



Associazione  
Italiana  
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XXIV CONGRESSO NAZIONALE  
**AIRO2014**

Padova, 8-11 novembre



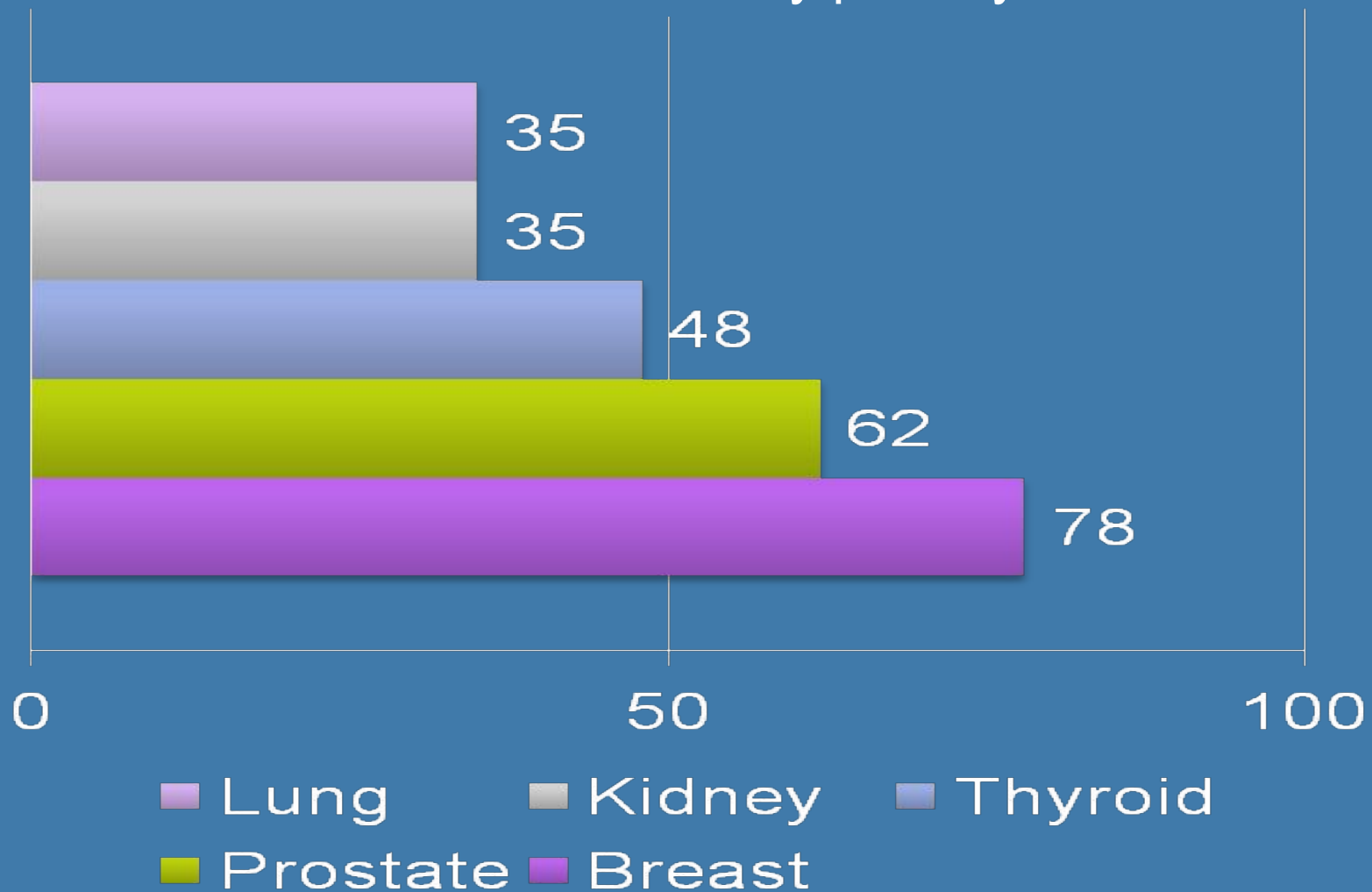
<b>MARTEDÌ 11 NOVEMBRE</b>	<b>SALA PLENARIA</b>
08.30-09.30	SIMPOSIO Trattamento delle metastasi ossee

## **Selezione clinica dei pazienti e score prognostici**

**Ernesto MARANZANO**  
Direttore  
Dipartimento di Oncologia  
S.C. di Radioterapia Oncologica  
Az. Ospedaliera di **Terni**

## Bone metastases

### Incidence by primary



## *Bone metastases*

### **Incidence by site & primary**

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

# *Bone metastases : clinical selection & prognosis*

## **✚ UNCOMPLICATED BONE METASTASES**

*(generally considered with a better prognosis with respect to)*

## **✚ COMPLICATED BONE METASTASES**

- ✓ an 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

## **✚ NEW THERAPEUTIC STRATEGIES**

- ✓ SBRT
- ✓ Targeted therapy

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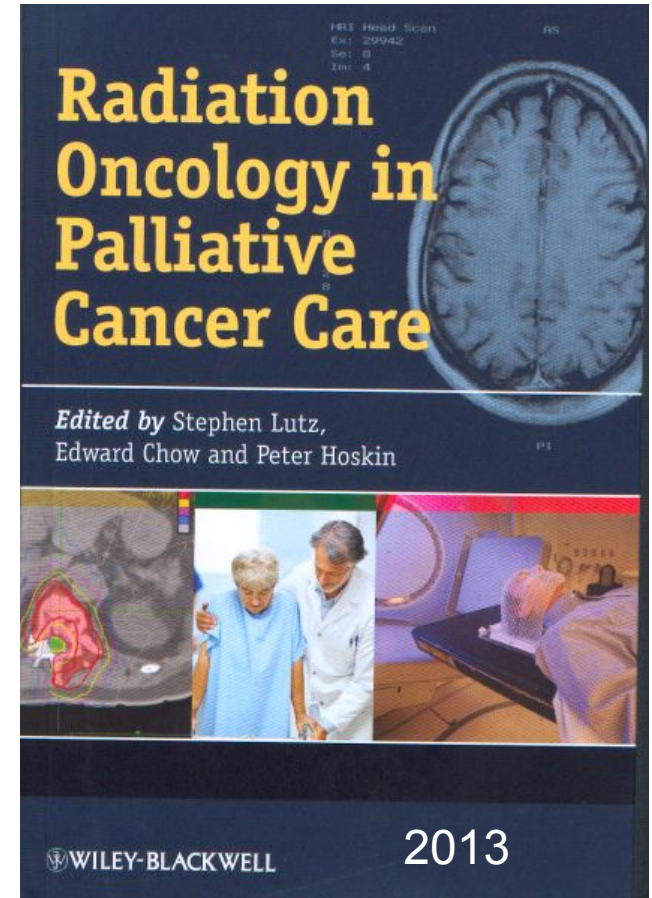
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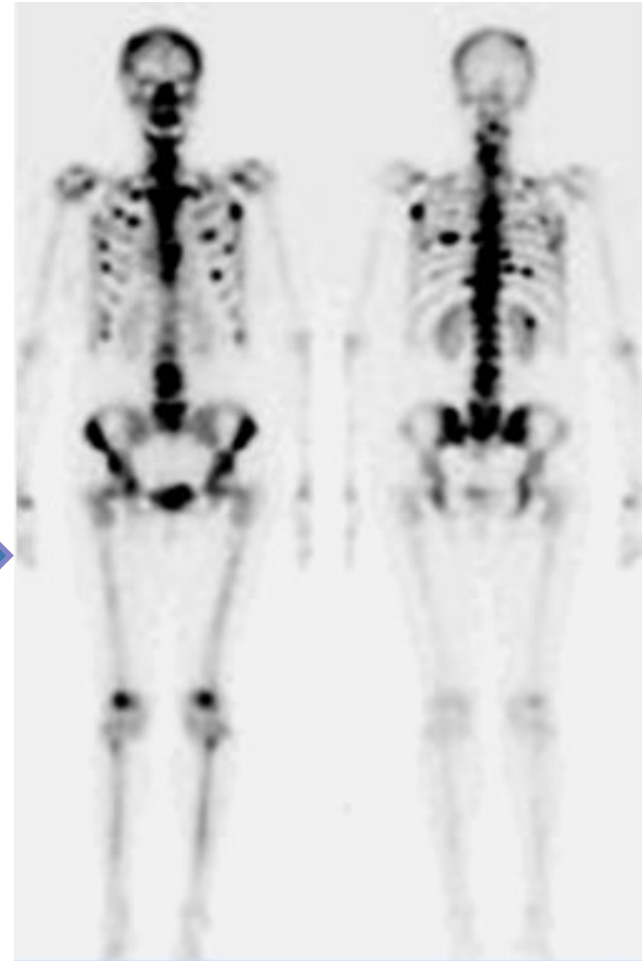
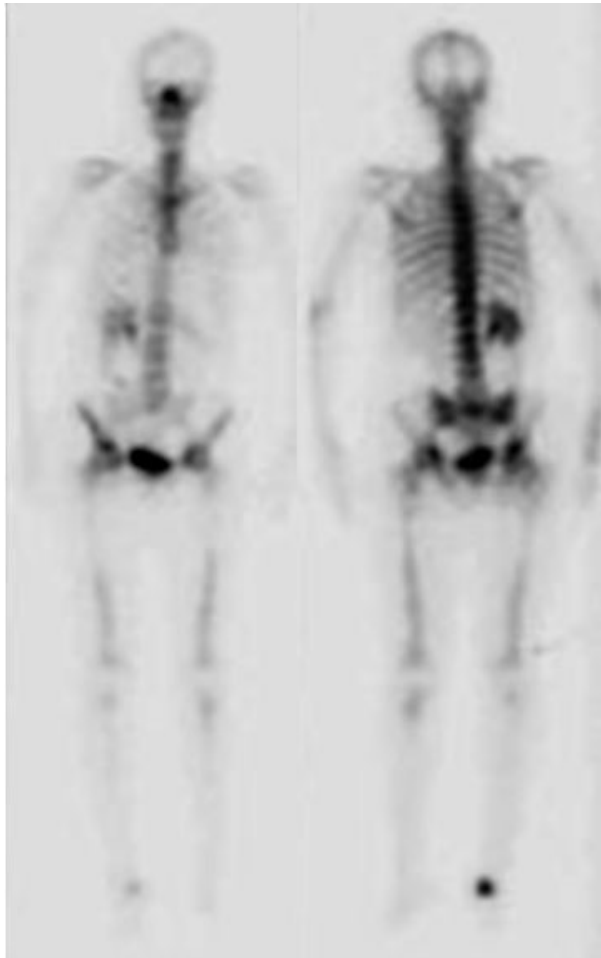
# PROGNOSIS

*Duration of survival after RT for bone metastases depends on a number of patient-related factors:*

1. **Clinical condition** → no comorbidity hampering the application of systemic treatments
2. **Metastatic burden** → 1-3 mets vs multiple mets
3. **Visceral metastasis** → yes vs no
4. **Type of primary tumor** → breast & prostate vs lung



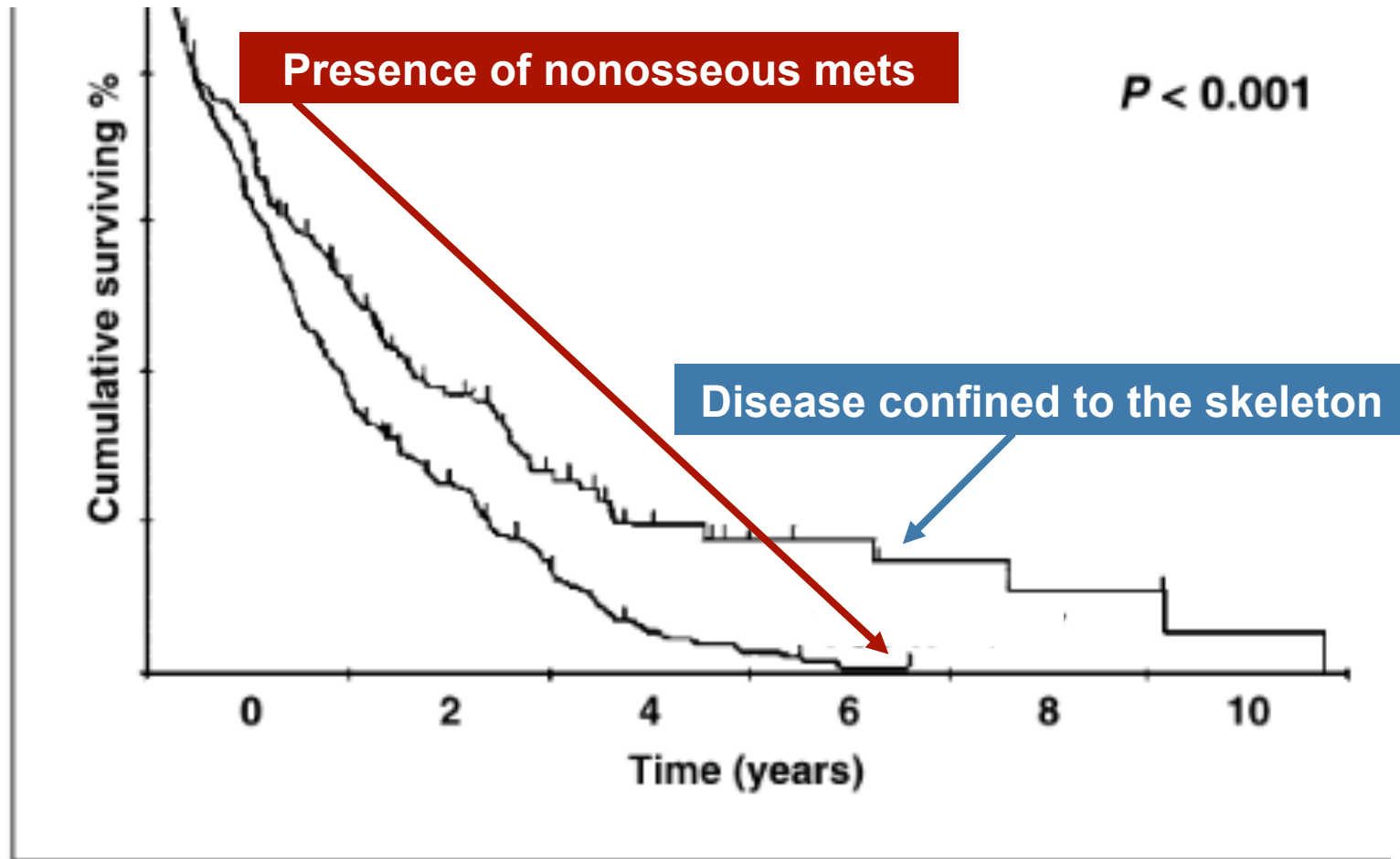
## Metastatic burden



**Bone only Oligometastasis**

**Multiple bone metastases**

## Visceral metastases



**Fig. 1.** Survival after bone metastases by subsequent development of nonosseous metastases or disease confined to the skeleton. Figure reprinted from Coleman et al. (7).



# PROGNOSIS

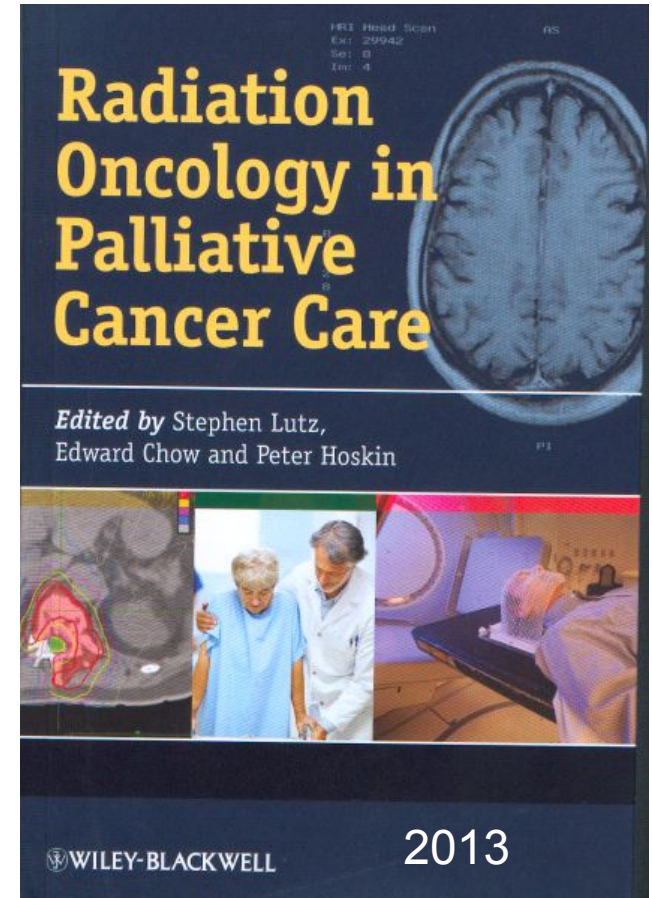
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3. Visceral metastasis → yes vs no
- 4. Type of primary tumor → breast & prostate vs lung**



Median survival:

- Breast → 15-15 months
- Prostate → 9-10 months
- Lung → 3-4 months



## Prognostic factors in patients with metastatic **breast and prostate cancer**

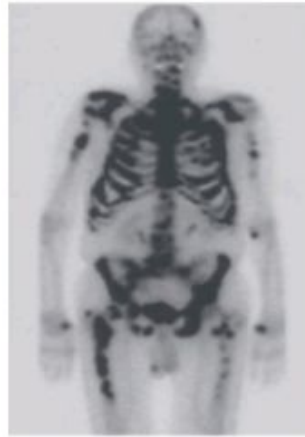
<u>Primary cancer</u>	Breast	Prostate
	<p> <u>Extraosseus</u> metastases            Estrogen receptor status            Metastasis free survival            Performance status            Age            Serological tumor marker levels            Histologic type (lobular vs ductal)            Histologic grade (ductal)            Bone metastases at presentation            Number of bone metastases            Symptomatic skeletal metastases         </p>	<p>           Performance status            Histologic grade            Baseline <u>prostatic</u> specific antigen            Hemoglobin level            Alkaline phosphatise            Lactate dehydrogenase            Aspartate aminotransferase            Extent of bone disease            Age            Gleason score            Clinical stage         </p>

*Vassiliou V., Chow E., Kardamakis and N. Lauzon:  
 Natural history, prognosis, clinical features and complications of metastatic bone disease, 19-36.  
 In: Vassiliou V., Chow E., Kardamakis D. Bone metastases, 2nd Ed. Springer, 2014.*

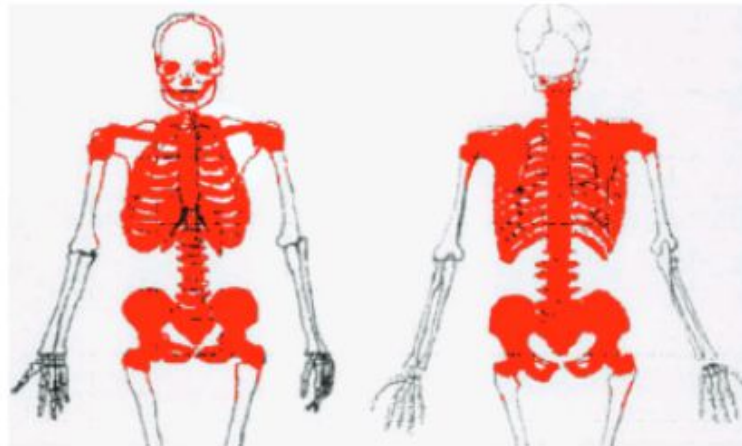
## Prognostic factors in patients with hormone-refractory metastatic prostate cancer

### The **BONE SCAN INDEX (BSI)**

is a quantitative expression of tumor burden seen on bone scintigraphy.



Tc-99m MDP:  
Extent of disease  
(numerator)



Skeletal mass  
(denominator)

The BSI is calculated first by determining the percentage of each bone that is involved by the tracer in relationship to the total skeletal mass, as determined from reference man. This procedure is done for every single bone, and all of the individual percentages are summed to arrive at a single number that represents the total tumor burden as a percentage of the total skeletal mass

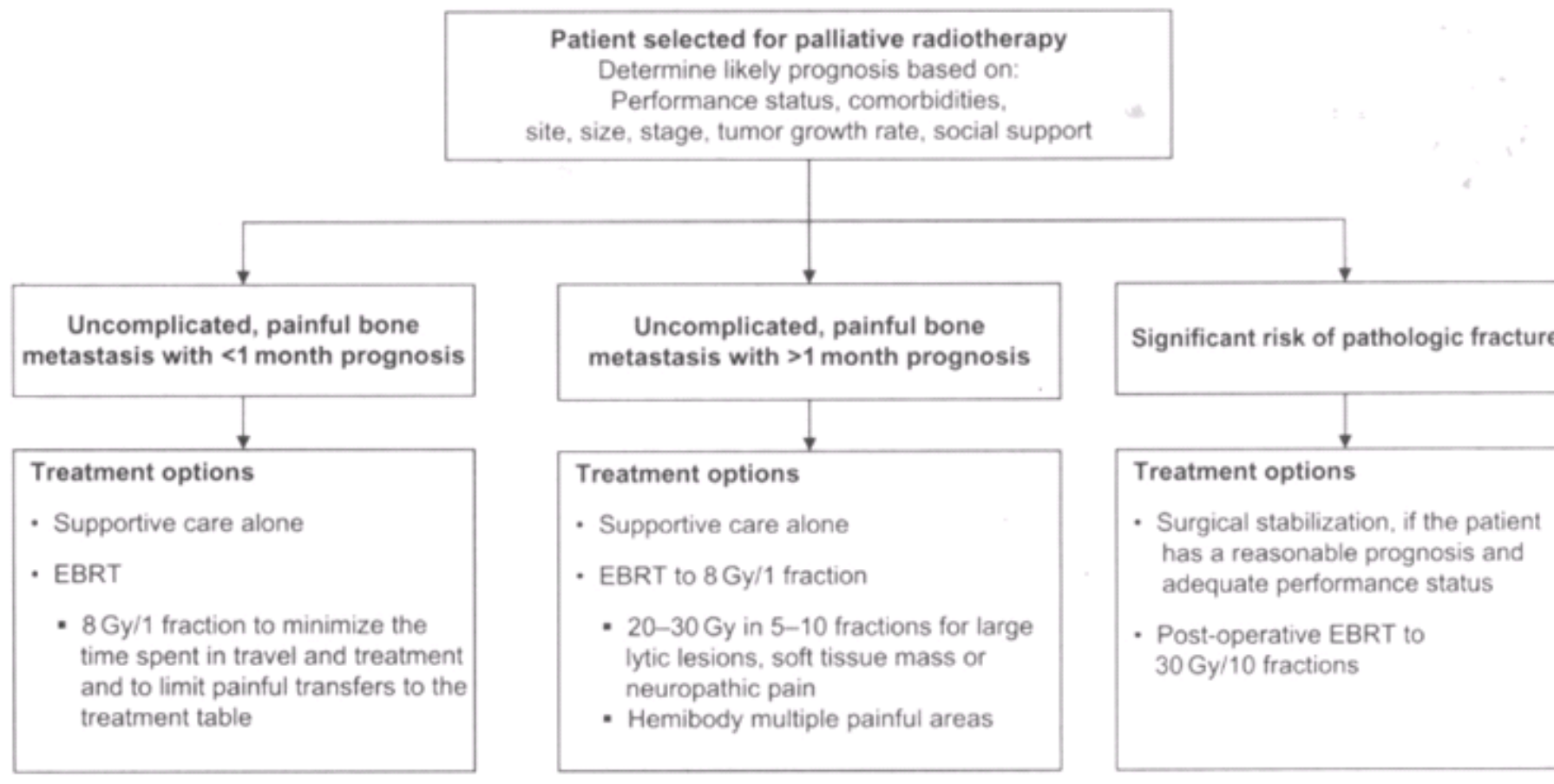
## Prognostic factors in patients with hormone-refractory metastatic prostate cancer

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

## Algorithm for use of palliative radiotherapy for patients with bone metastases



*van der Linden Y. and Rades K. Bone metastases, pagg. 241-256.  
In Lutz S., Chow E., Hoskin P., Radiation oncology in palliative cancer,  
Ed. Wiley-Blackwell, 2013.*

## **Algorithm for use of palliative radiotherapy for patients with bone metastases**

**Patient selected for palliative radiotherapy**

**Determine likely prognosis based on:**

**Performance status, comorbidities,  
site, size, stage, tumor growth rate, social support**

## Algorithm for use of palliative radiotherapy for patients with bone metastases

**Uncomplicated**, painful bone metastasis with **<1** month prognosis

### Treatment options

- Supportive care alone
- EBRT
  - 8Gy/1 fraction to minimize the time spent in travel and to limit painful transfers to the treatment table

## Algorithm for use of palliative radiotherapy for patients with bone metastases

**Uncomplicated**, painful bone metastasis with **>1** month prognosis

### Treatment options

- Supportive care alone
- EBRT to 8Gy/1 fraction
- 20-30Gy/5-10 fractions for large lytic lesion, soft tissue mass or neuropathic pain



# An Easy Tool to Predict Survival in Patients Receiving Radiation Therapy for Painful Bone

Metastases for the Dutch Bone Metastasis Study Group

Paulien G. Westhoff, MD,\* Yvette M. van der Linden, PhD,†

IJROBP, 90, 739-47, 2014

In the Dutch Bone Metastasis Study, 1157 patients were treated with radiation therapy for painful bone metastases. The best predictive model included

- **sex**
- **primary tumor**
- **visceral metastases**
- **KPS**
- **visual analogue scale**
- **verbal rating scale**

## Conclusion:

In predicting survival in patients with painful bone metastases, ***a reduced model with only KPS and primary tumor*** showed comparable discriminative capacity to a more complex model.

Considering the amount of variables in complex models and the additional burden on patients, the simple model is preferred for daily use

# *Bone metastases : clinical selection & prognosis*

## ✚ UNCOMPLICATED BONE METASTASES

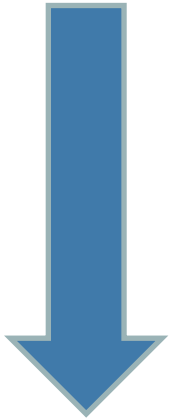
## ✚ COMPLICATED BONE METASTASES

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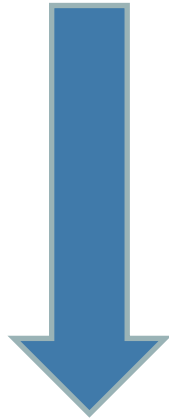
## ✚ NEW THERAPEUTIC STRATEGIES

- ✓ SBRT
- ✓ Targeted therapy

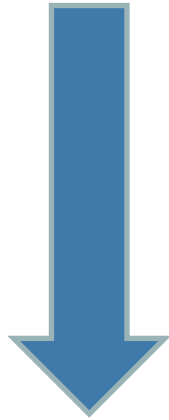
**PATHOLOGICAL FRACTURE** can have consequence on



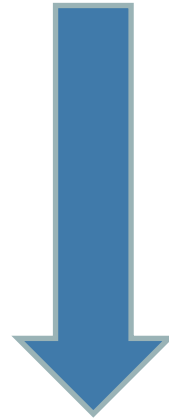
Clinic



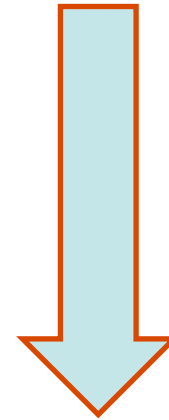
Social status



Economic status



QoL



**Prognosis**

## Impact on Survival: Fractures Negatively Affect Survival

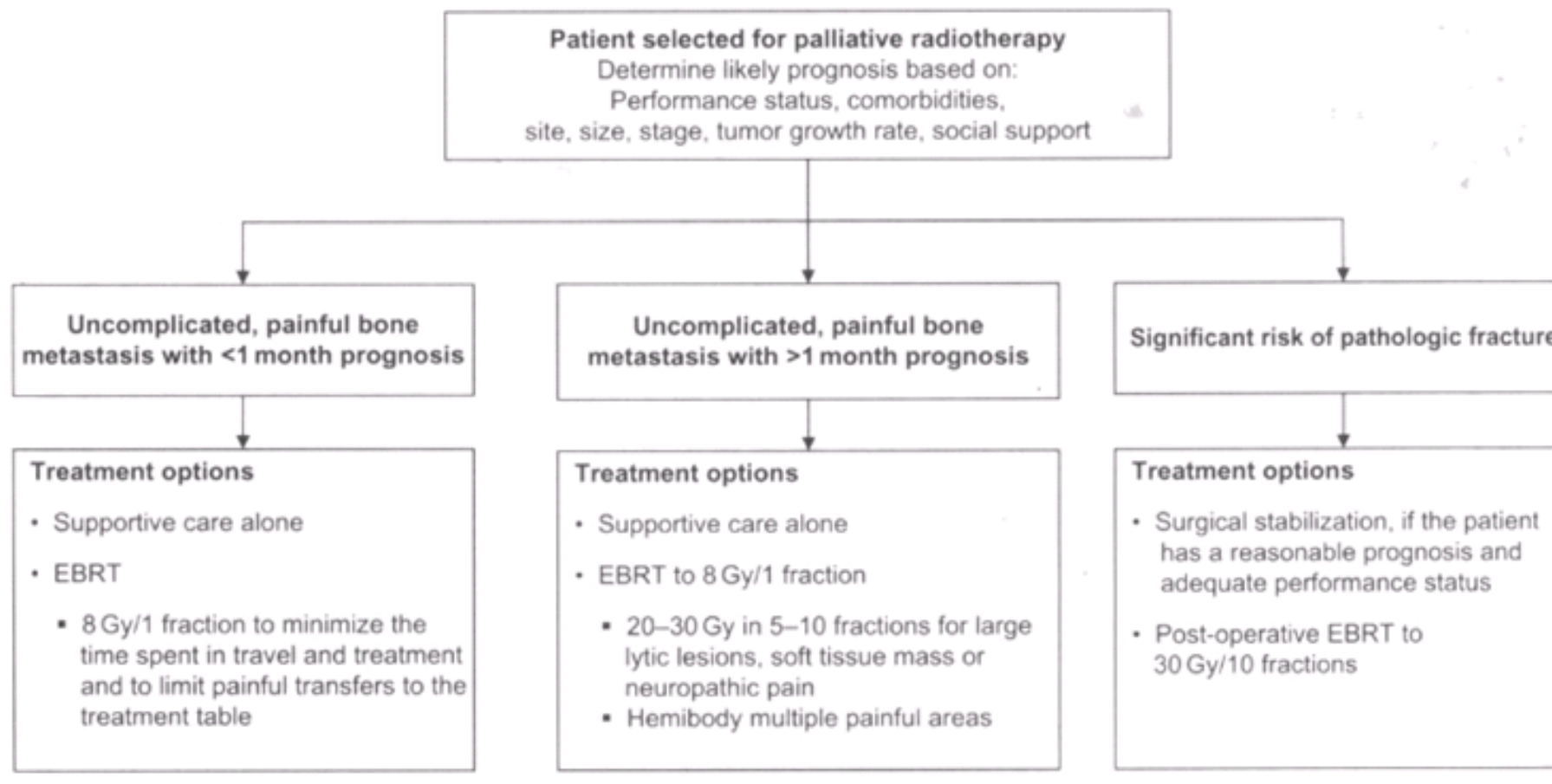
- Pathologic fractures correlate with a significantly increased relative risk of death<sup>1,2</sup>

– Breast cancer	1.52 (1.28, 1.81)	<i>P</i> < .0001
– Multiple myeloma	1.44 (1.06, 1.95)	<i>P</i> = .02
– Prostate cancer	1.29 (1.01, 1.65)	<i>P</i> = .04
– Lung cancer / Other	1.08 (0.87, 1.34)	<i>P</i> = .49

1. Hei Y-J, et al. Presented at: 28th Annual SABCS, 2005, Abstract 6036.

2. Saad F, et al. Presented at: ECCO 2005. Abstract 1265.

## Algorithm for use of palliative radiotherapy for patients with bone metastases



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In Lutz S., Chow E., Hoskin P., Radiation oncology in palliative cancer,  
Ed. Wiley-Blackwell, 2013.*

## Algorithm for use of palliative radiotherapy for patients with bone metastases

↓

Significant **risk of** pathologic **fracture**

↓

### Treatment options

- **Surgical stabilization**, if the patient has a reasonable prognosis and adequate performance status
- Post-operative EBRT to **30Gy** in 10 fractions

# *Bone metastases : clinical selection & prognosis*

## ✚ UNCOMPLICATED BONE METASTASES

## ✚ COMPLICATED BONE METASTASES

- ✓ an 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

## ✚ NEW THERAPEUTIC STRATEGIES

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

A phase II trial of hypofractionated radiotherapy (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)*

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[Appendix 4: EORTC QLQ-BM22 and EORTC QLQ-C30](#)

[Appendix 5: Consent Form](#)

**Ongoing trial**



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# ***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, JCO '98*

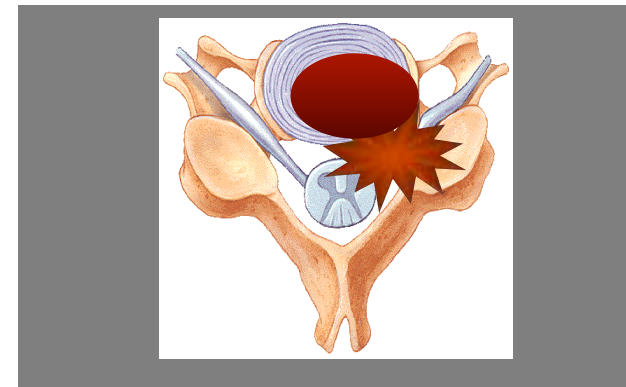


Table 1. Results of the multivariate analysis ( $N = 2096$ ) for  
post-RT ambulatory status

Potential prognostic factor	Relative risk (95% CI)	<i>p</i>
Age	1.09 (0.80–1.48)	0.591
Gender	1.39 (0.92–2.03)	0.124
ECOG performance status	14.28 (4.38–46.54)	<0.001*
Type of primary tumor	7.75 (3.48–16.06)	<0.001*
Interval between tumor diagnosis and MSCC	1.81 (1.29–2.54)	0.001*
Other bone metastases at the time of RT	1.25 (0.92–1.71)	0.162
Visceral metastases at the time of RT	1.58 (1.14–2.20)	0.007*
Number of involved vertebrae	1.15 (0.77–1.69)	0.753
Motor function before RT	21.41 (7.72–59.40)	<0.001*
Time of developing motor deficits before RT	8.20 (5.59–12.05)	<0.001*
RT schedule	1.21 (0.71–2.04)	0.178

# Metastatic spinal cord compression:

Diagnosis and management of patients at risk of or with metastatic spinal cord compression

**NICE Guideline 2008**

*...new onset back pain in a patient with known cancer must be considered **vertebral metastatic disease** until proven otherwise*

*...early diagnosis and prompt therapy are the most important prognostic factors in **Metastatic Spinal Cord Compression** patients*

# Metastatic spinal cord compression

## 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

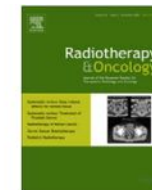
*E. Maranzano et al*



Contents lists available at ScienceDirect

Radiotherapy and Oncology **2009**

journal homepage: [www.thegreenjournal.com](http://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

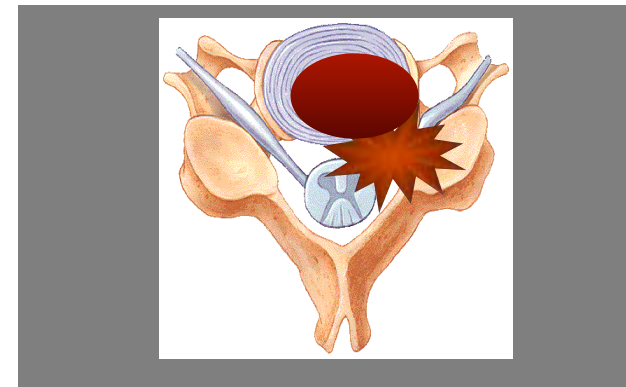
Ernesto Maranzano<sup>a,\*</sup>, Fabio Trippa<sup>a</sup>, Michelina Casale<sup>a</sup>, Sara Costantini<sup>a</sup>, Marco Lupattelli<sup>b</sup>, Rita Bellavita<sup>b</sup>, Luigi Marafioti<sup>c</sup>, Stefano Pergolizzi<sup>d</sup>, Anna Santacaterina<sup>d</sup>, Marcello Mignogna<sup>e</sup>,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

# ***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<sup>†</sup>

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

C. I. Ripamonti<sup>1</sup>, D. Santini<sup>2</sup>, E. Maranzano<sup>3</sup>, M. Berti<sup>4</sup> & F. Roila<sup>5</sup>, 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].



# *Bone metastases : clinical selection & prognosis*

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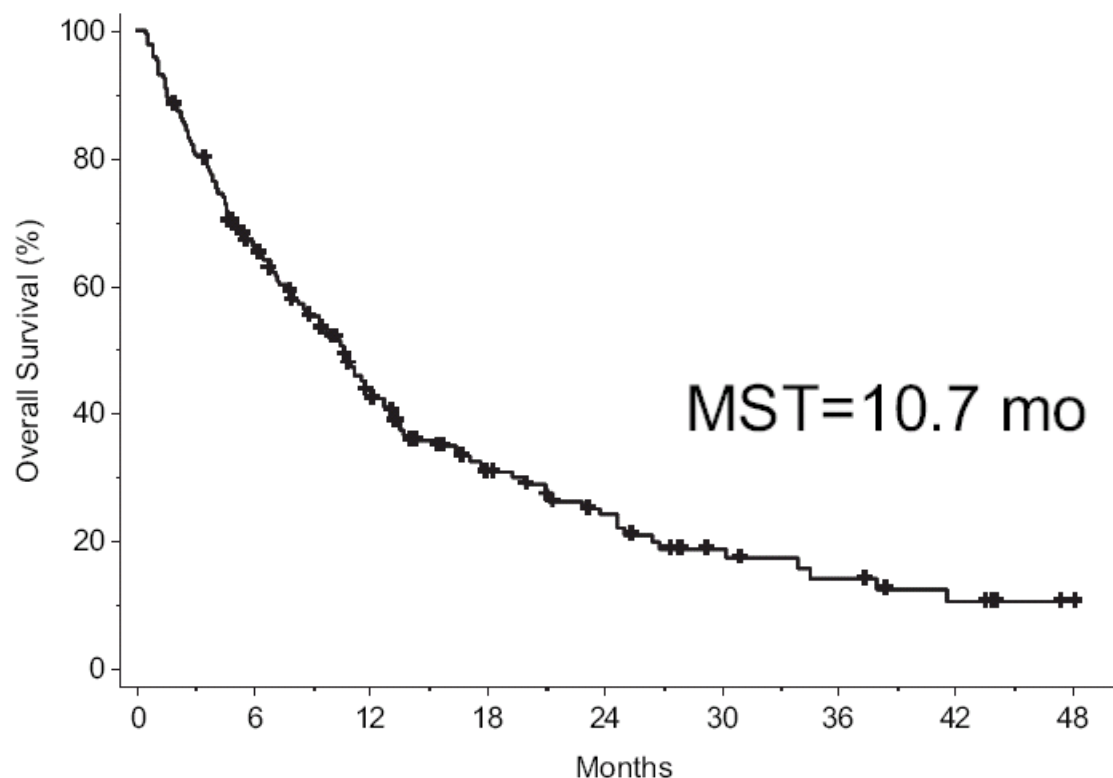
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# **RECURSIVE PARTITIONING ANALYSIS INDEX IS PREDICTIVE FOR OVERALL SURVIVAL IN PATIENTS UNDERGOING SPINE STEREOTACTIC BODY RADIATION THERAPY FOR SPINAL METASTASES**

SAMUEL T. CHAO, M.D., \*†§ SHLOMO A. KOYFMAN, M.D., \*§ NEIL WOODY, B.S., \*§

**Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1738–1743, 2012**



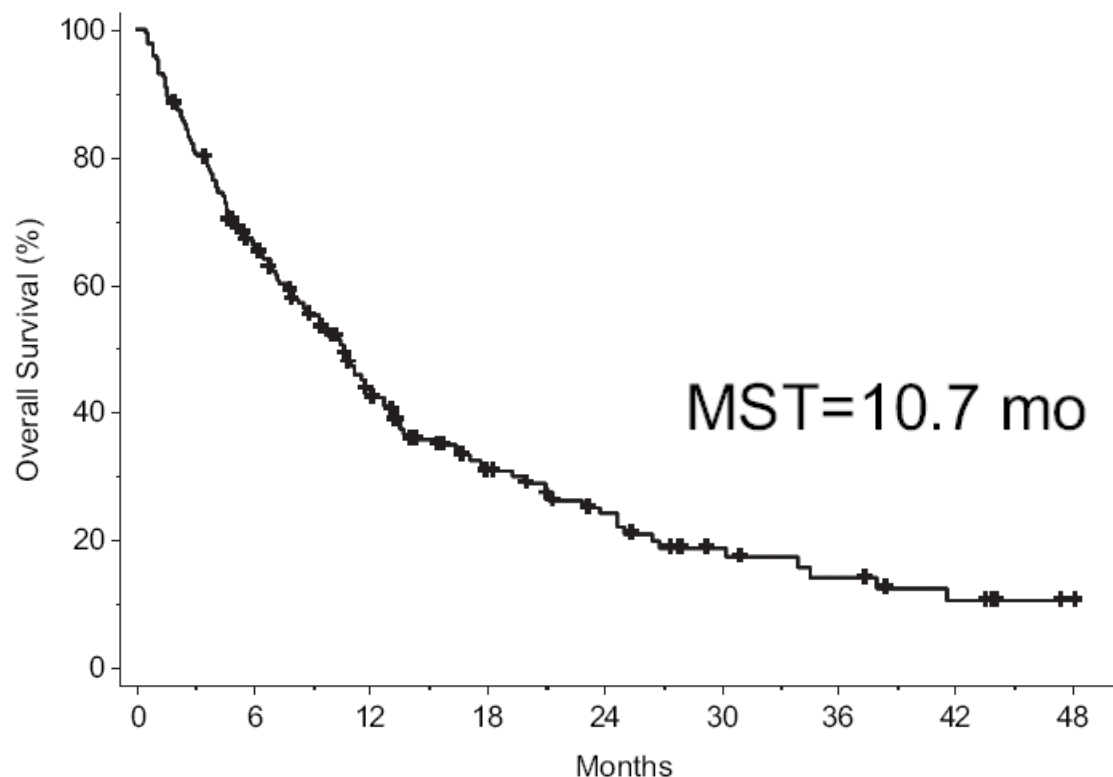
## **RPA prognostic factors:**

Histology, gender, KPS, age, TPD (time from primary diagnosis), spinal disease extension, extraosseous disease, upfront/salvage therapy, previous chemo, SBRT dose

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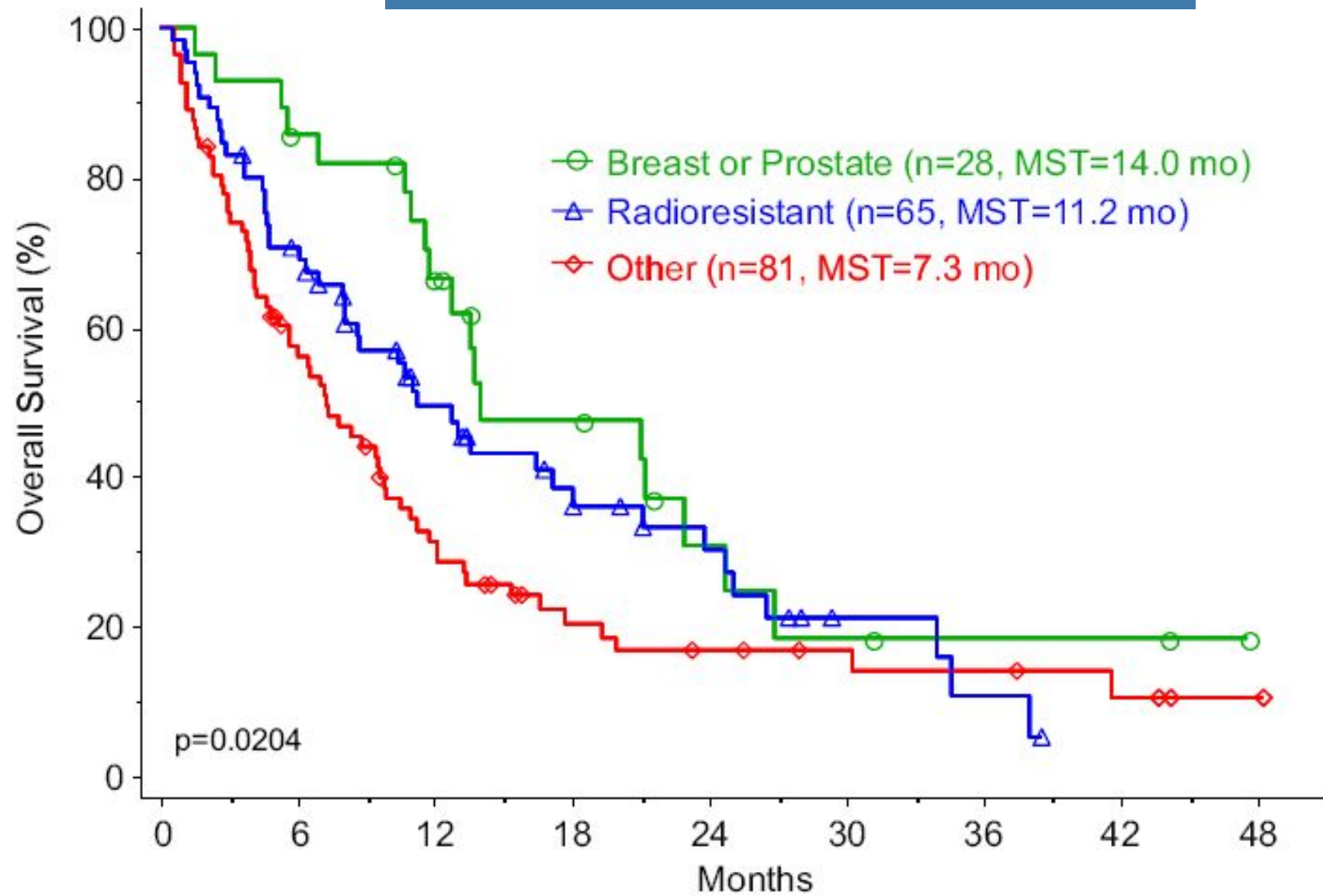
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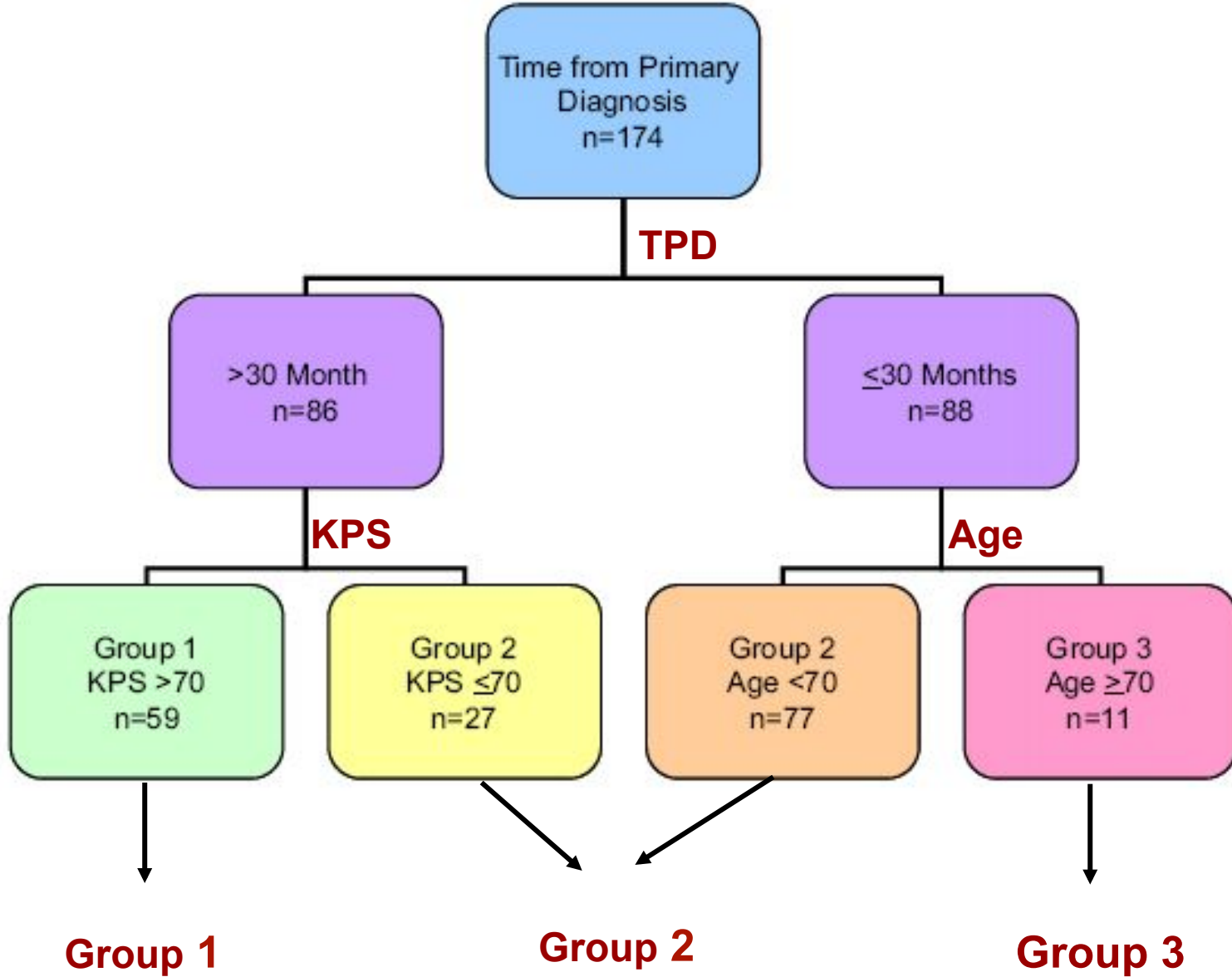
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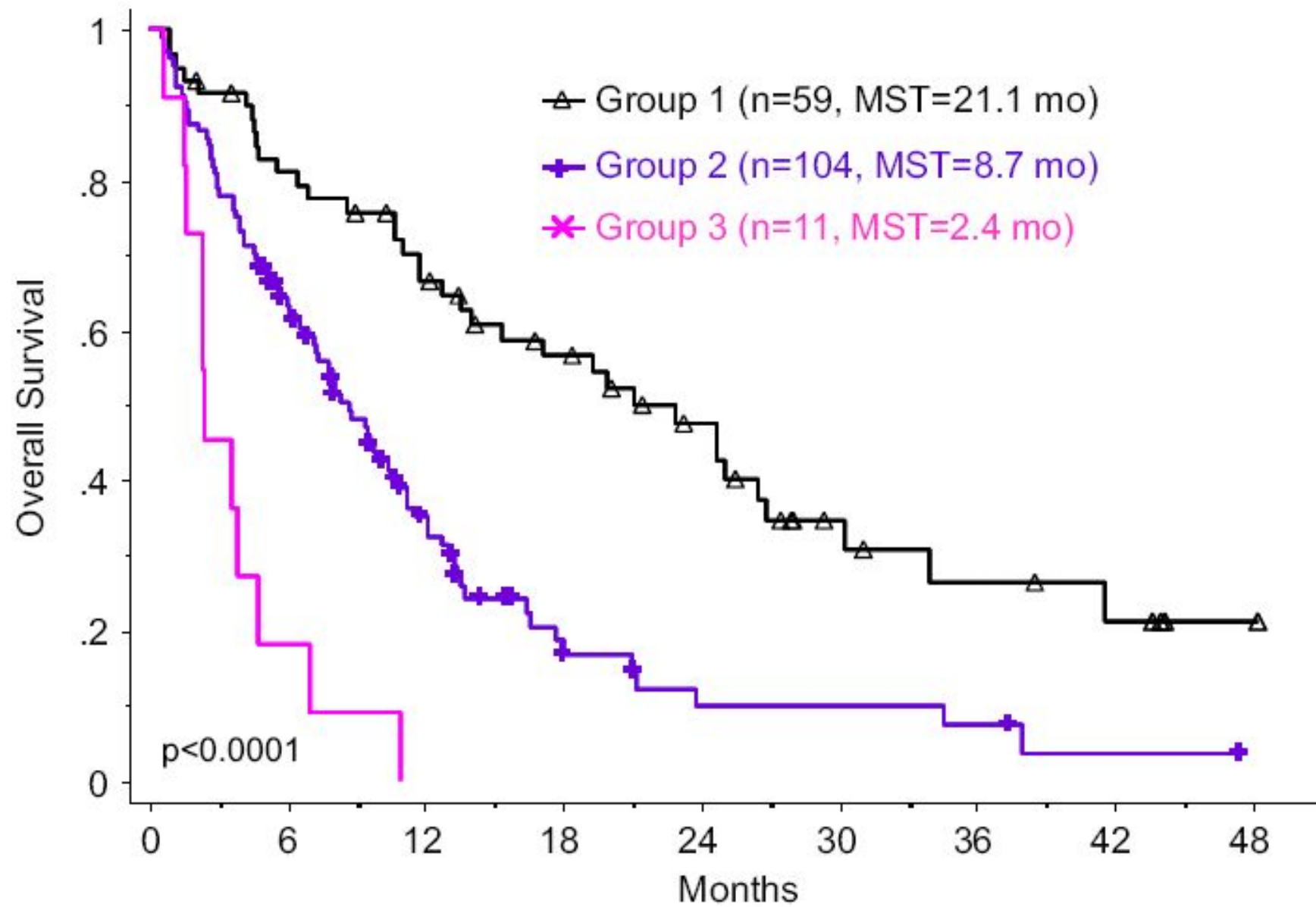
Histology, gender, KPS, age, TPD (time from primary diagnosis), spinal disease extension, extraosseous disease, upfront/salvage therapy, previous chemo, SBRT dose

## RPA prognostic factors: **histology**



RPA prognostic factors: **TPD**, **KPS** & **age**







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# LA RADIOTERAPIA PALLIATIVA CON TECNICHE SPECIALI DELLA MALATTIA METASTATICA

**Treviso il 7 giugno, Terni il 21 giugno,  
Cosenza il 28 giugno e Genova il 13 settembre 2013**





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LA RADIOTERAPIA  
PALLIATIVA CON  
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METASTATICA

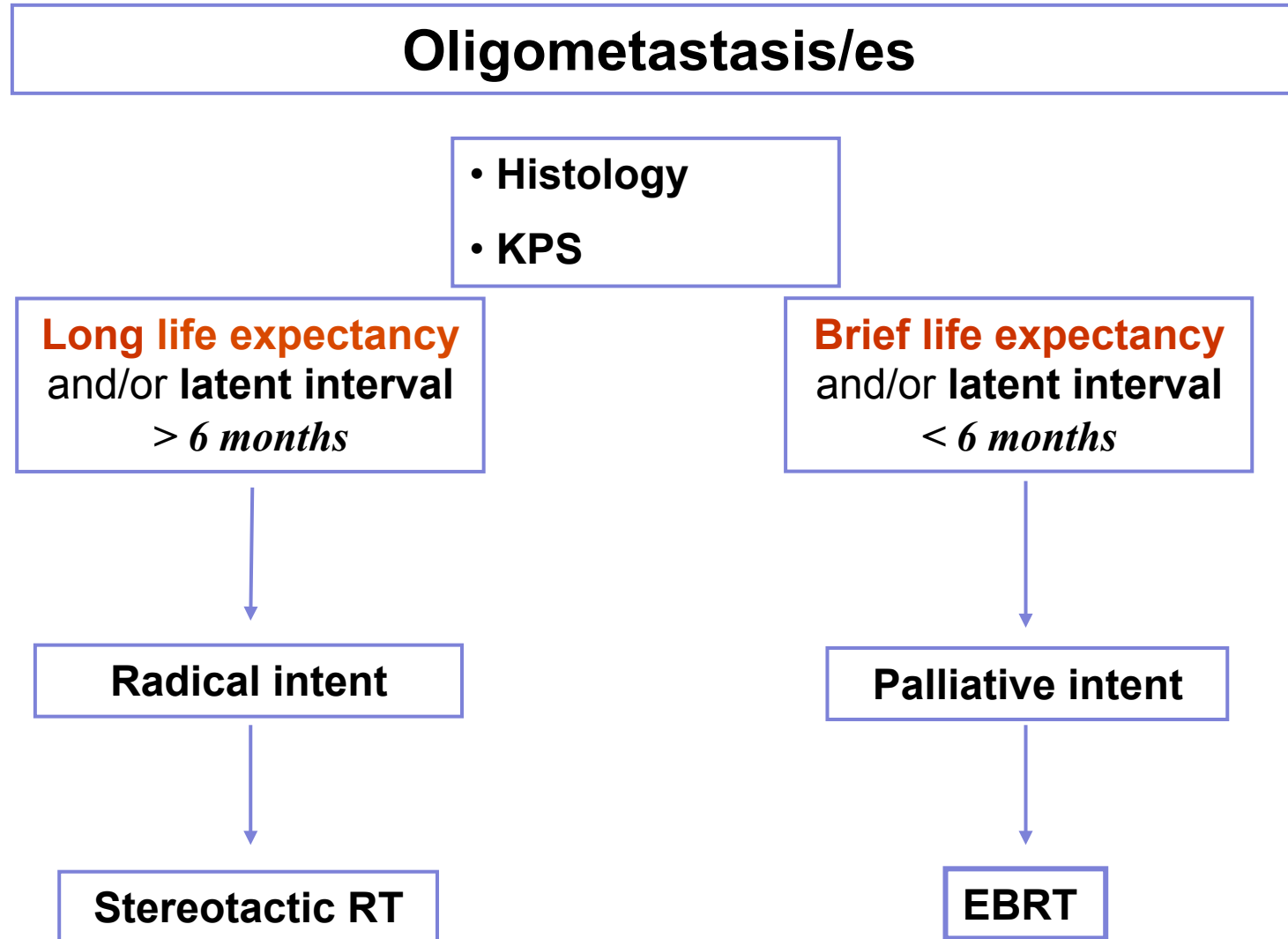


# OLIGOMETASTASES



**Patient selection for  
stereotactic RT**

# PATIENT SELECTION for stereotactic RT



# *Bone metastases : clinical selection & prognosis*

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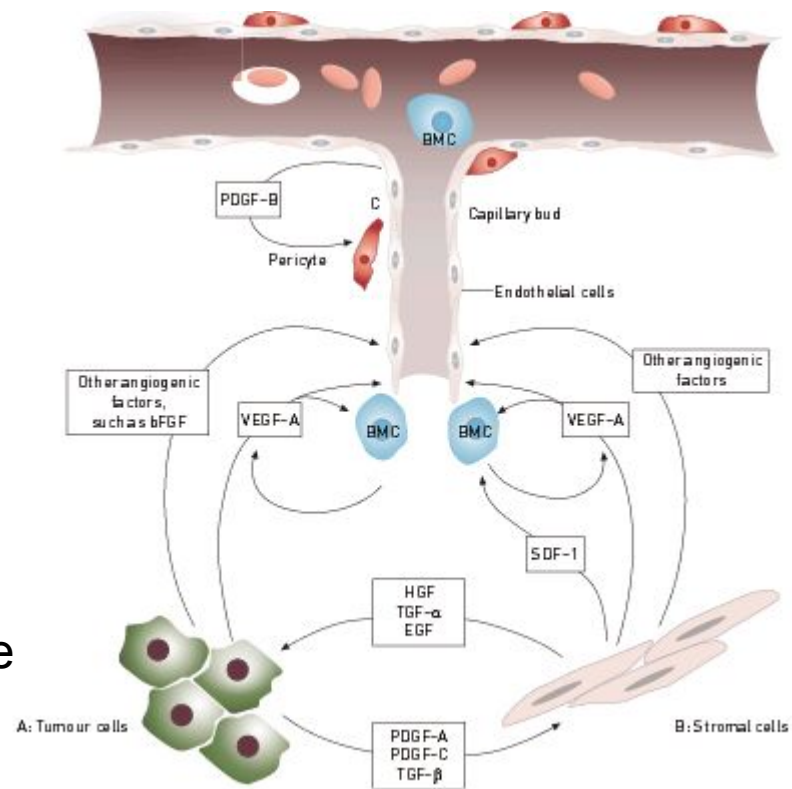
## ✚ NEW THERAPEUTIC STRATEGIES

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# METASTATIC NON SMALL CELL LUNG CANCER

**EGFR mutations** is a positive prognostic factor for survival in advanced NSCLC patients treated with chemotherapy with or without erlotinib,

Non-small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (**EGFR**) is highly responsive to **EGFR** tyrosine kinase inhibitors such as gefitinib and erlotinib

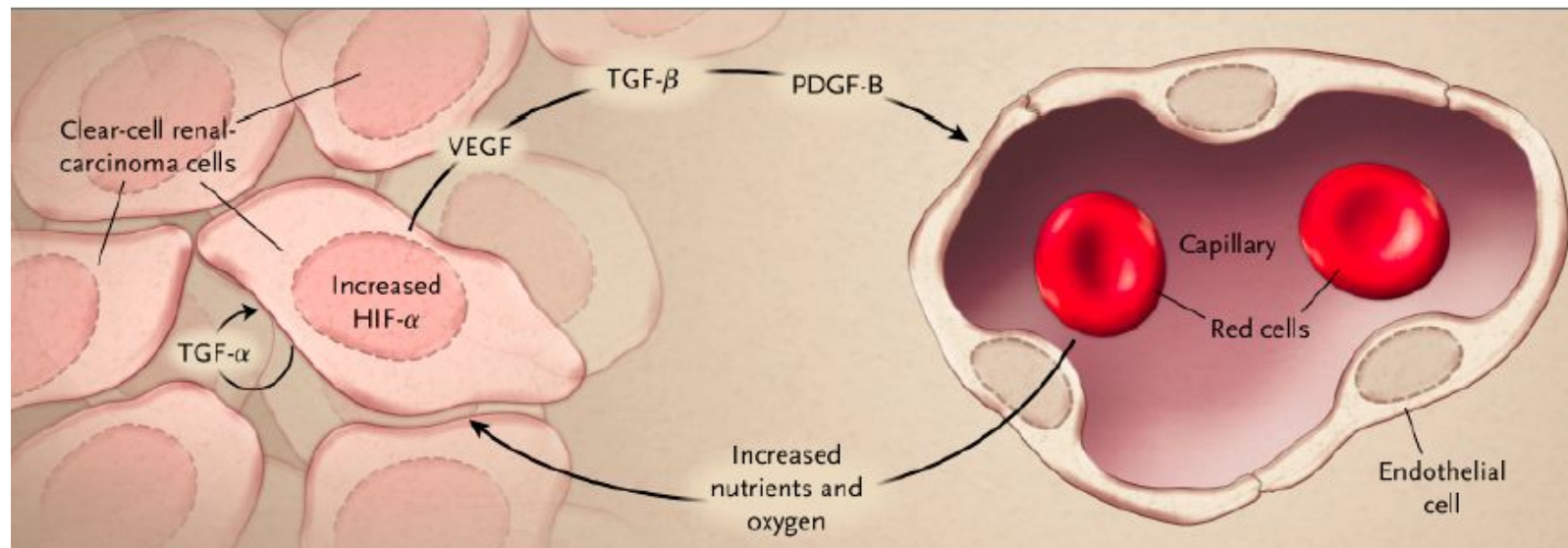


# METASTATIC RENAL CELL CARCINOMA

**From 2005:** Drugs that target signaling pathways involved in tumor proliferation and angiogenesis have transformed the treatment of metastatic renal cell carcinoma (mRCC) the *tyrosine kinase inhibitor* (TKI) **sorafenib** was shown to prolong overall survival

**Than** other drugs have been approved for mRCC on the basis of randomized controlled trials

- ✚ 3 TKIs/VEGF receptor inhibitors (**sunitinib**, **pazopanib** and **axitinib**),
- ✚ 1 monoclonal antibody (**bevacizumab**)
- ✚ 2 mTOR inhibitors (**temsirolimus** and **everolimus**)



Sorafenib as first- or second-line therapy  
in patients with metastatic renal cell  
carcinoma in a community setting

Future  
**ONCOLOGY**

10,1141-50, 2014

*G. Procopio et al.*

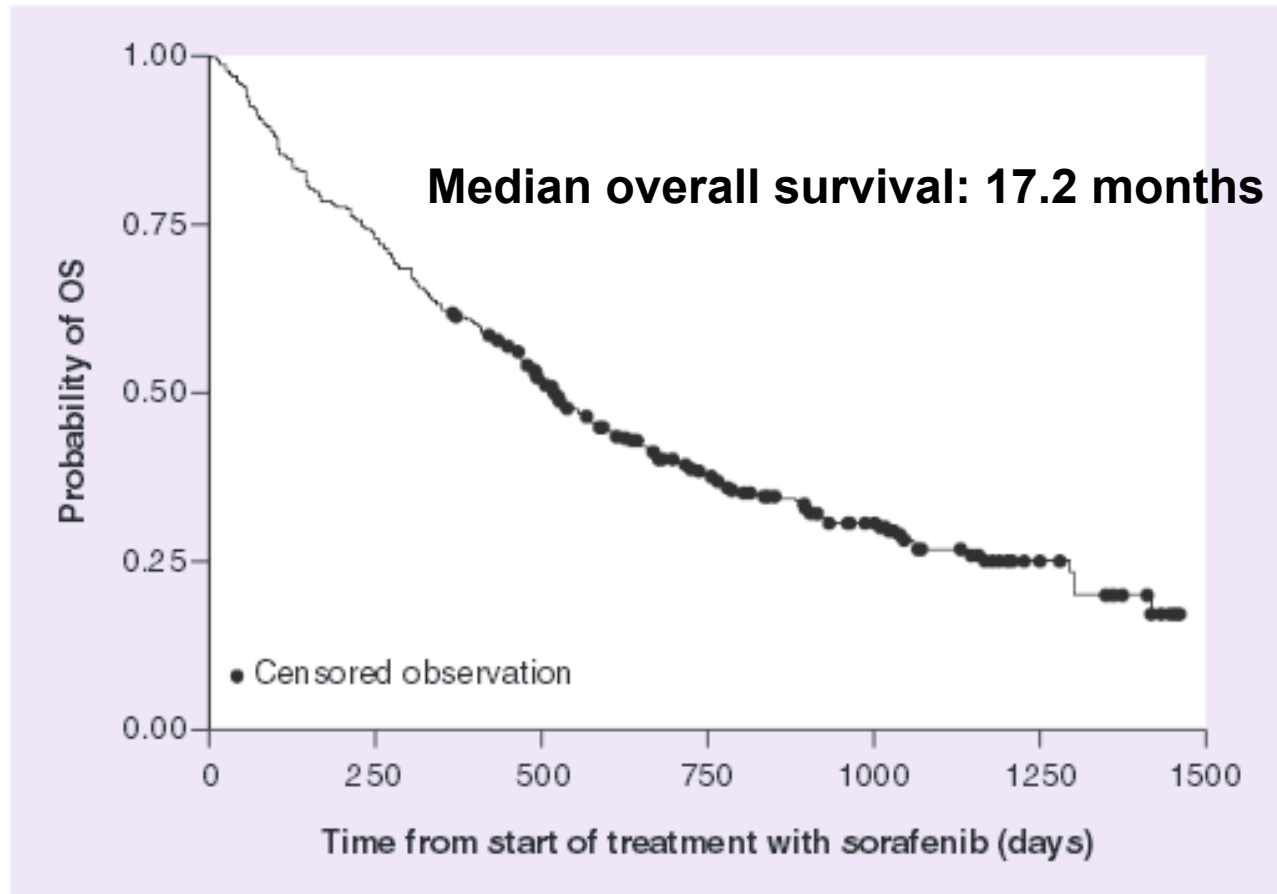


Figure 1. Overall survival (total population). OS was analyzed in 353 patients

## CONCLUSIONS

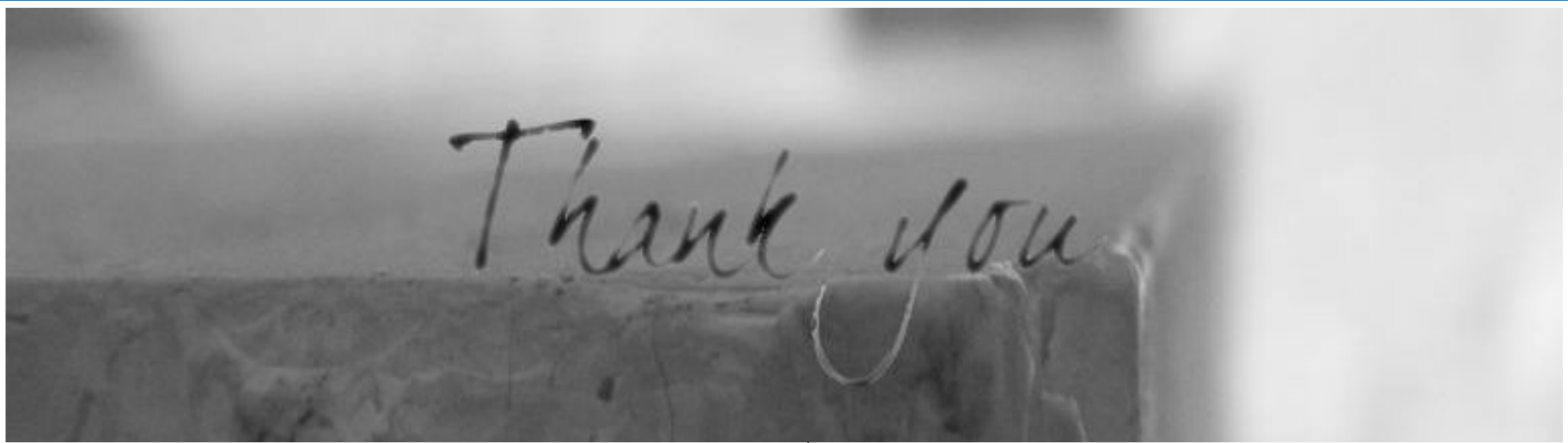
- ✦ There are many prognostic factors to predict survival in pts receiving RT for painful bone mets
- ✦ However, some prognostic factor could be more important than others (perhaps for their capacity to “contain” other variables), i.e.
  - ***KPS & primary tumor histology*** for bone mets;
  - ***early diagnosis & prompt therapy*** for spinal cord compression

## CONCLUSIONS *(cont.)*

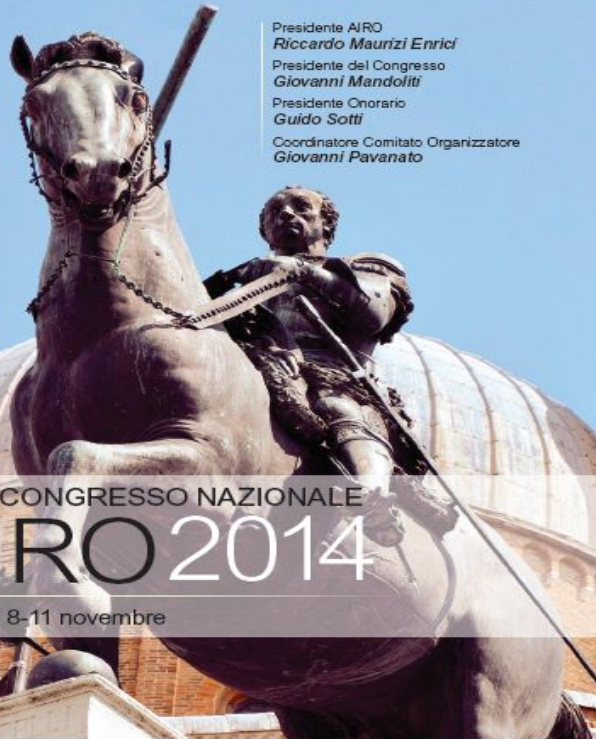
✚ Median survivals of patients with bone mets from poor radiosensitive tumors (e.g., kidney cancer and NSCLC) have significantly improved due to the effectiveness of **Stereotactic radioablation** and **Targeted therapy**

Pay attention in giving prognostic “numbers” on median survival in daily clinical practice !!!





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**AIRO 2014**

Padova, 8-11 novembre

