MOGUĆNOSTI ZRAČNE TERAPIJE U LEČENJU BOLNIH KOŠTANIH METASTAZA

Possibilities of radiotherapy in cancer pain management

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IORS

The goals of palliative radiotherapy

- The relief or prevention of symptoms KM (pain releasing, pathological fractures, compression ...)
- Improving the Quality of Life
- Prolongation of survival if possible
- Rationale: maximum effect with a minimum treatment

PLANNING palliative RT

- Evaluation of the expected survival time
- Expected acute and late complications RT
- Potential hospitalization for treatment of chronic complications
- Rationale RT doses and techniques of treatment for potential benefit
- Price of palliative RT

Principles of palliative radiotherapy

- Applied total dose of less than radical (radical 2/3 dose with fractionation for the conventional regime)
- the shortest possible time and duration of therapy
- (**hypofractionated regime**)- nonstandard modes: a small number of fractions with higher single doses)
- the simple technique of irradiation
- without pronounced acute and late complications
- Urgency in tretment

Bone metastases (BM)

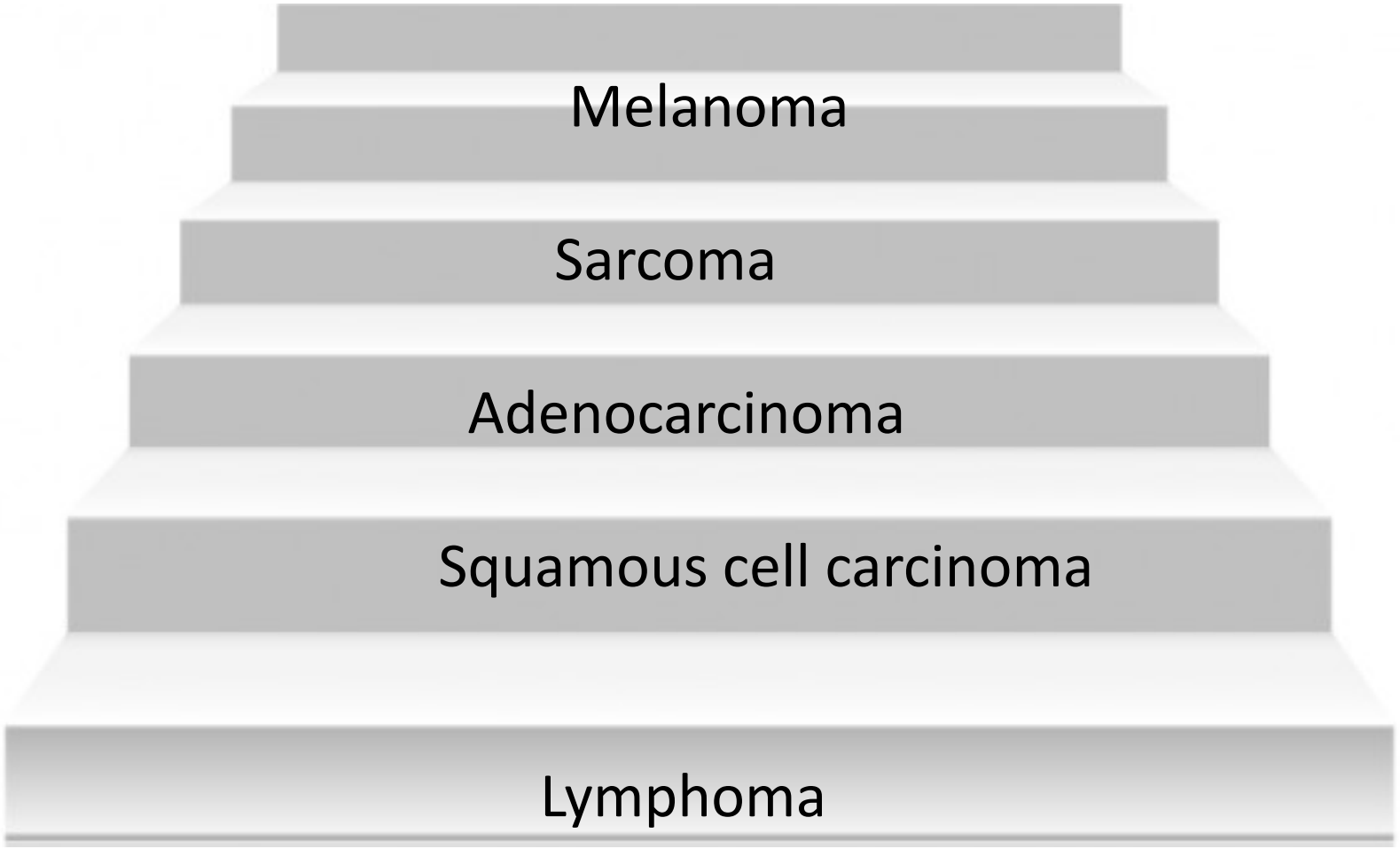
- Carcinoma of the breast, prostate, lungs and make up 50-80% of all bone metastases
- follow renal cancer and thyroid
- hematological malignancies, can lead to bone destruction -lymphoma, myeloma
- 70% axial skeleton, ribs, skull,
- 75% of patients with BN have pain

MECHANISM OF RADIOTHERAPY EFFECT ON PAIN RELIEF AT BM

1. Pain releasing effect that is achieved directly after the RT may be the result of **cytotoxic activity on normal bone cells** (macrophages, osteoclast-mediated) → **Inhibition of the release of chemical pain mediators**

2. Pain releasing effect can be the results of **inhibition of osteoclastic activity** MARKERS (bisphosphonates are chemical inhibitors of the osteoclast)
3. At a small percentage of patients with a pain releasing effect achieved 4-8 weeks after RT the **lethal effect on the tumor cells** can be the possible cause

Radiosensitivity



Pain-Diagnostic

- Bone metastasis are the most common cause of pain in cancer patients

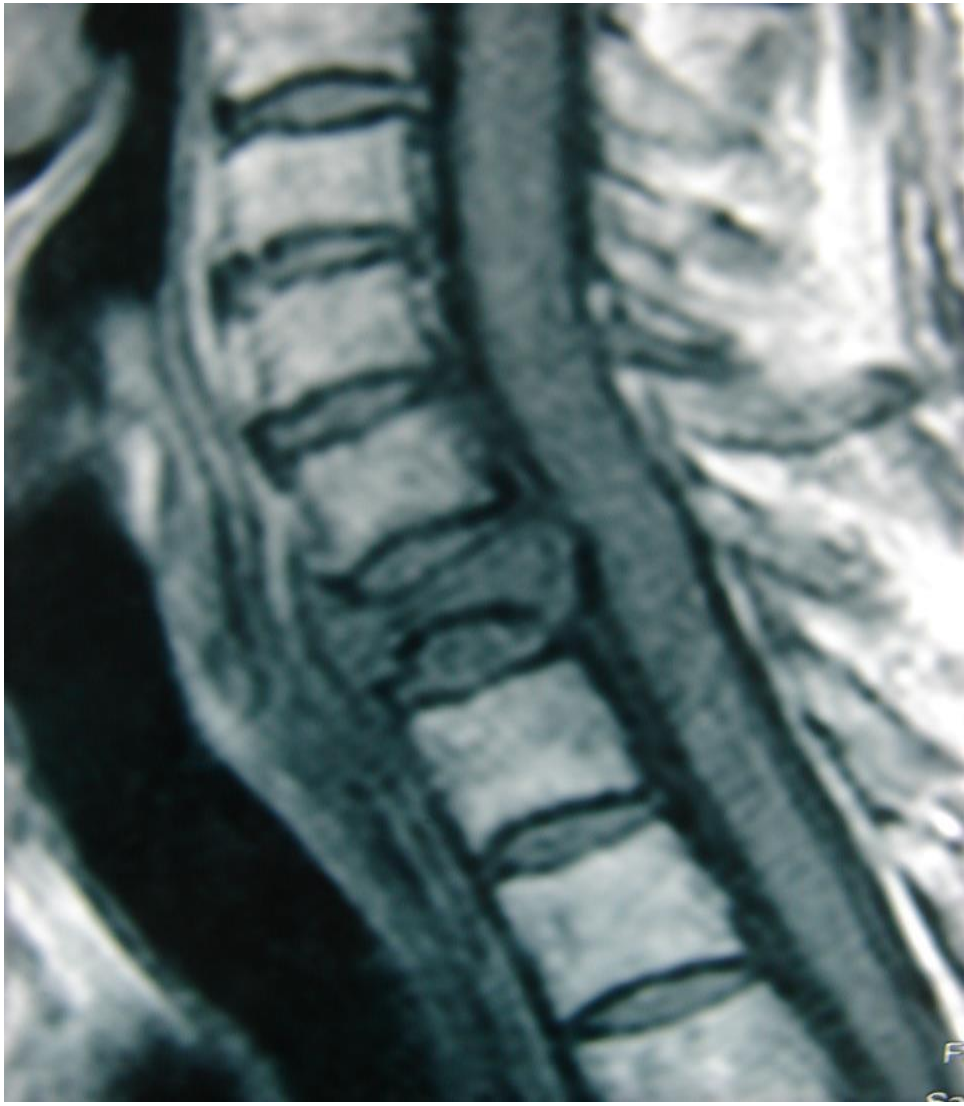
- **Cause:**
  - **C**ompression of nerve endings,
  - periosteal stretching or
  - growth in the nerves and the surrounding tissue
- Pain can be **intermittent or constant**; related to activity; can get worse during the day

- **RTG** can be visualized in the form of lytic or sclerotic lesions or fractures
- **On scintigraphy better** can be visualised some sclerotic or blast lesions
- **MR** examination of the bones contributes to a better evaluation of bone metastasis - Gold Standard

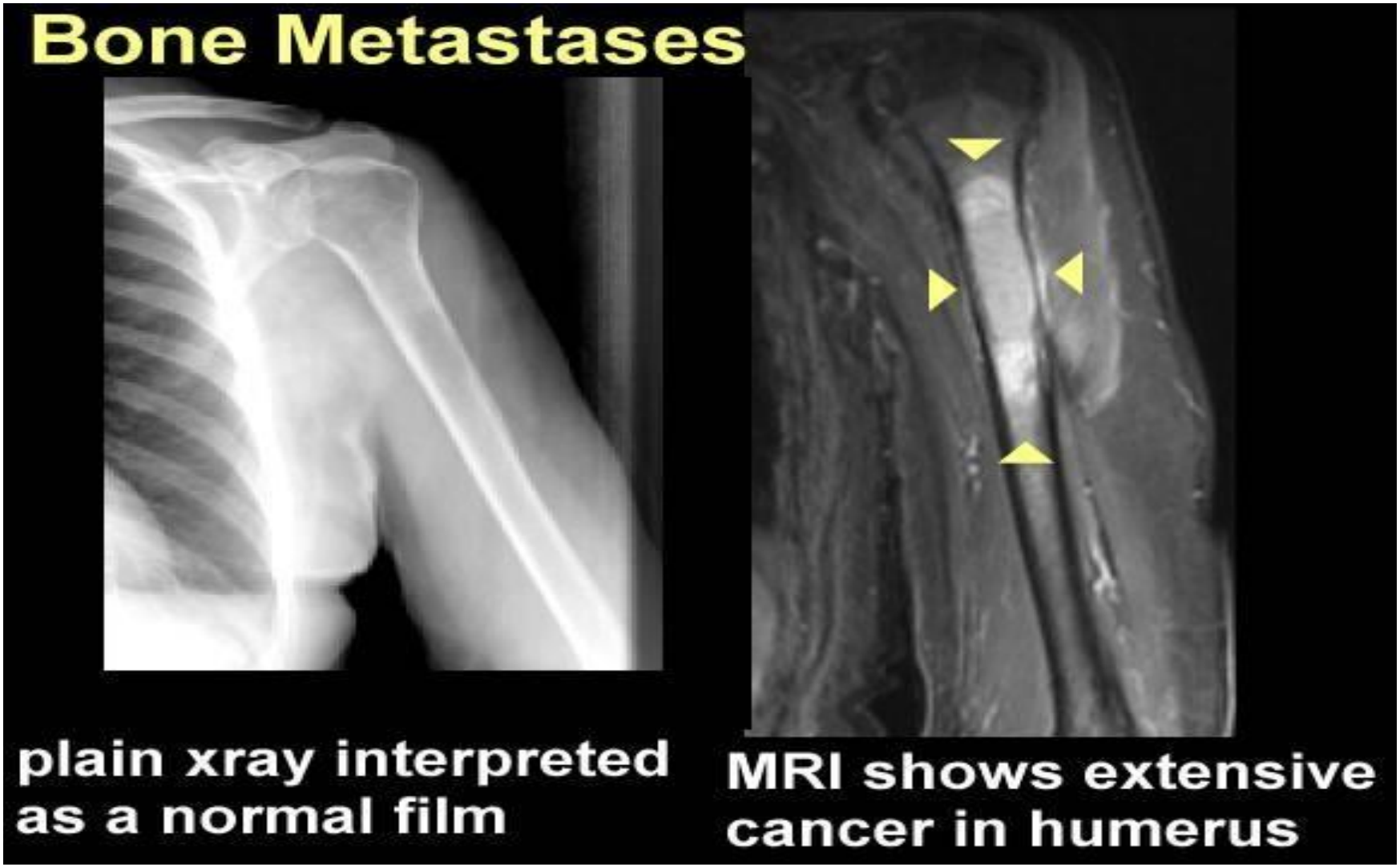
Type of BM: lytic, blastic and mixed

Primary bone response to some tumors

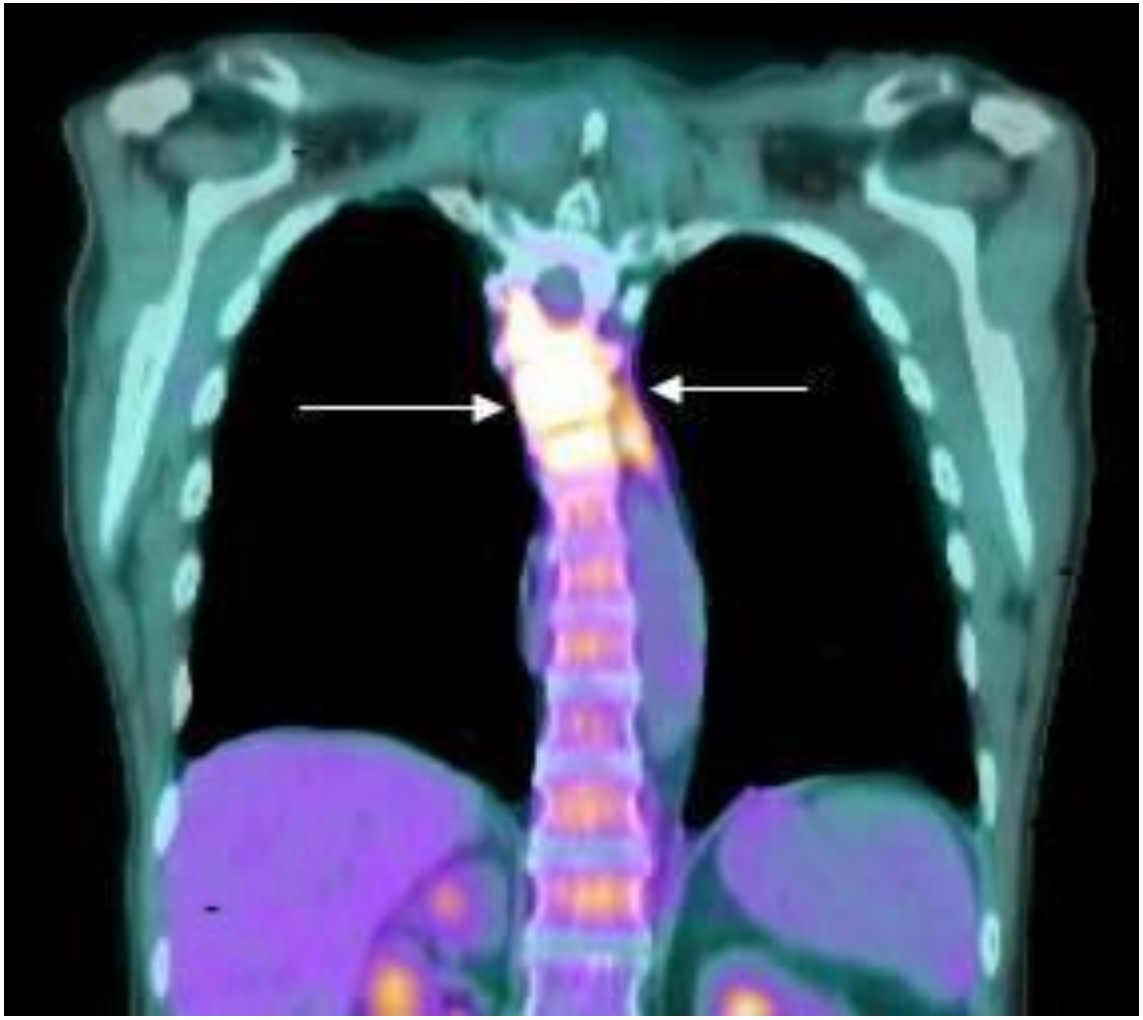
Predominantly osteoblastic
Prostate
Carcinoid
Gastrinoma
Small cell lung cancer
Hodgkin's disease
Medulloblastoma
Predominantly osteolytic
Renal cell cancer
Melanoma
Squamous cell cancers of the aerodigestive tract
Multiple myeloma
Non-small cell lung cancer
Thyroid cancer
Non Hodgkins lymphoma
Mixed osteoblastic and osteolytic
Breast cancer
Gastrointestinal cancers
Squamous cancers at most primary sites



An MRI may show a bone met better than a regular X-ray



PET scans very clearly visualize the bone metastasis



- TH-L -70%
- L-S-20%
- C-10%

Biopsy of metastasis

Palliative therapy of bone metastasis

A) **LOCAL /REGIONAL:**

- Radiotherapy
- Surgery

B) **SYSTEMIC THERAPY:**

Chemotherapy

Hormone Therapy

Bisphosphonates

C) **SUPORTIVE THERAPY**

Analgesics

Psychosocial Care

Indications for palliative RT bone metastases

- RT bone metastases due to:
  1) pain relief;
  2) to prevent threatening fractures
  3) to prevent neurological compression of the roots
     nerves
     cauda equina
     spinal cord

Compression spinal cord-emergency condition requiring immediate radiation therapy

Palliative RT of lytic BM

• Mostly at generalise dissemination of breast, prostate,lung and endometrial cancer

The goal:

• Pain release effect (pain is the major symptom at 75% pac)

•Prevents the development of pathological fractures

• Improves mobility and function - improving performance status

• Possibility of prolonging survival

- 15-20% of patients treated with palliative RT for painfyl meta of bones live longer than 2 years (Danish Bone Trial, Radiother Oncol 1998)

PALLIATIVE RT OF UNCOMPLICATED BM

• Last 10 years – a great number of randomised study analysed pain release effect of RT (about 2000 patients with BM)

• **Second Consensus Workshop in Palliative Radiotherapy (London 2000. god.) – meta-analiza rezultata sprovedenih studija**

CONCLUSION :

• At uncomplicated BM (without fractures and compression of spinal cord)

– palliation with one fraction (8Gy) or more fraction (16Gy/4fr., 20Gy/5fr., 30Gy/10fr., 40Gy/20fr.)

• **Result :**

–Achieves the same effect

–The same level of acute complications-nausea, vomiting, diarrhea, pathological fractures.

–Success of pain release effect in 50-80% at solitary meta

• - The effect - after a few days and a maximum effect for 2-4 weeks-

• Single-dose RT **may be repeated** in the same volume (relapse) if the initial pain releasing effect is achieved and the answer at reiradiation can be at the same level

• No correlation between the releasing effect and the type of cancer .

RT bone metastasis: 8 Gy x 1 vs. 30 Gy x 10 –RTOG 9714

- Pain and using of analgesics are same after **30Gy in 10 fractions and after 8Gy in 1 fraction**
- Pathologic fracture as consequence in 5% after 8 Gy x 1 s vs. 4% 3 Gy x 10s
- Retreatment is statistically significant higher after 8 Gy x 1: 18% vs. 9% ($p<.001$) –decision for retreatment

"left to discretion of treating physician

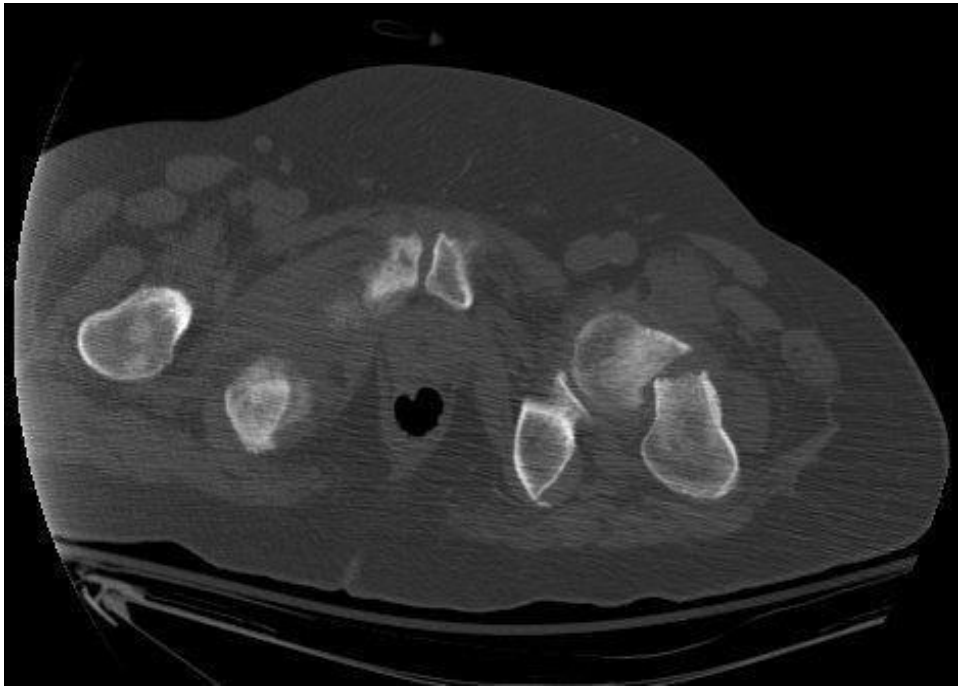
• **8 Gy in 1 fraction-new standard?-** recommended regimen for the treatment of the symptomatic and uncomplicated bone metastases, Wu et al BMC Cancer4 (2004) p.1-7

Effective fractionation regimes

- 8 Gy / 1 fraction Single shoot
  16 Gy / 4 fractions
  20 Gy / 8 fractions
  30Gy / 10 fractions
  - performance status (PS) of the patient will determine what size fractions.
  - 30 Gy provides a longer control of pain in patients with long life expectancy
  - In many surveys have shown that there is no difference between the modes of fractionating
- Oligometastases - ?

Complicated BM

Previous irradiatied volume, pathologic fracture, spinal cord compression



Pathologic fracture –prostate cancer

Compression of caude ekvina: Lymphoma

- Early diagnosis
- Basic question: primary RT or primary surgery

METASTASES WITH SPINAL CORD COMPRESSION

•In 90% of the patients symptom is pain in the back (with or without radicular components) along with the progression of neurological deficits

• At the time of diagnosis, 50% of patients have lower paraparesis / plegia

•External or internal fixation of the affected part of the spine is preferred in the case of fracture and instability

•

Palliative RT is conducted URGENT

•

20-30Gy fractionation regimens in 4-10 fractions (Clinical studies examine the effectiveness of short radiation regimens: 8Gy in 2 fractions)

•Effect in 50% of patients: stabile or improved neurological deficit

•

THERAPY CONTROVERSY: SURGERY or RADIOTHERAPY (initially RT only in radiosensitive tumor sites if there is no vertebral fracture)

SURGERY IN THE TREATMENT OF SPINAL CORD COMPRESSION

- General indications for the use of surgery as an initial treatment:

  UNKNOWN Basic Diagnosis - Primary Malignant Tumor
  Spine metastases of RADIORESISTENT tumors
  MAJOR Fractured DISLOCATION
  Spinal cord compression level in a IRRADIATED REGION

  New studies suggests that better results are achieved by **anterior access** to the affected part of the spine with **removal of the visible mass** and reconstruction of the vertebral body in a precisely selected group of patients.

  OPTIMAL THERAPY FOR THE MOST PATIENTS WITH SPINAL COMPRESSION IS YET NOT KNOWN

Surgical decompression

•Slow progression of neurologic symptoms,

• Ambulation that is maintained or has only been lost in the previous 48 hours,

•A single level of compression,

•The absence of visceral or brain metastases,

• An estimated survival of at least three months,

• A lengthy interval between the initial diagnosis and spinal cord compression,

•Age less than 65 years,

•Spine instability, and

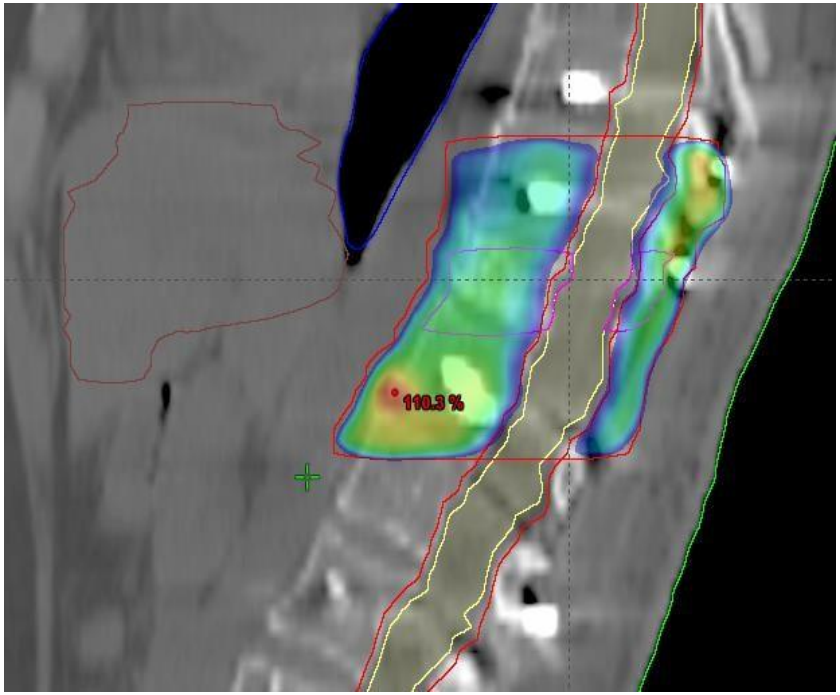
•Tumors that arise in the prostate, breast, or Kidney

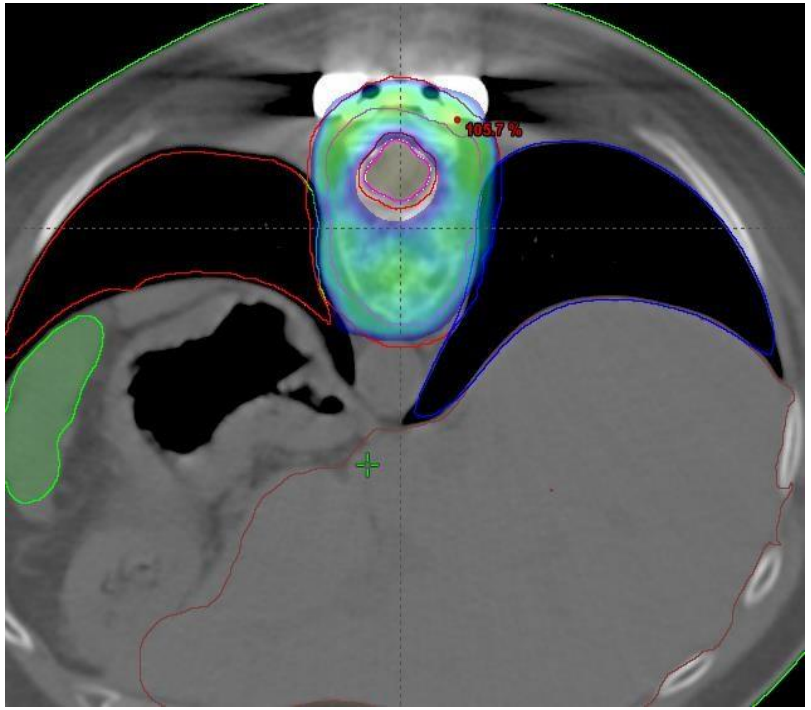
Surgery and RT

- Surgery does not obviate the need for post op RT
- The choice for surgical decompression should be made by an interdisciplinary team

- The optimal dose not defined, but longer schedules, like 30 Gy in 10 fractions recommended

Postoperarative RT-IMRT





- **Protection of the spinal cord**
- **Option for retreatment**

PALLIATIVE RT - MULTIPLE BM

- External RT to large (wide) fields is better than application of multiple local fields, but requires centers with experience in large field dosimetry and treatment of acute therapeutic toxicity

  HBI in one session: 6-7Gy upper half body, 7-8Gy lower half body. If implemented in two acts, the interval is 2-4 weeks

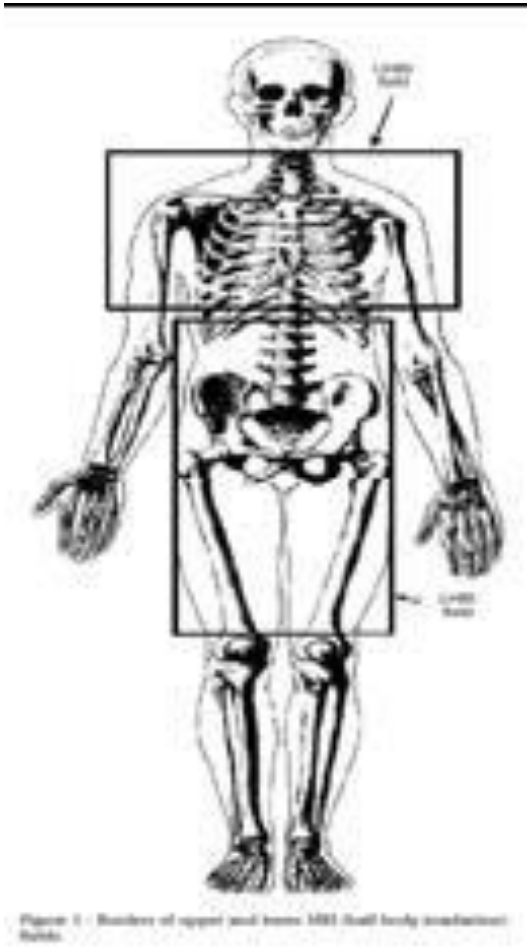
  Medicinal premedication due to acute toxicity is required
  Antidolorosis effect in 55-100% of patients, complete loss of pain in 5-50%

  Onset of response 1-14 days after RT, approximately 50% of patients record pain reduction / loss within the first 48 h after RT

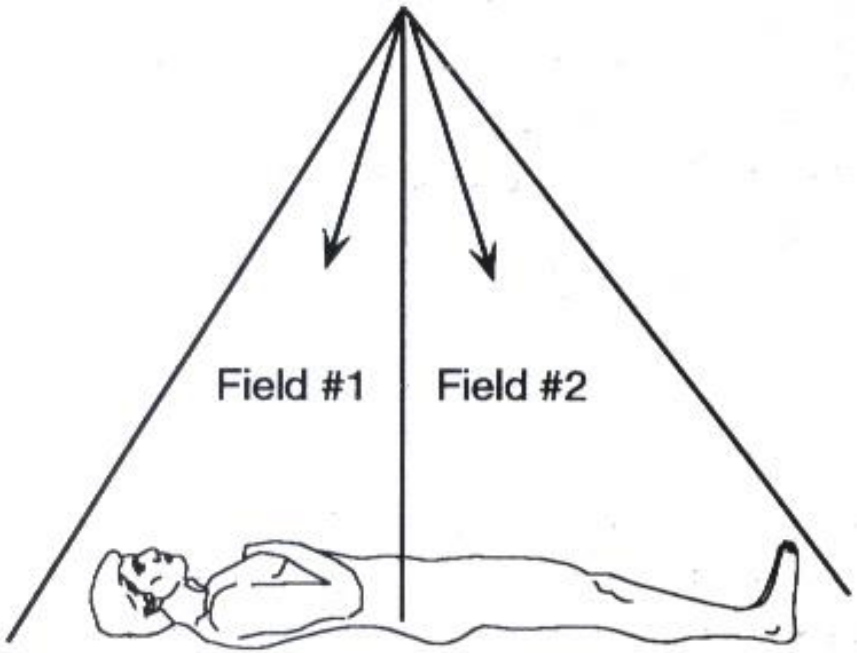
  In more than 50% of patients with a positive response, it lasts until the end of the disease

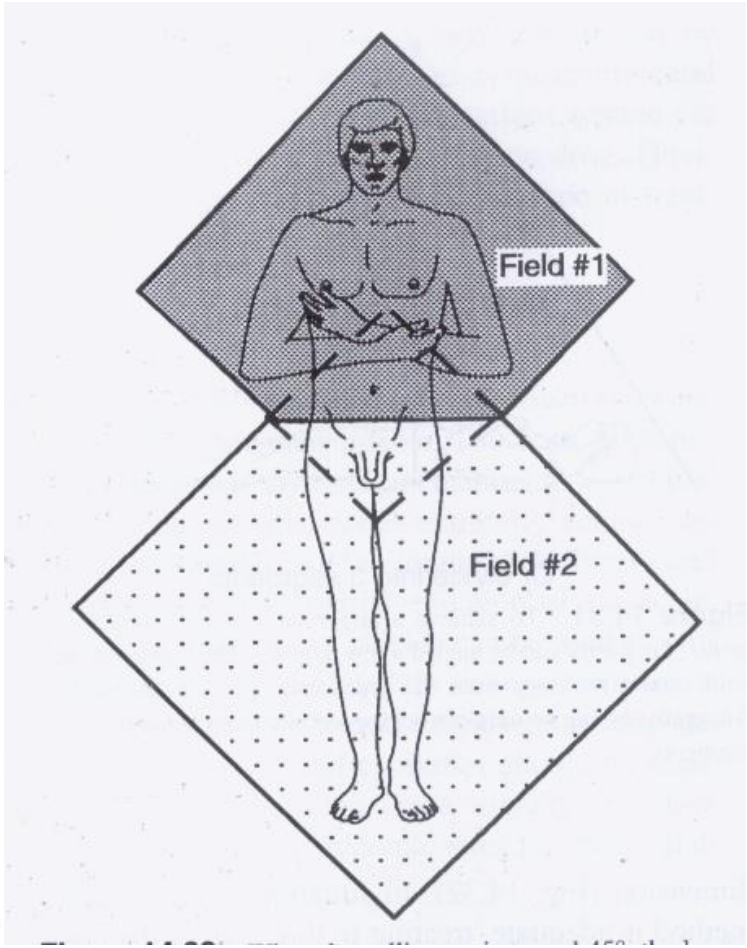
HBI paliative RT

- HBI be used for patients with multiple bone metastases, especially in patients with prostate cancer
- HBI extending the time to appearance of new lesions
- REDUCE the number of patients requiring retreatment within one year



Palliative RT multiple BM (HBI – half body irradiation)





HBI

- Upper half body radiation - the maximum tolerated dose is limited by the toxic effects on hematopoietic tissue and gastrointestinal organs.

- Inhomogeneous dose distributions in the upper half of the body — correction for the pulmonary parenchyma (air) to avoid pnumonitis as a therapeutic complication

- The maximum tolerated dose applied in one fraction for upper body irradiation is 6 Gy, or 7 Gy with dose adjustment for the lungs. For the lower body, the maximum tolerated dose applied in one fraction is 8 Gy.

EVALUATION OF BM RESPONSE TO PALIATIVE RT

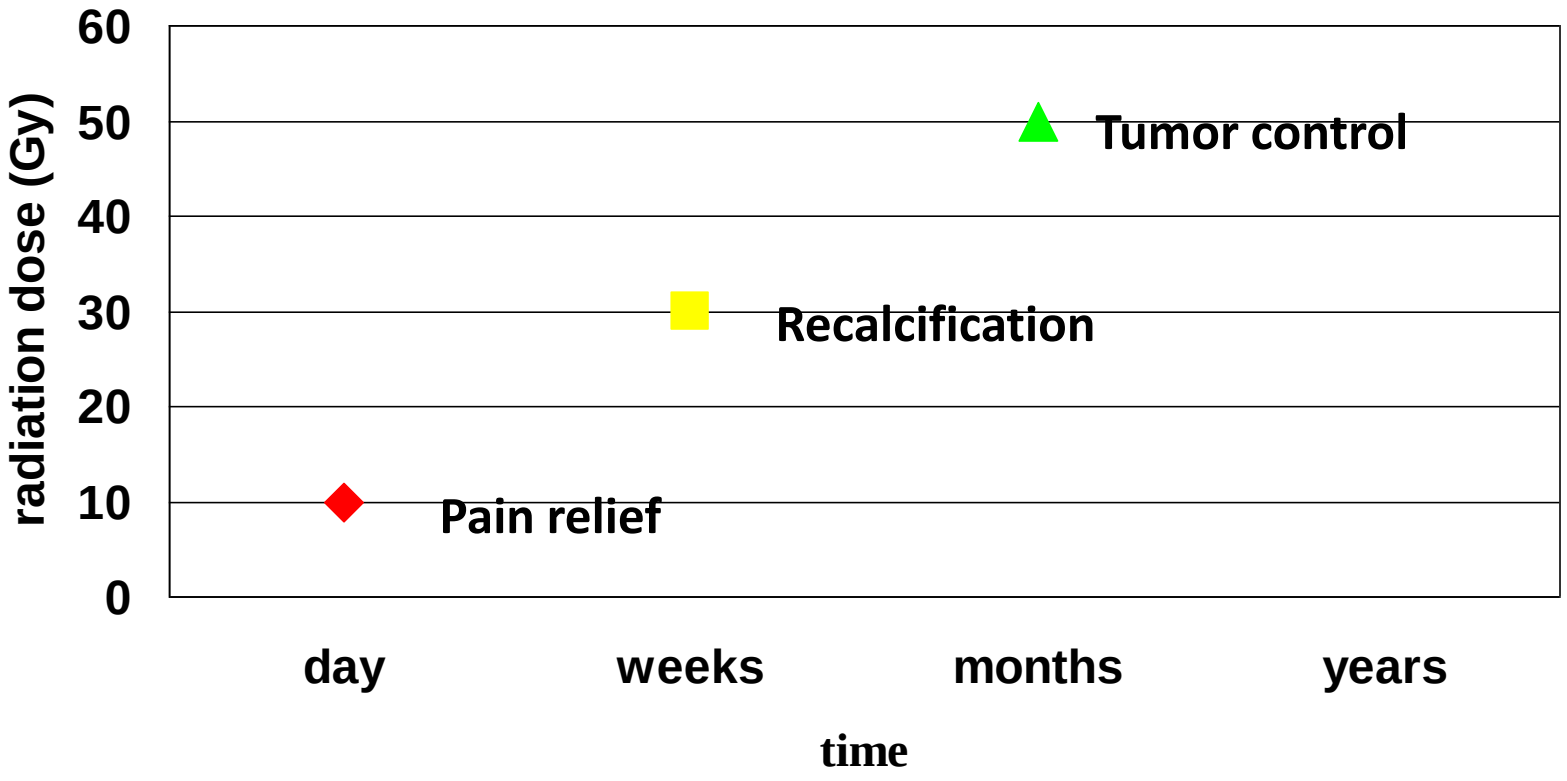
- Classical **biochemical and radiological- scintigraphic methods** often do not correlate with clinical benefit and improved performance status

  Evaluation criteria:

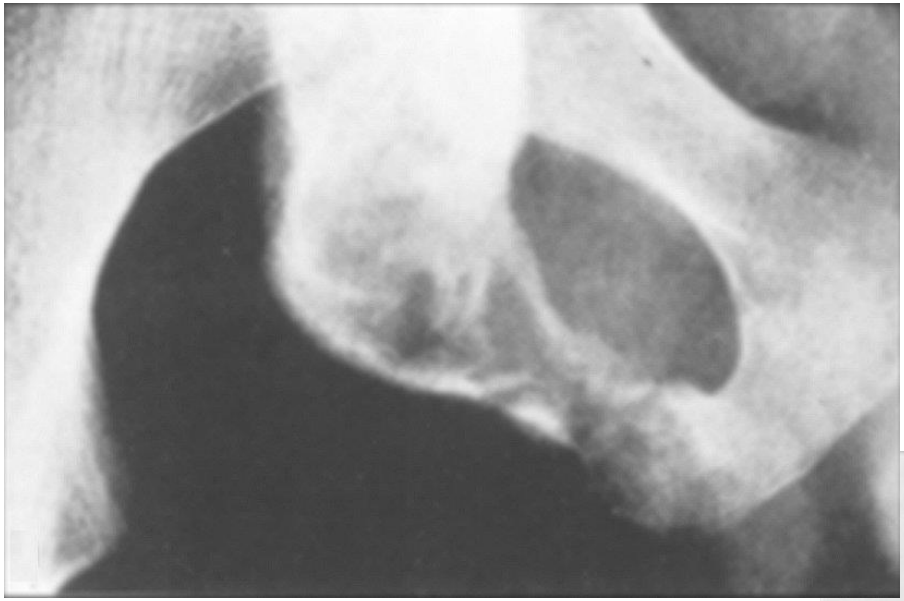
  Antidolorous score
  Quality of life
  Clinical Examination
  Radiological - scintigraphic examinations
  Biochemical analyzes
  Histology (biopsy)

- **METHODS FOR EVALUATION** OF PAIN AND QUALITY OF LIFE
  LASA pain scale
  Categorical pain scale
  Analgesic score
  Rotherdam check list
  EORTC score 30 questionnaire
- ASTRO and ESTRO have set up the CONSESUS GROUP, which has the task - the goal of developing a standardized method for evaluating the response to palliative bone target radiotherapy that will be administered in future studies.

Dose - effect RT BM



RT in pain control



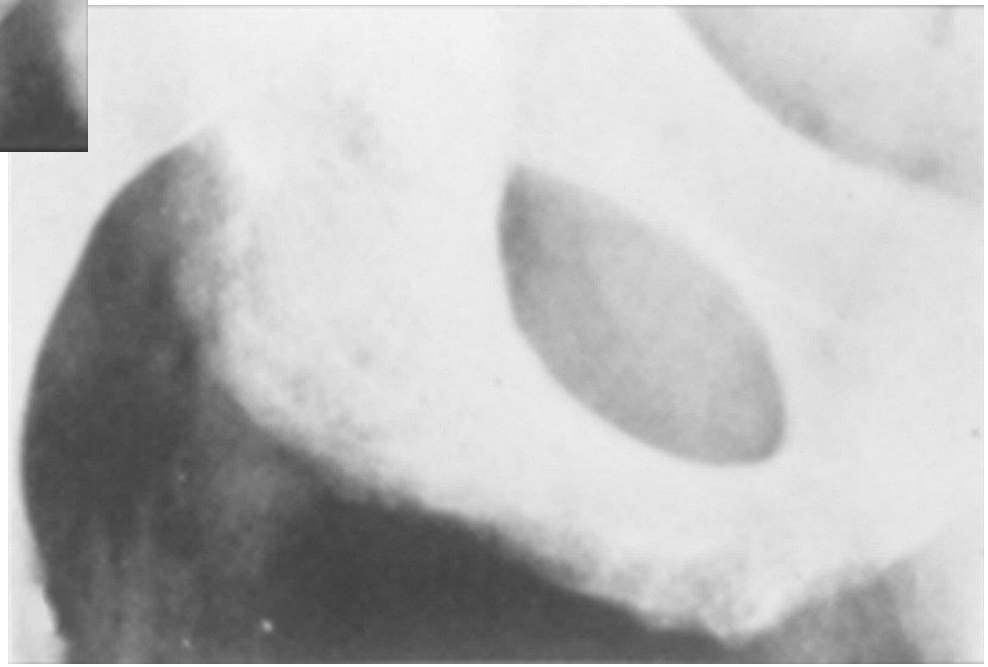
12 weeks after RT:

Completly regression of pain + recalcification

Before RT :

Pain
Risc for fracturs

10 x 3 Gy



RESPONSE DEFINITIONS

Complete response

- defined as pain score zero at treated site with no concomitant increase in analgesic intake.

Partial response

- defined as pain reduction of two or more at the treated site on a 0–10 scale without analgesic increase or analgesic reduction of 25% or more from base line without an increase in pain.

Progression / no response

- defined as increase in the two or more points in 0–10 scale above base line at the treated site with stable analgesic use or increase of 25% or more, with pain score stable or one point above base line.

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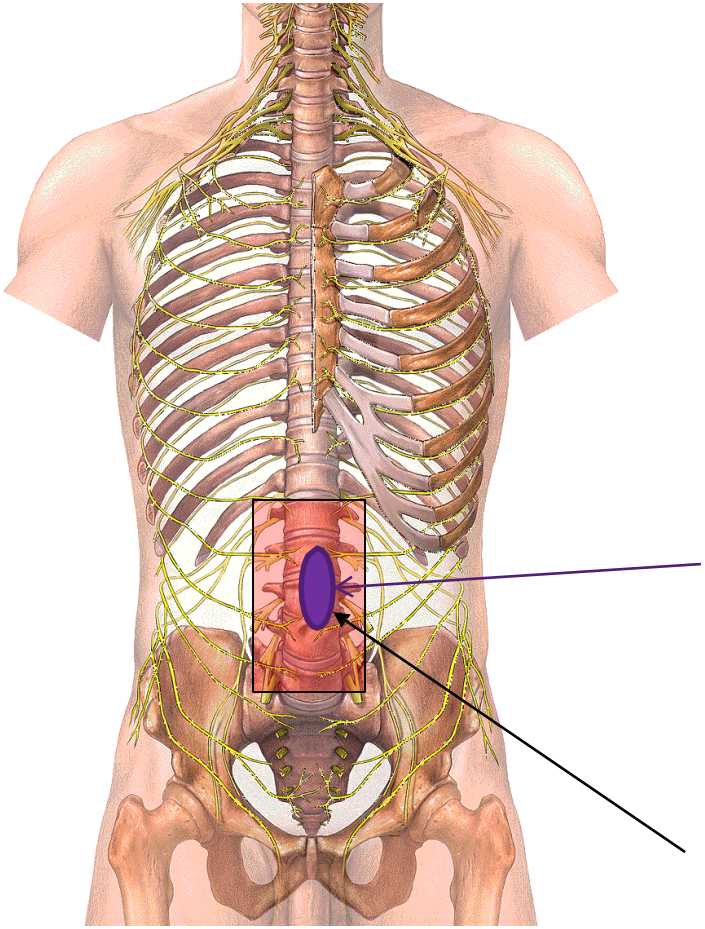
Criteria for Palliation of Bone Metastases – Clinical Applications

Conventional simulator

Radiation field- conventional RT



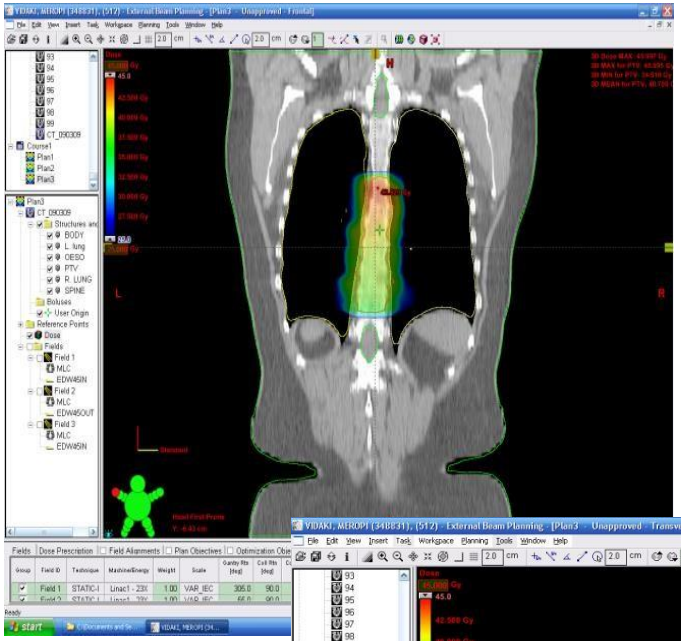
- most often in pronation position, arms next to the body
- radiation field involves vertebrae above and below the lesion
- direct field X-rays at a certain depth

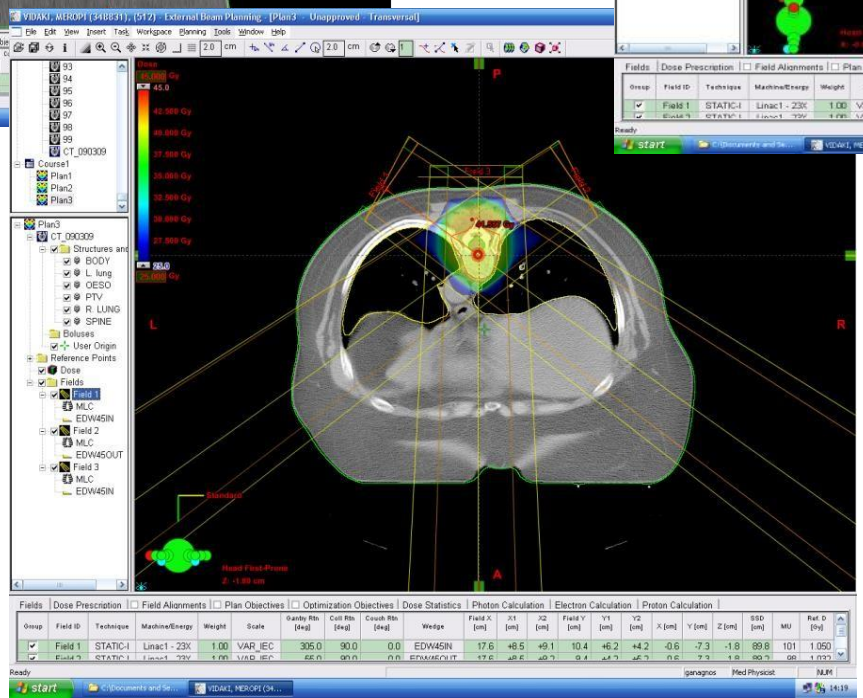
L2, L3

Radiation field

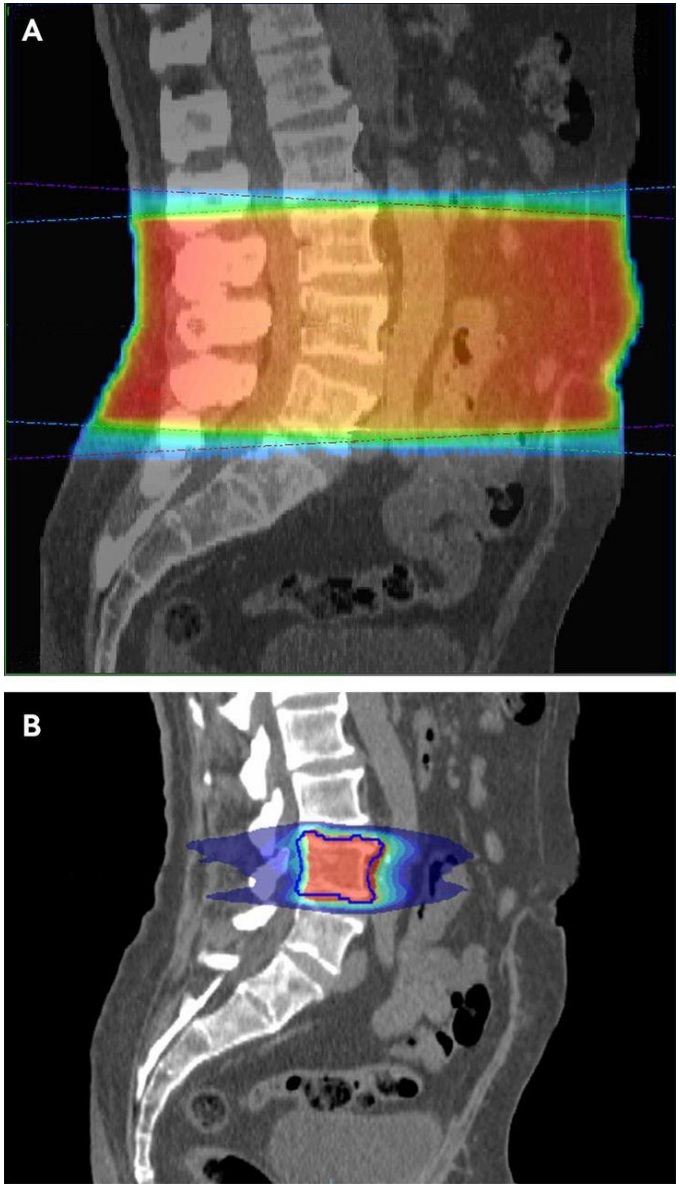
LINAC- irradiation

3D conformal RT



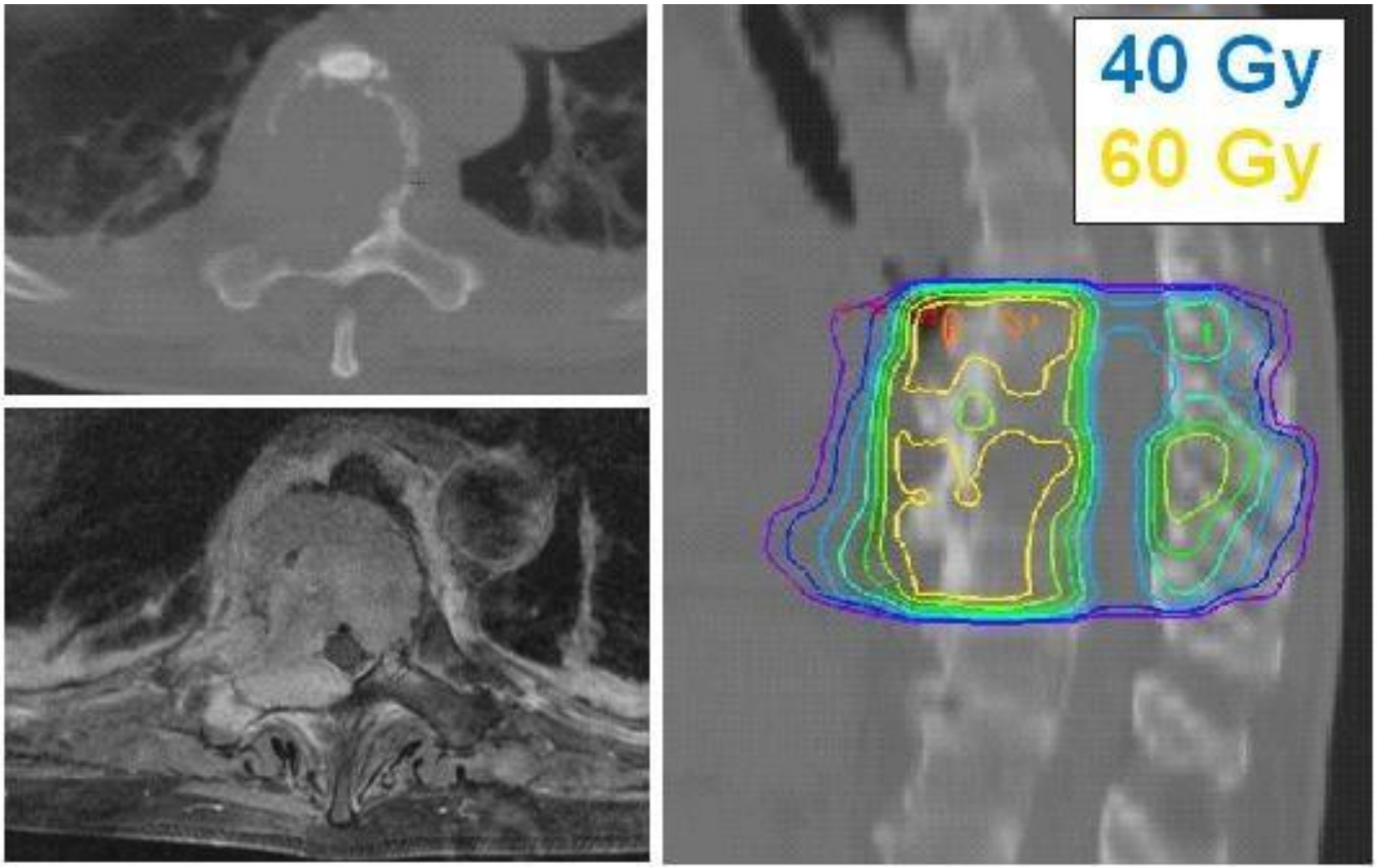


Computed tomograms showing the difference in radiotherapy dose distribution between simple, conventional palliative radiotherapy (A), and targeted stereotactic radiotherapy (B).



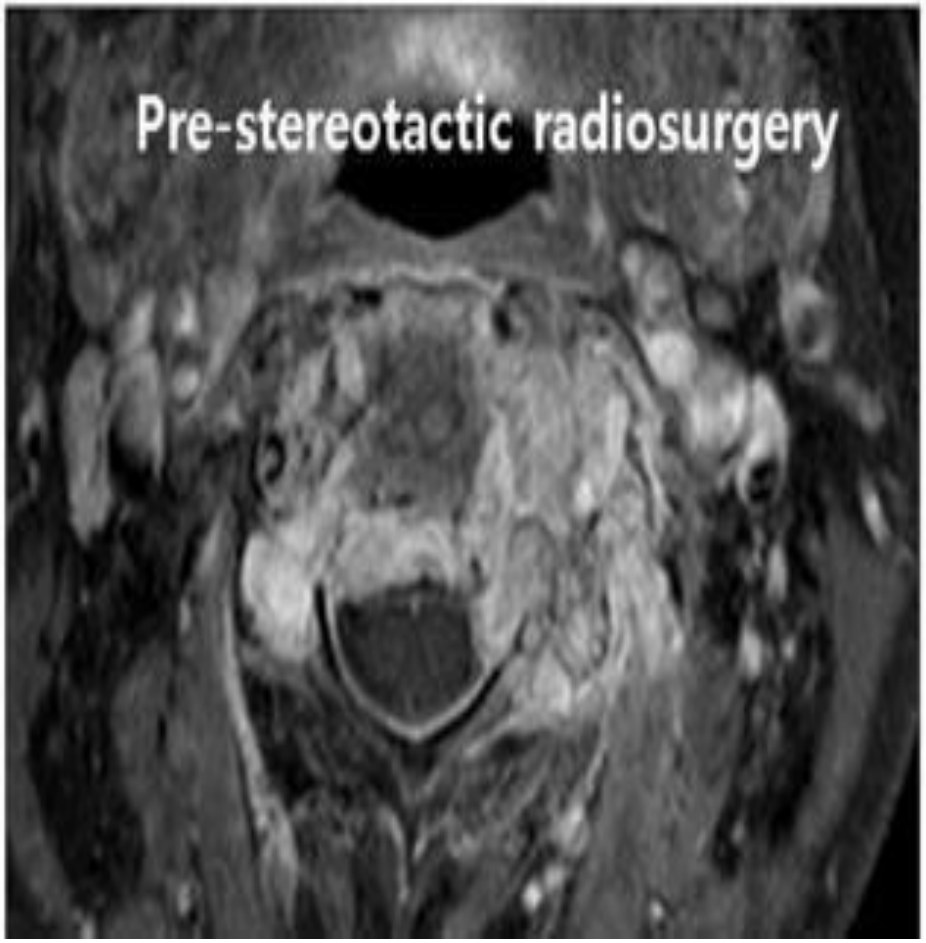
Katie Spencer et al. BMJ 2018;360:bmj.k821

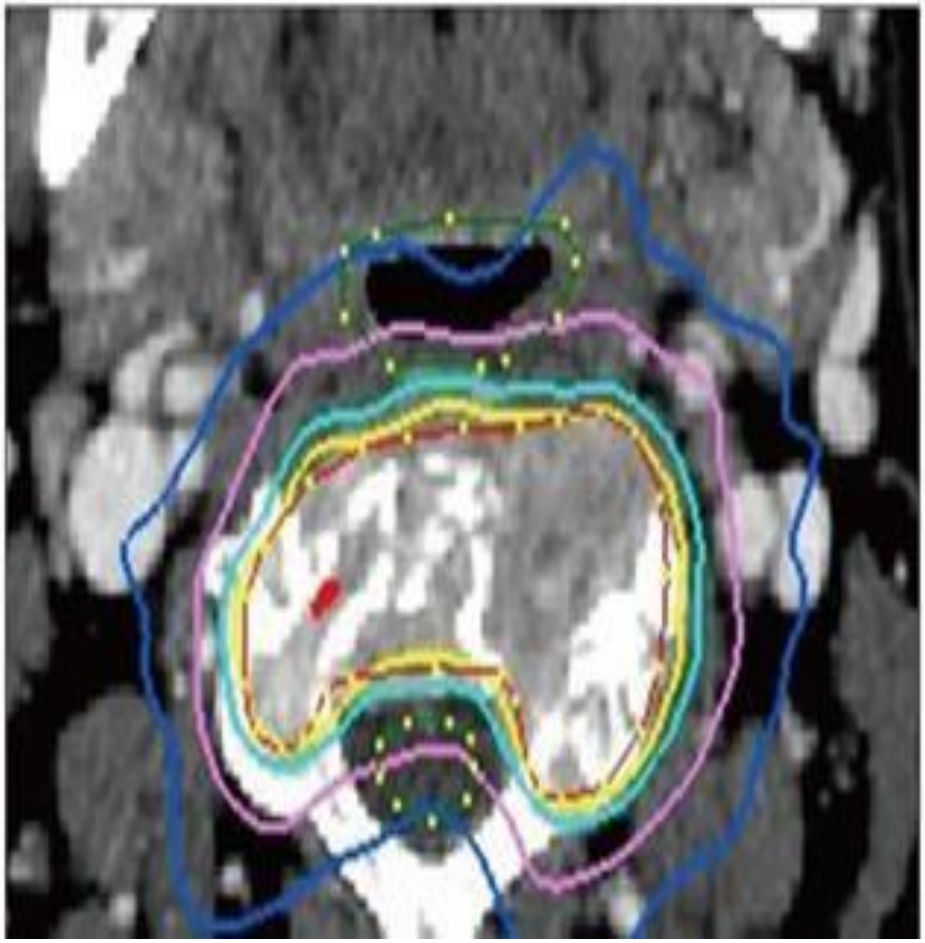
Intensity Modulated Radiotherapy - IMRT



- **IMRT- increase the dose and better spare - effect at surrounding tissue**

Stereotactic body radiotherapy SBRT

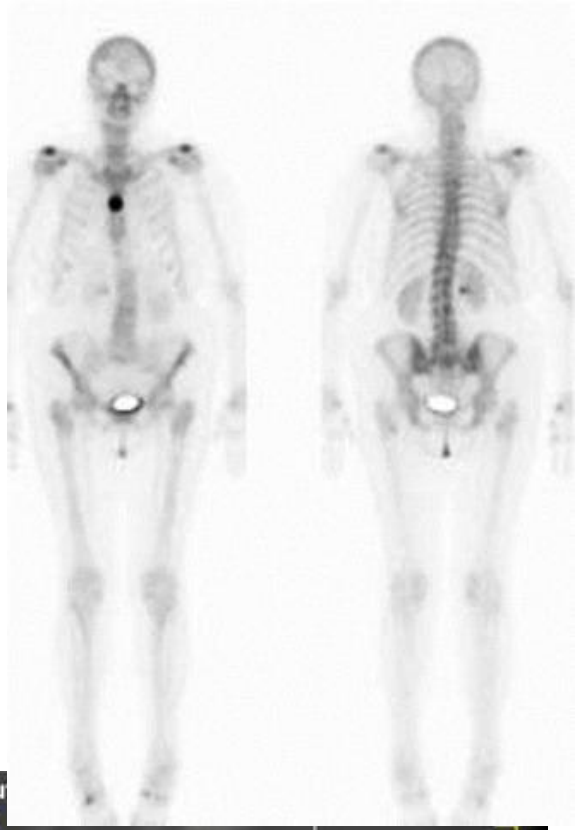




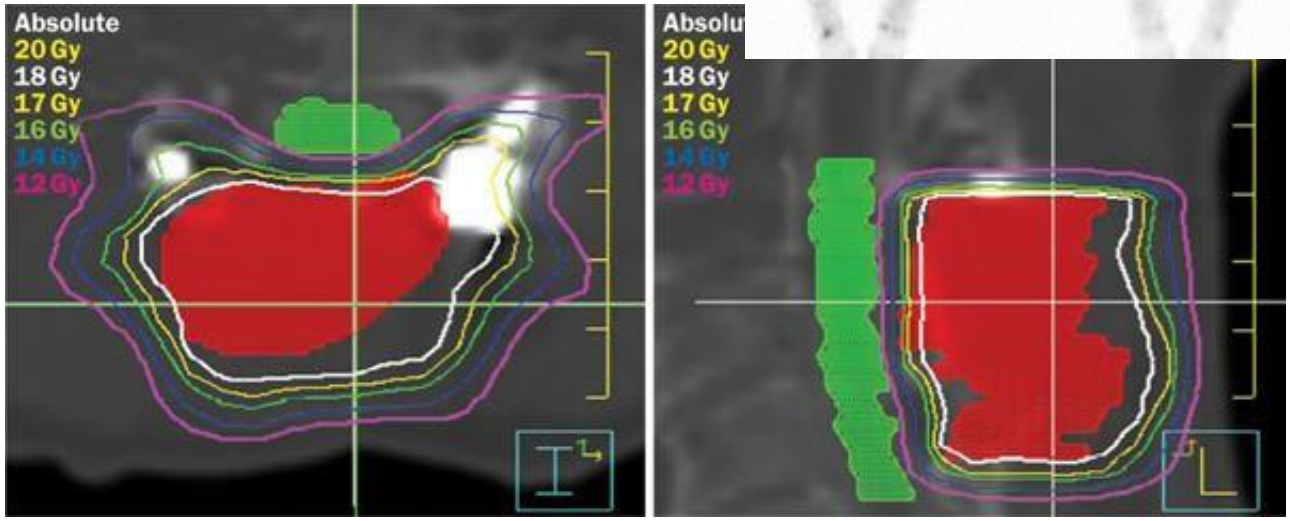
- **Extracranial Body Radiotherapy (SBRT)**

Indication for IMRT or SBRT

Oligometastaze →



Retretman →



Bisphosphonates and RT

- Concurrent delivery - successfully palliates bone pain and promotes re-ossification of the damaged bone
- Decrease bone pain scores and reduces skeletal related events
- Drawbacks to the delivery of bisphosphonates - renal impairment and osteonecrosis of the jaw

Bisphosphonates and RT

Bisphosphonates are internalized by osteoclasts, causing a decrease in both their activity and viability.

Radiotherapy is also thought to influence the activity of osteoclasts by reducing tumor produced osteoclast activating factors (OAF's), act synergistically

Could not find data to recommend one bisphosphonate or fractionation scheme combination as having greater efficacy than another.

Conclusion

- EBRT has been and continues to be the mainstay for the treatment of painful, uncomplicated bone metastases

- Either 8 Gy in single fraction, 16 Gy in 4 fractions, 20 Gy in 8 fractions, or 30 Gy in 10 fractions can provide excellent pain control and minimal side effects.
- Re-irradiation with EBRT may be safe, effective, and less commonly necessary in patients with a short life expectancy.

- Bisphosphonates do not obviate the need for EBRT for painful sites of metastases and may indeed act effectively in combination with EBRT.

- Surgical decompression and stabilization plus post- operative radiotherapy should be considered for selected patients with single level spinal cord compression or spinal instability