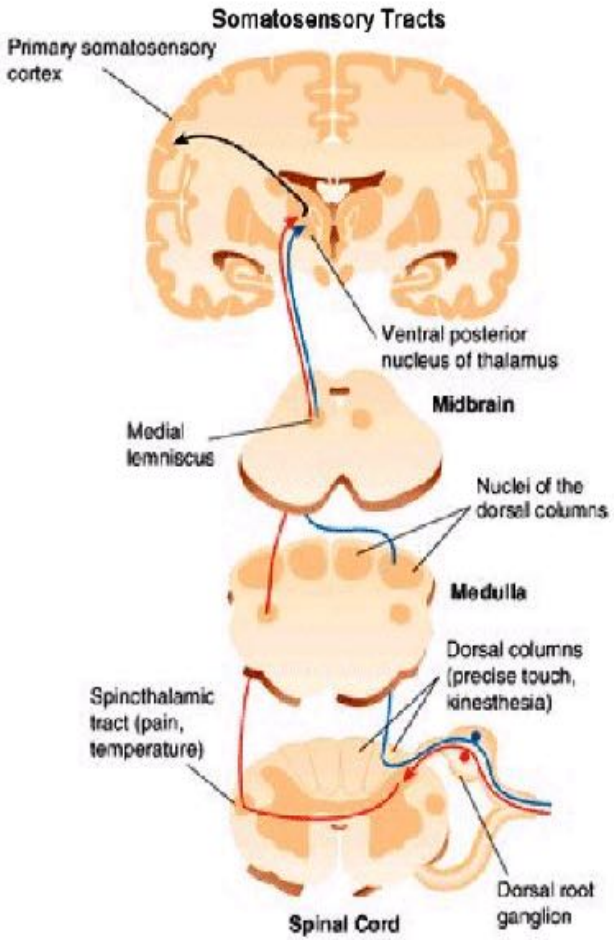
parasthesia, allodynia and hyperalgesia (‘*hypersensitive’ symptoms*)

or

decreased perception for mechanical, vibratory, thermal and noxious stimuli (‘*hyposensitive’ symptoms*)

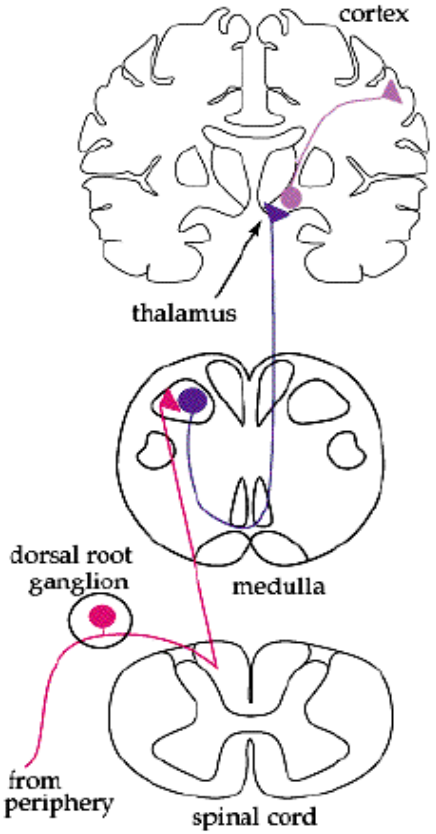
CLINICAL EVALUATION

Neuropathic pain

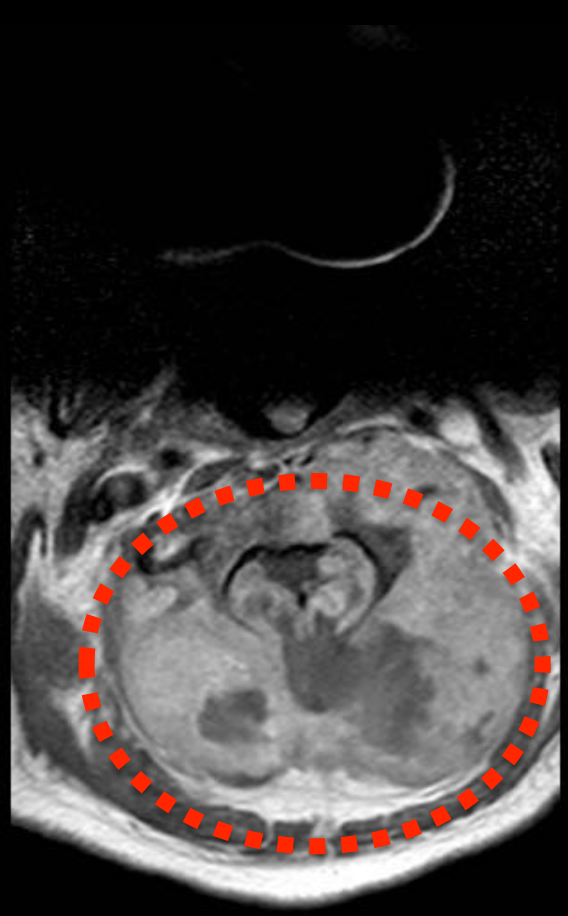


Pain arising as a direct consequence of a lesion in regions (*e.g., vertebral body*) that are innervated by <u>dermatomes</u> of the <u>somatosensory system</u>

This pain is often resistant to analgesics, opioids too



Neuropathic pain



Neuropathic pain:
Pathogenesis and possible therapeutic implication

Mechanical pressure on nerves from the adjacent tumor

(mass arising in bone or soft tissue)

↓

Higher RT doses → grater **tumor shrinkage**

Chemical irritation of nerves by cytokines elaborates by tumor

or by host cells in response to the tumor (e.g., osteoclast)

↓

Lower RT doses → **anti-inflammatory effect**

Ross D. Neuropathic Bone metastases; pp301-308.
In: Vassiliou V., Chow E., Kardamakis D. Bone metastases, 2nd Ed. Springer, 2014

Neuropathic pain

TROG 96.05 *(Roos et al. 2005; Radiother Oncol 75:54-63.)*

- It is the only study that examined RT for neuropathic bone pain.
- **272** patients randomized to: **8Gy** *vs.* **5x4Gy** (*29% with primary prostatic cancer*).
- Overall response **53%** vs. **61%** (not significant).
- No statistically difference in rates of **re-treatment**, **cord compression**, **pathological fracture**.

Neuropathic pain

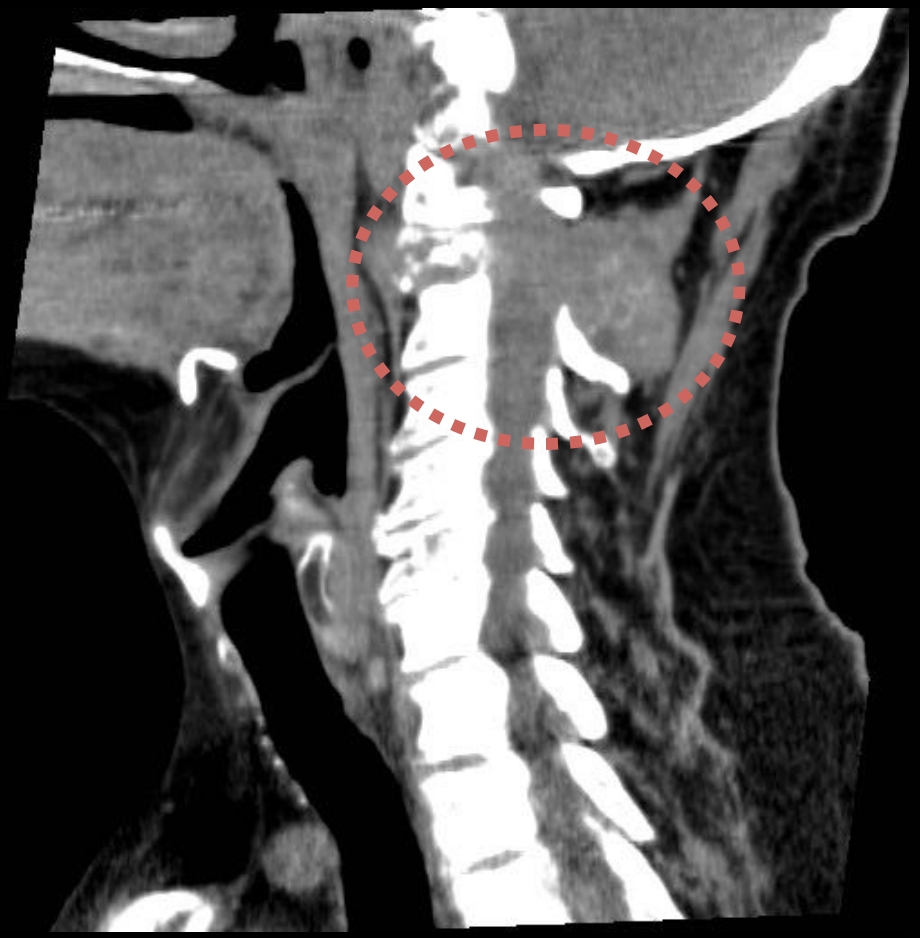
Conclusions

- The TROG data argues against the "tumor shrinkage" hypothesis, mirroring the situation with uncomplicated bone metastasis.
- However in clinical practice, **multifraction RT regimens** are generally used.
- Waiting for prospective trials, for patients with poor prognosis **single RT fraction** is recommended.

Complicated bone metastases

- associated pathologic fracture or high fracture risk
- soft tissue or extraosseous component penetrating the normal cortical boundary
- neuropathic pain
- **associated spinal cord/cauda equina compression**

Spinal cord compression

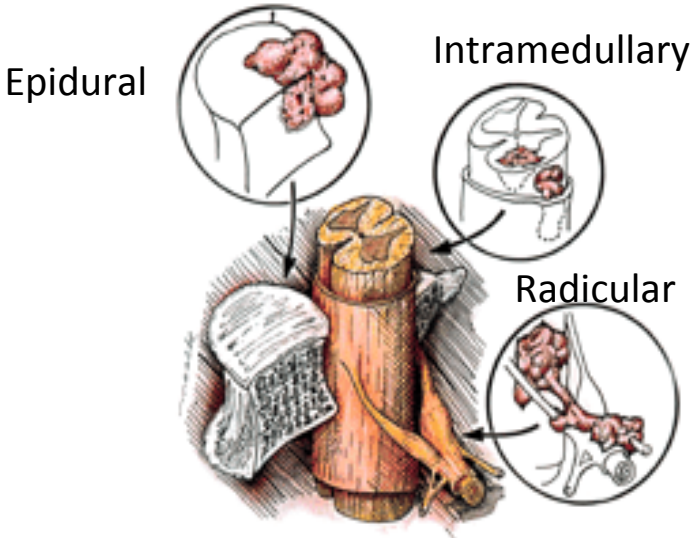


Metastatic spinal cord compression

Definition

The Princess Margaret Hospital of Toronto, Canada, definition:

*"Compression of the dural sac and its contents (*spinal cord and/or cauda equina*) by an* **extradural tumor mass**. *The minimum radiologic evidence for cord compression is* **indentation** **of the theca** at the level of clinical features. *Clinical features include any or all of the following:* pain *(local or radicular),* weakness, sensory disturbance, *and/or evidence of* sphincter dysfunction*"*.



Loblaw et al. 1998 JCO '98

Surgery + RT *vs.* RT alone

Randomized trial (***Patchel 2005***) ⟶ Surgery **>** efficacy

…….. *direct decompressive surgery and post-op RT* ***is superior*** *to RT alone for patients with metastatic spinal cord compression*

Be careful in getting cost-effectiveness conclusions from a debatable trial!
Maranzano E, Trippa F. Int J Radiat Oncol Biol Phys. 2007 68(1):314

Tailored surgery!

1. **posterior, anterior, and/or lateral approach**
2. **plus stabilization of the spine**

(i.e., no laminectomy)

Selected patients!

1. **Single site**
2. **Adult age with good medical status**
3. **Histology not lymphoma or myeloma**
4. **Absence of paraplegia**
5. **Expected survival > 3 months**

Metastatic spinal cord compression

RT alone - Randomized trials

JOURNAL OF CLINICAL ONCOLOGY | VOLUME 23 · NUMBER 15 · MAY 2005

Short-Course Versus Split-Course Radiotherapy in Metastatic Spinal Cord Compression: Results of a Phase III, Randomized, Multicenter Trial

E. Maranzano et al

Contents lists available at ScienceDirect

Radiotherapy and Oncology 2009

journal homepage: www.thegreenjournal.com

Phase III randomised trial

8 Gy single-dose radiotherapy is effective in metastatic spinal cord compression: Results of a phase III randomized multicentre Italian trial

Ernesto Maranzano[a,*], Fabio Trippa[a], Michelina Casale[a], Sara Costantini[a], Marco Lupattelli[b], Rita Bellavita[b], Luigi Marafioti[c], Stefano Pergolizzi[d], Anna Santacaterina[d], Marcello Mignogna[e], Giovanni Silvano[f], Vincenzo Fusco[g]

Single-Fraction Versus 5-Fraction Radiation Therapy for Metastatic Epidural Spinal Cord Compression in Patients With Limited Survival Prognoses: Results of a Matched-Pair Analysis

Dirk Rades, MD,* Stefan Huttenlocher, MD,* Barbara Šegedin, MD,†

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Int J Radiation Oncol Biol Phys, Vol. 93, No. 2, pp. 368–372, 2015

A total of 121 patients receiving 8 Gy × 1 fraction for metastatic epidural spinal cord compression (MESCC) were matched to 121 patients (age, sex, performance status, primary tumor type, involved vertebrae, other bone metastases, visceral metastases, interval between tumor diagnosis and MESCC, ambulatory status, and time developing motor deficits) receiving 4 Gy × 5

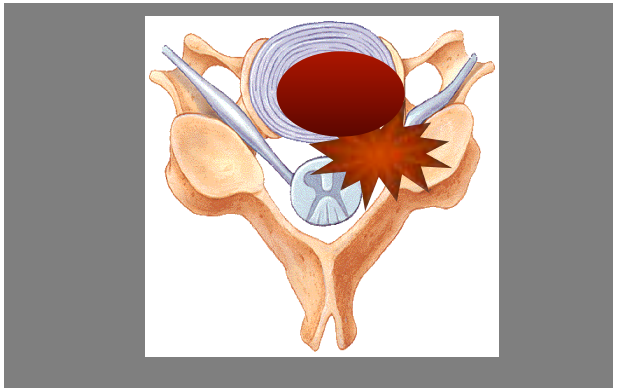
Conclusions:

The need for in-field repeated radiation therapy (RT) for MESCC, survival, and effect on post-RT motor function was not significantly different in either group.

Metastatic spinal cord compression

Prognostic factors

- **EARLY DIAGNOSIS**
- **EARLY THERAPY** *(within 24/48 h from radiologic diagnosis)*



Metastatic spinal cord compression

Results after Radiotherapy

- ***Back pain relief***: **50-58% (30-35% complete response)**

- ***Walking capacity***

  function maintained: 85-90%

  function recovered: from paresis: 30-35%

  from plegia: 0-10%

- ***Bladder function***

  function maintained: 85-90%

  function recovered: 10-15%

Management of cancer pain: ESMO Clinical Practice Guidelines†

Annals of Oncology 23 (Supplement 7): vii139–vii154, 2012

C. I. Ripamonti[1], D. Santini[2], E. Maranzano[3], M. Berti[4] & F. Roila[5], on behalf of the ESMO Guidelines Working Group*

METASTATIC SPINAL CORD COMPRESSION (MSCC)

recommendations

Early diagnosis and prompt therapy are powerful predictors of outcome in MSCC [I, A]. The majority of patients with MSCC should receive RT alone and surgery should be reserved only for selected cases [II, B].*

- ****necessity of stabilization;***
- ***vertebral body collapse causing bone impingement on the cord or nerve root;***
- ***compression recurring after RT;***
- ***unknown primary requiring histological confirmation for diagnosis.***

COMPLICATED BONE METASTASES: high fracture risk, soft tissue/extraosseous component, or neuropathic pain

A phase II trial of hypofractionated RT (16 Gy in 2 fractions with an interval of one week) for the palliation of complicated bone metastases in patients with poor performance status

(*E. Chow* ***Odette Cancer Centre Sunnybrook Health Sciences Centre Toronto Canada***)

- **associated pathologic fracture or high fracture risk**
- **soft tissue or extraosseous component penetrating the normal cortical boundary**
- **neuropathic pain**
- associated spinal cord/cauda equina compression

Ongoing trial

Abstract – 2016 ESTRO – Turin - Italy

Hypofractionated radiotherapy for the palliation of complicated bone metastases in patients with poor performance

Authors:

Mauricio F Silva, MD, PhD; Gustavo N Marta, MD, MSc; Felipe PC Lisboa, MD; Guilherme Watte, PT, MSc; Fabio Trippa, MD; Ernesto Maranzano, MD; Neiro W da Motta, MD, PhD; Edward Chow MBBS.

This was a phase 2 multicenter study of patients with complicated bone metastases and Karnofsky performance status from 30 to 60 who underwent 2 fractions of radiotherapy with 8 Gy each one week apart. **Pain response and quality of life (QOL)** were measured using the International Consensus on Palliative Radiotherapy Endpoints and EORTC QOL Pal15 and BM22 questionnaires.

30 patients were enrolled from **4** centres in **Brazil**, **Italy** and **Canada** during July 2014 to September 2015

Conclusion: The 2 fractions of radiotherapy with 8 Gy each one week apart appears to be **efficacy and well tolerated without serious side effects** in patients with complicated bone metastases and poor performance status. **QoL remained stable**.

You cannot discover new oceans until you have not the bravery to lose sight of the beach. (Anonymous)

By courtesy of Cecilia Trippa