DICHIARAZIONE

Relatore: Ernesto Maranzano

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

Sessione (9)

Metastasi scheletriche

Quadri clinici della malattia ossea metastatica

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

SYMPTOMS COMMONLY ASSOCIATED WITH BONE METASTASES (BM)

- Pain
- Impending/Pathologic fracture
- Spinal cord/Nerve root compression
- Hypercalcemia

SYMPTOMS COMMONLY ASSOCIATED WITH BONE METASTASES (BM)

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The most common complaint in patients with bone metastasis (BM) are pain and/or impaired mobility

BONE PAIN IN PATIENT WITH CANCER

Type of pain:

- Localized bone pain
- Pain with a radiating component (i.e., neuropathic pain)

MECHANISMS of Bone Metastatic PAIN (it is not clear):

- Periosteum compression/infiltration/stretching
  → nociceptor stimulation
  → nerve stimulation

- Chemical mediators* of pain released by BM

* ***Prostaglandins, leukotrienes, substance P, bradykinin, interleukins-1 and -6, endothelins and tumor necrosis factor-α (TNF- α)***

BONE PAIN IN PATIENT WITH CANCER

Type of pain:

- Pain from **extremity lesions** tend to be well defined
- **Spinal or pelvic** involvement may produce vague, diffuse symptoms.
- If the lesion is in a **weight-bearing area**, eventually the pain tends to worsen with weight-bearing activity

- **Functional pain** is caused by the strength weakness of the bone that can no longer support the normal stresses of common daily activities. The development of functional pain may be a marker for bone at risk of fracture

- **Mechanical pain** is more typically associated with the focal bone loss within lytic lesions

Caveat! → **it is important to note that radiographically, osteoblastic lesions may also weaken the bone through associated areas of osteolysis. (**This increases osteoclastic activity in osteoblastic lesions and therefore also compromises structural integrity**).**

SYMPTOMS COMMONLY ASSOCIATED WITH BONE METASTASES (BM)

- Pain
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Impending or pathologic fractures

- Progressive involvement of the bone cortex weakens the axial strength of the bone and give rise to instability
- To minimize the risk of pathologic fractures lesions at risk of fracturing must be detected and treated assertively
- Preventive surgery is easier to do for surgeon and has less morbidity and mortality for patient!

HOW TO PREDICT IMPENDING FRACTURE?

Comparative analysis of risk factors for pathological fracture with femoral metastases

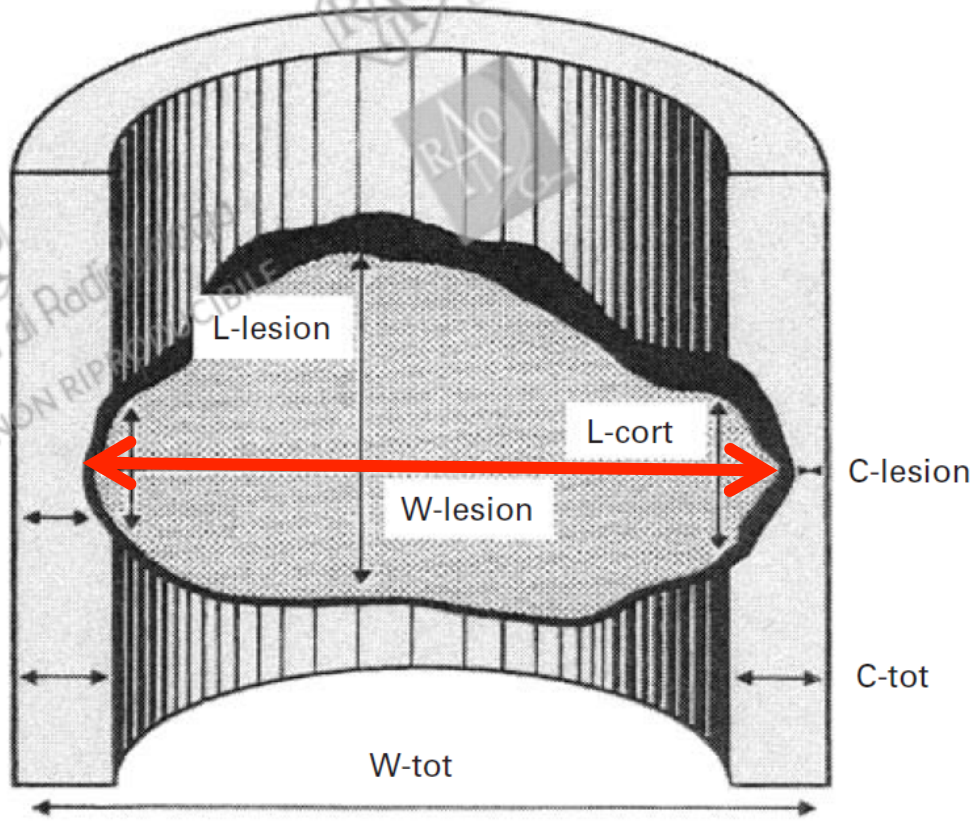
RESULTS BASED ON A RANDOMISED TRIAL OF RADIOTHERAPY

Dutch bone metastasis study: 110 femoral metastases **Y. van der Linden et al. 2004**

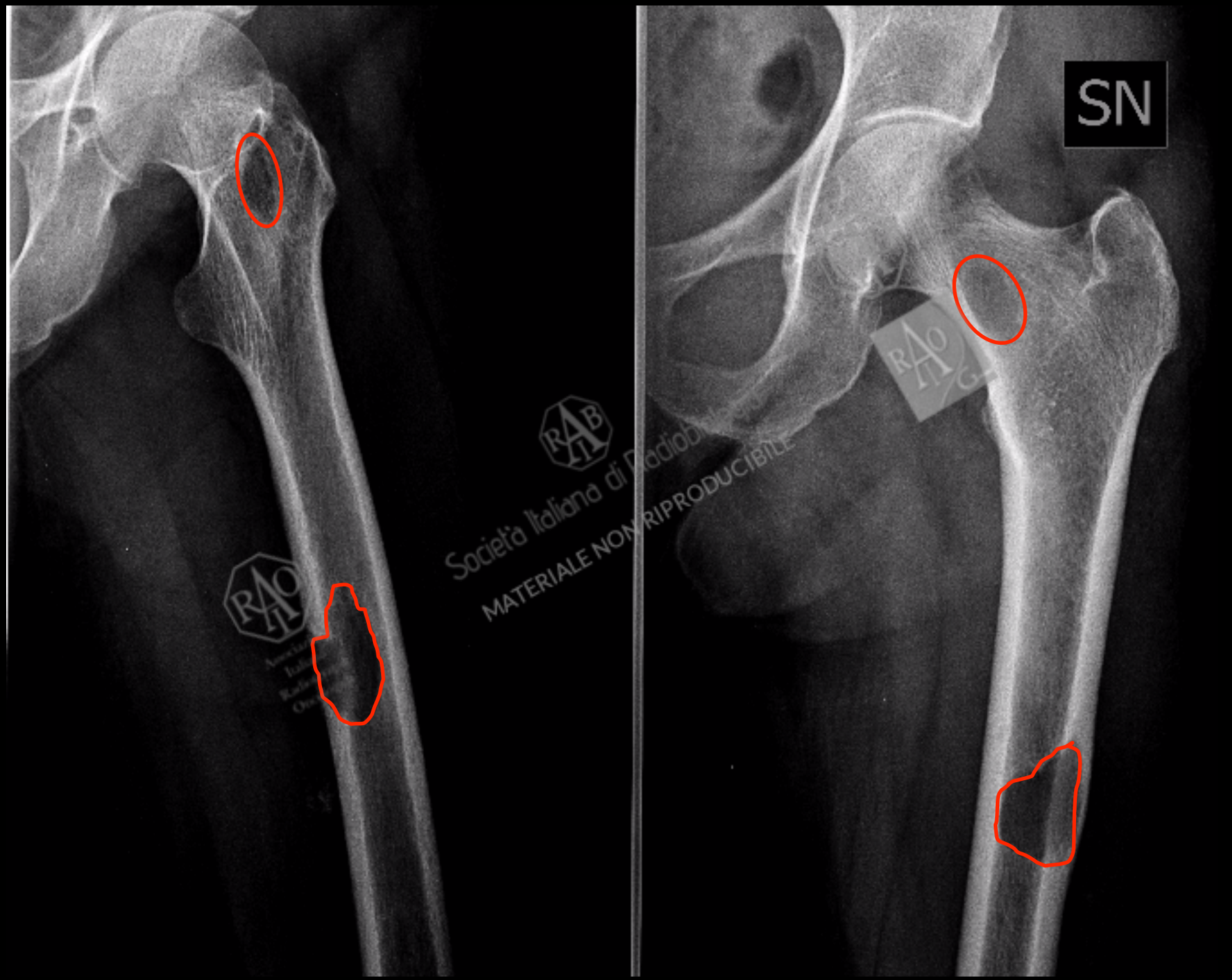
The risk factors studied were:

1. **increasing pain,**
2. **the size of the lesion,**
3. **radiographic appearance,**
4. **localization,**
5. **transverse/axial/circumferential involvement of the cortex**
6. **the scoring system of Mirels.**

- **Only axial cortical involvement >30 mm (p = 0.01), and**
- **Circumferential cortical involvement >50% (p = 0.03) were predictive of fracture.**



Measurements of metastatic lesions in the femur (mm): largest axial length of the entire lesion *(L-lesion)*, largest transverse extension of the lesion *(W-lesion)*, largest axial cortical involvement *(L-cort)*. Measurement of the femur (mm): largest transverse width of the bone *(W-tot)*, maximal thickness of cortex without lesional involvement *(C-tot)* and minimal thickness of cortex with lesional involvement *(C-lesion)*.



THE JOURNAL OF BONE & JOINT SURGERY

■ ONCOLOGY

The assessment of the risk of fracture in femora with metastatic lesions

COMPARING CASE-SPECIFIC FINITE ELEMENT ANALYSES WITH PREDICTIONS BY CLINICAL EXPERTS

Y. van der Linden et al. 2012

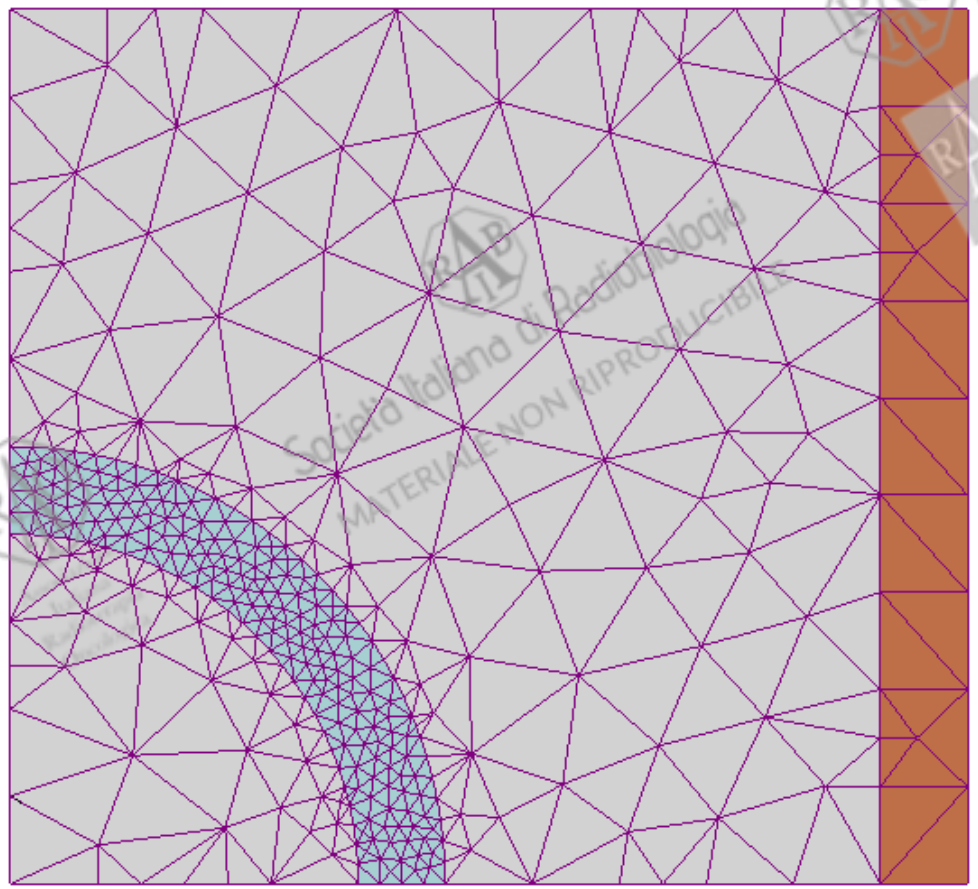
Finite element analysis (FEA)

- FEA is a classic engineering computational technique used in design and failure analysis that provides information on parameters such as estimated load failure, and stress distribution.
- This technique has been used in bone imaging to improve estimation of bone strength in vivo.
- Mechanical properties are assigned to each finite element high-resolution CT model following segmentation and decomposition. (hexagonal, tetrahedral, or curved scaled versions of CT voxels)

Griffith JF & Genant HK: New Imaging Modalities in Bone *Current Rheumatology Reports · March 2011*

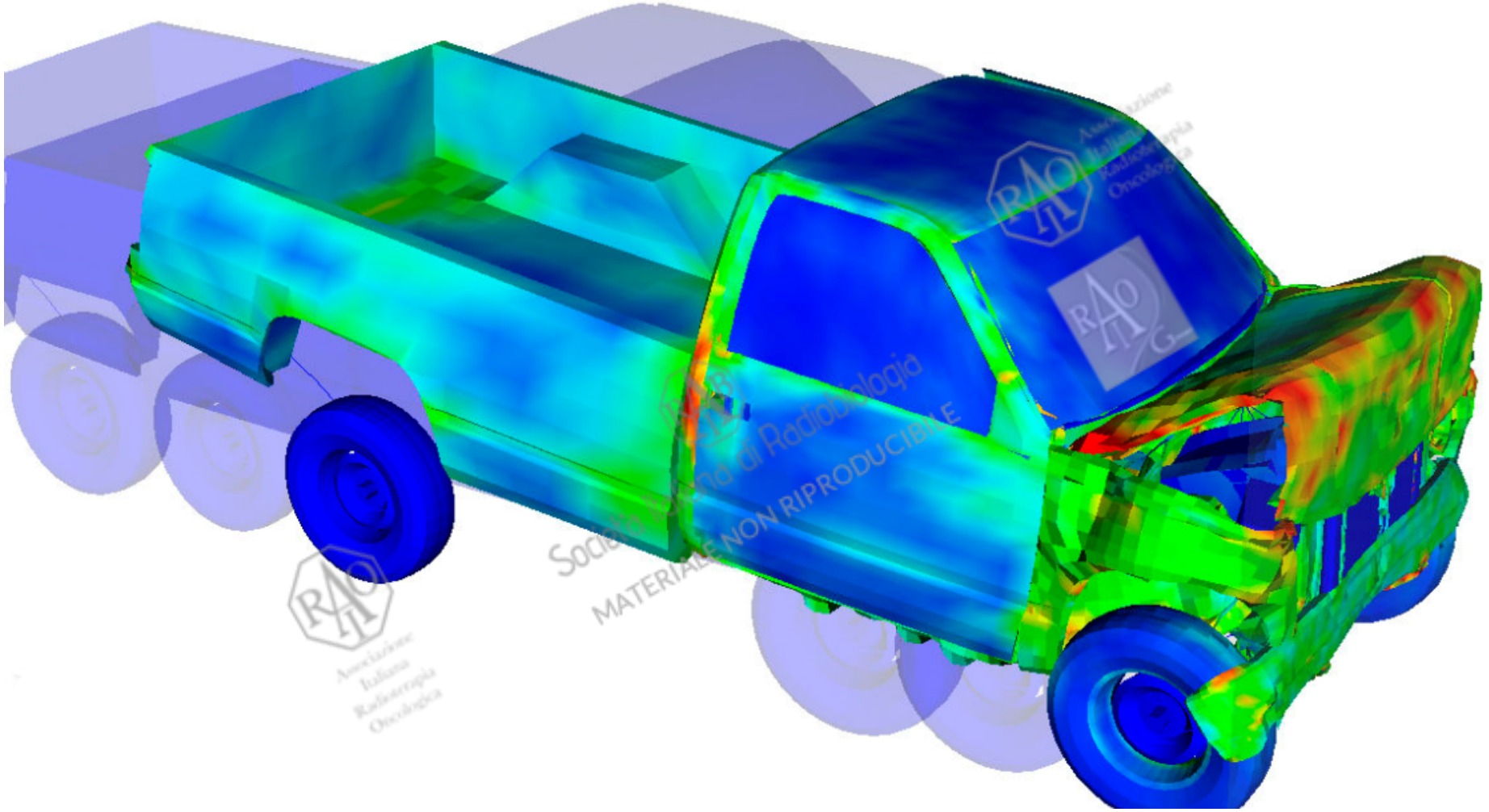
METODO DEGLI ELEMENTI FINITI

Il metodo degli elementi finiti trova origini nelle necessità di risoluzione di problemi complessi di *analisi elastica e strutturale.* Si fonda sull'idea di suddividere il dominio del problema in sottodomini di forma semplice (gli elementi finiti).



Esempio di ***griglia di calcolo***: la griglia è più fitta vicino all'oggetto di interesse

METODO DEGLI ELEMENTI FINITI



Esempio di Simulazione tramite analisi agli elementi finiti dell'impatto di un veicolo contro una barriera simmetrica (**crash test**)

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Finite element analysis

- This technique has been adopted to improve estimation of bone strength using CT bone imaging
- This volumetric quantitative CT is based on **segmentation** of imaging in CT voxel (i.e., finite element)
- Based on bone density and stress applied, mechanical properties are assigned to each finite element

Griffith JF & Genant HK: New Imaging Modalities in Bone *Current Rheumatology Reports · March 2011*

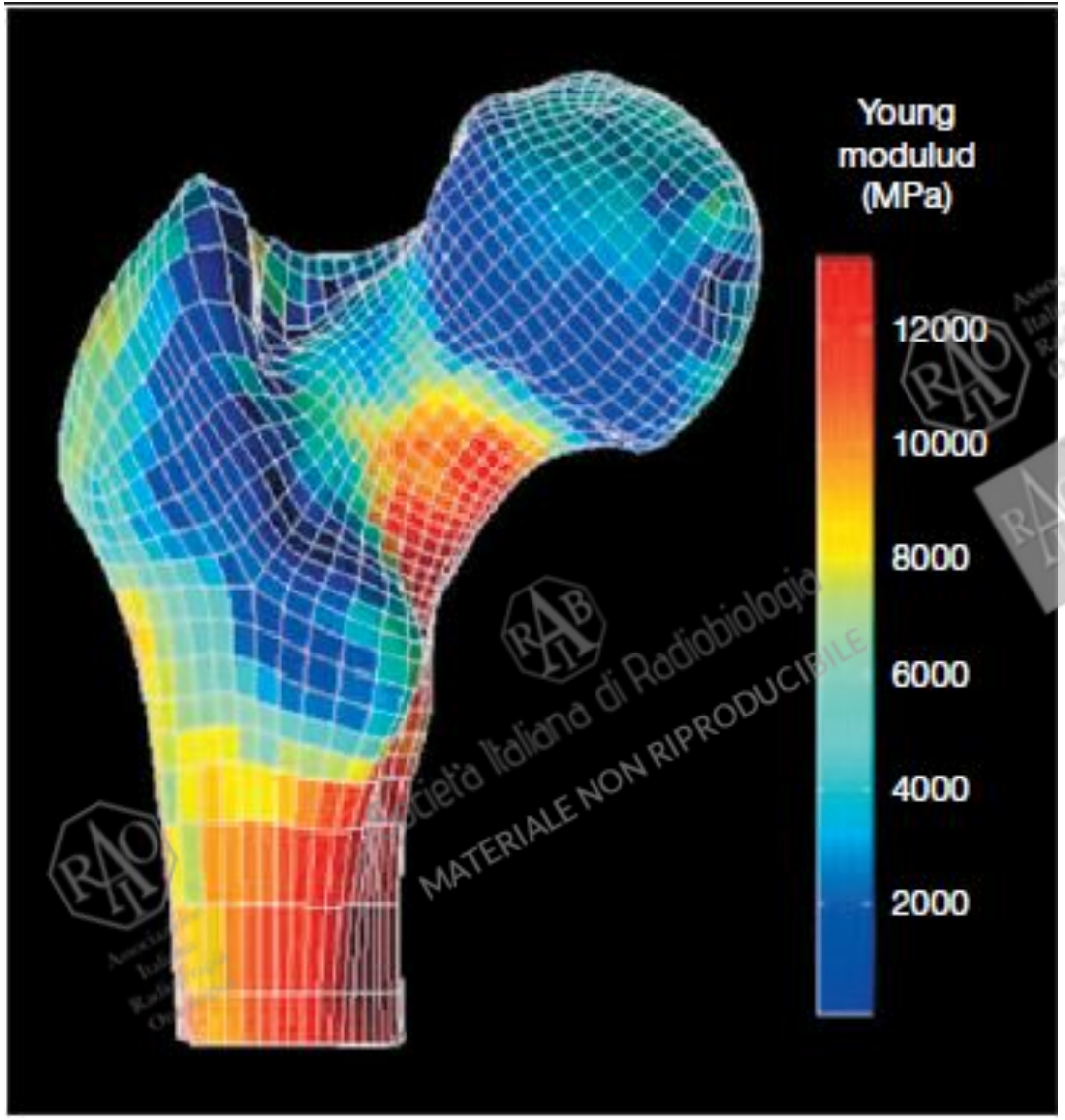

Figure 5. *Volumetric quantitative computed tomography provides a basis for finite element analysis of the proximal femur.*

Note how stress distribution as related to color code is highest along the infero-medial aspect of the femural neck and proximal third

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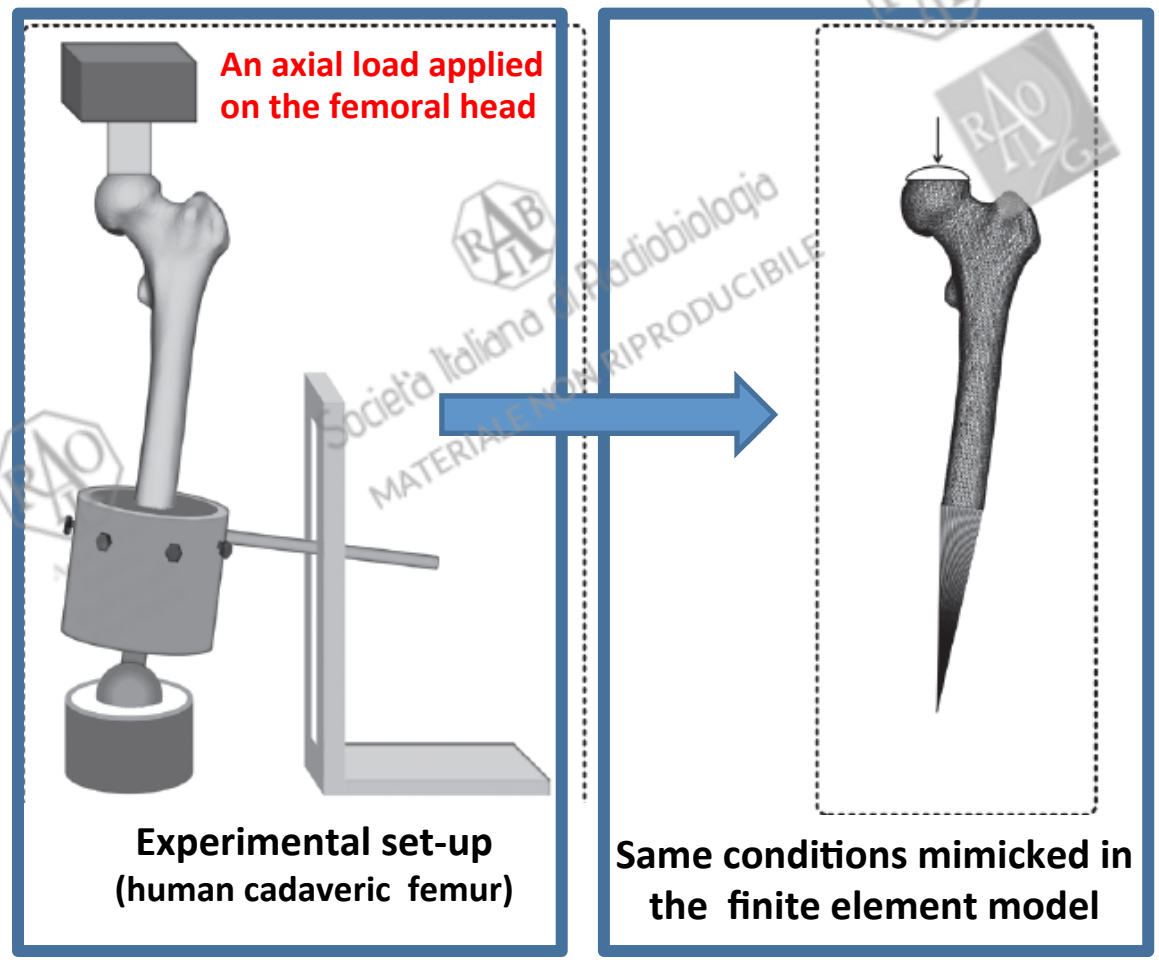

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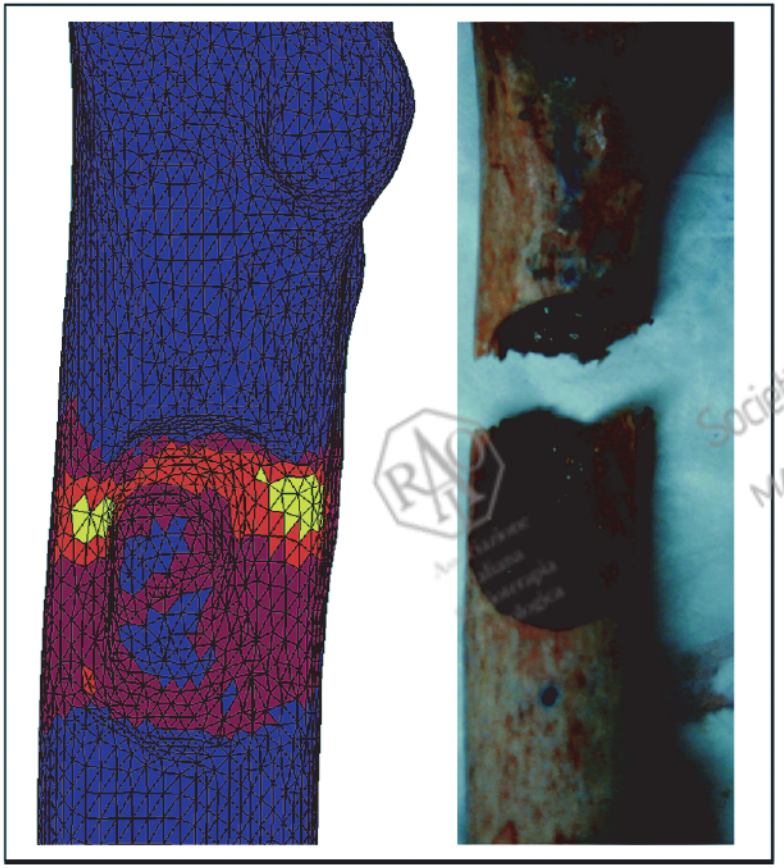
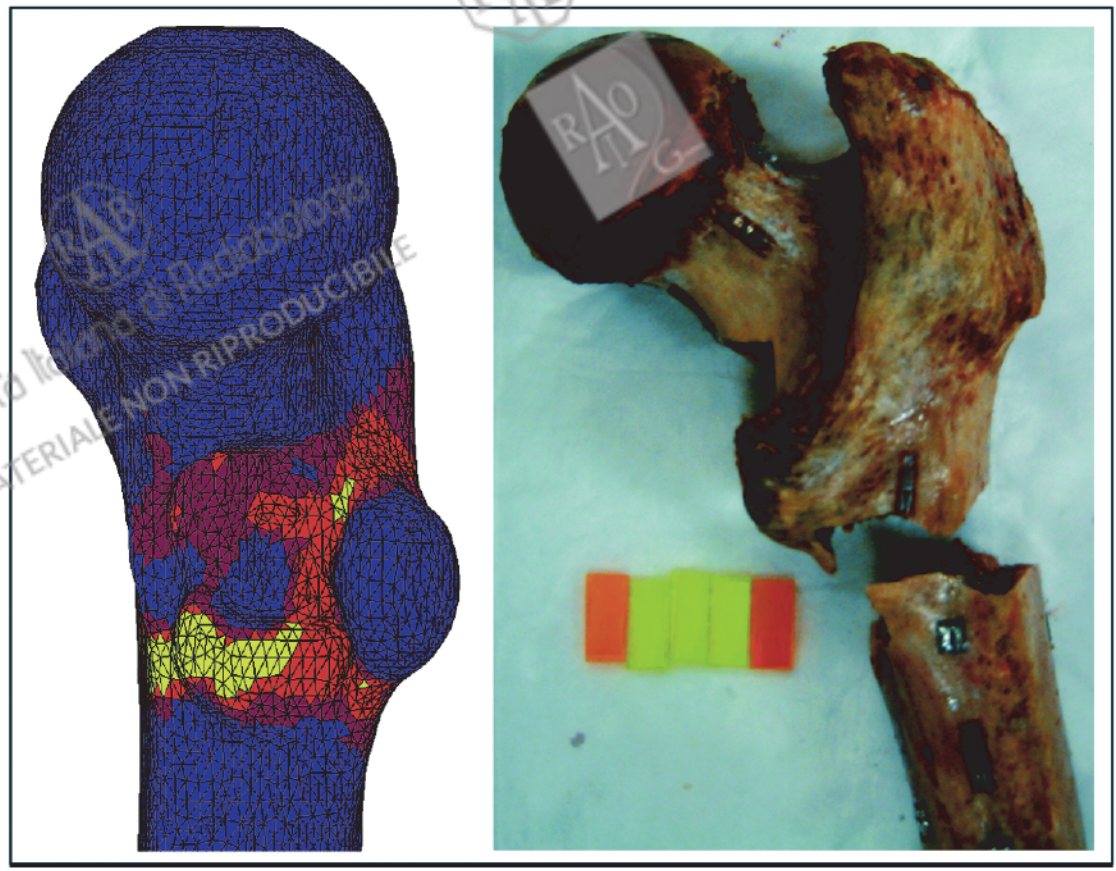
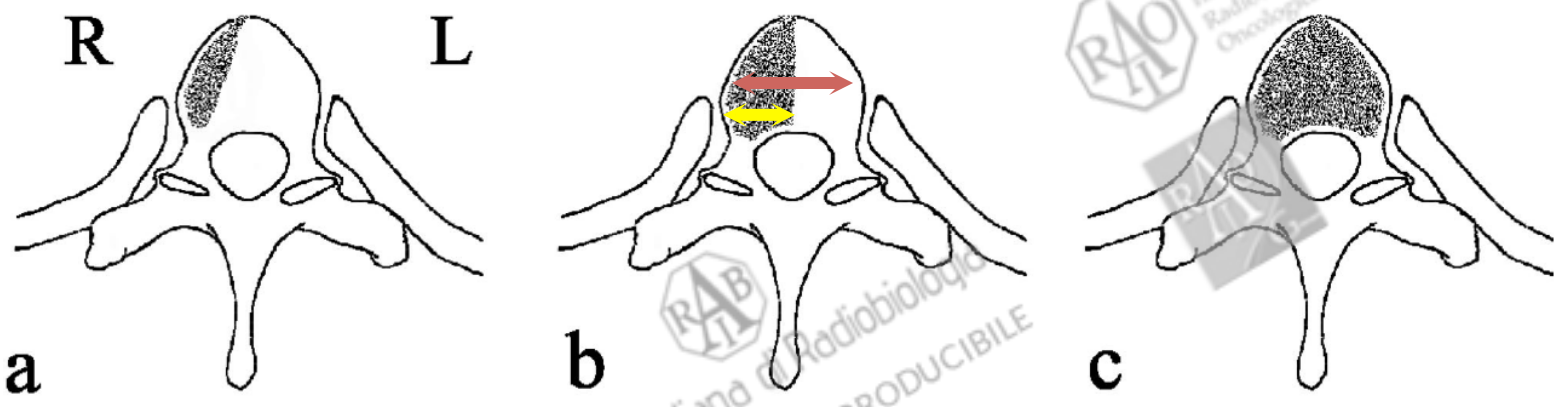




Finite element images predicting two representative fracture locations, showing areas of plastic deformity (indicated in red/orange/yellow), with experimental photographs showing fracture sites corresponding to those predicted by the FE model.

Impending or pathologic fractures in SPINE



Defect ratio : 0.25 0.40 0.75

- 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

Fisher *et al. Radiation Oncology* 2014, **9**:69
http://www.ro-journal.com/content/9/1/69

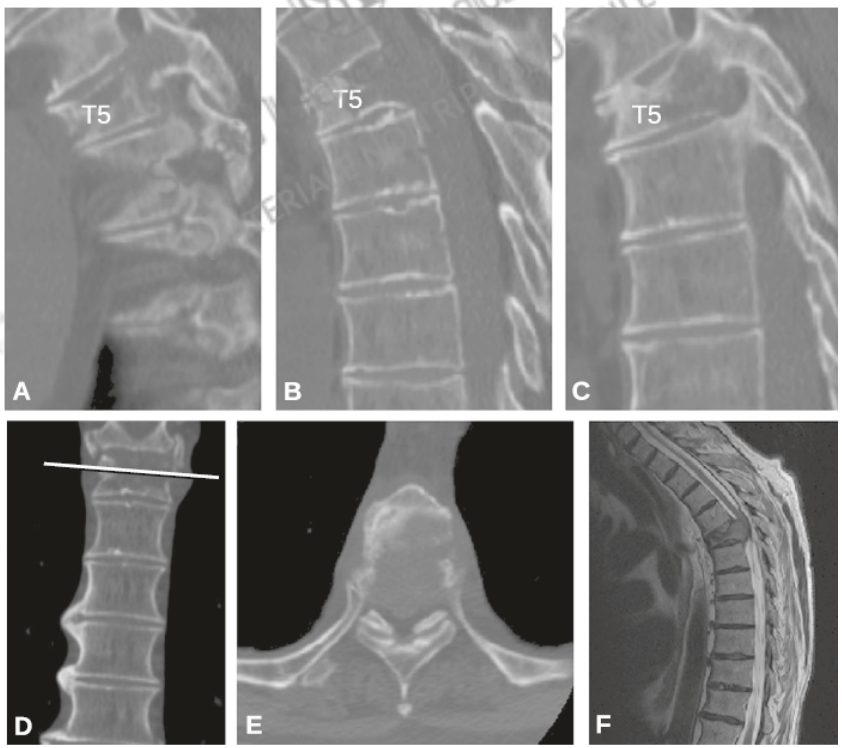
SPINAL INSTABILITY

RADIATION ONCOLOGY

RESEARCH Open Access

Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases

Charles G Fisher[1,16*], Rowan Schouten[2], Anne L Versteeg[3], Stefano Boriani[4], Peter Pal Varga[5], Laurence D Rhines[6],



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.

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- Pain
- Impending/Pathologic fracture
- **Spinal cord/Nerve root compression**
- Hypercalcemia

Spinal cord/Nerve root compression

Definition

The Princess Margaret Hospital of Toronto, Canada, definition:

The **minimum radiologic evidence** for cord/radicular compression of the theca at the level of back pain also in absence of neurologic symptoms: → → → Patient has a spinal cord compression

Loblaw, JCO '98

A SCORE PREDICTING POSTTREATMENT AMBULATORY STATUS IN PATIENTS IRRADIATED FOR METASTATIC SPINAL CORD COMPRESSION

IJROBP, 2008

DIRK RADES,

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

Potential prognostic factor	Relative risk (95% CI)	p
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

Spinal cord/Nerve root compression

Prognostic factors

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

Spinal cord/Nerve root compression

In patients with known cancer, the presence of back pain cannot be under evaluated, because they can be suggestive of bone metastases until proven otherwise by radiological exams (RX ± CT and/or MRI).

In particular, back pain and osteolysis are enough to warrant a ***full-spine MRI*** which allows:

- the diagnosis of BM ± spinal cord compression,
- the numbers of interested sites and
- a correct differential diagnosis between benign and malignant causes of vertebral body compression fracture

NICE guideline 2008; Rades Radiother Oncol 59, 307- 309 ,2001.

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].

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- **Hypercalcemia**

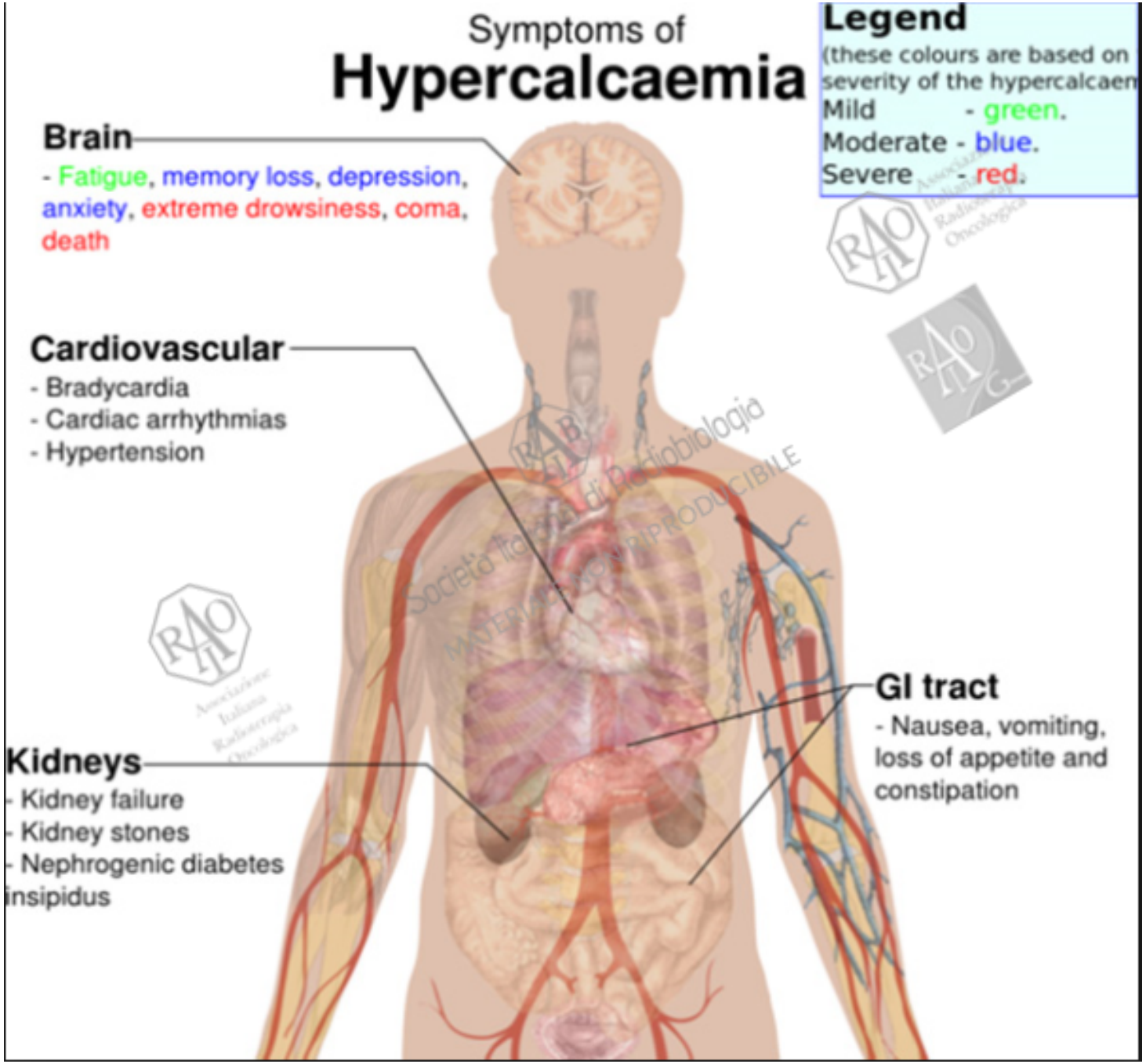
Hypercalcemia

Incidence:

- The incidence of hypercalcemia has fallen markedly over the past two decades through the increasingly widespread use of ***bisphosphonates*** and ***chemotherapy***.
- Hypercalcemia traditionally occurs in patients with **breast**, **lung** and **kidney cancers** and in certain hematological malignancies such as **myeloma** and **lymphoma**.
- In most cases, hypercalcemia is a result of metastatic bone destructions, with osteolytic lesions present in 80% of cases.

Pathogenesis:

1. First, an increased osteoclastic activity, especially in patients with advanced metastatic disease and severe bone destruction at multiple sites.
2. Second, a mobilization of skeletal calcium into the blood circulation and stimulation of the kidney to inappropriately reabsorb calcium by parathyroid hormone-related protein (PTHrP) secreted by certain tumors, particularly squamous cell histology.


Symptoms of
Hypercalcaemia
Legend
(these colours are based on
severity of the hypercalcaem
Mild - green.
Moderate - blue.
Severe - red.
Brain
- Fatigue, memory loss, depression, anxiety, extreme drowsiness, coma, death
Cardiovascular
- Bradycardia
- Cardiac arrhythmias
- Hypertension
GI tract
- Nausea, vomiting, loss of appetite and constipation
Kidneys
- Kidney failure
- Kidney stones
- Nephrogenic diabetes insipidus

Hypercalcemia

Symptoms:

With mild degrees of hypercalcemia, patients are often asymptomatic but, as the level of calcium rises, patients become progressively dehydrated and may develop symptoms such as

- Neurologic symptoms: memory loss/confusion/, disorientation/ lethargy
- GI symptoms: nausea, vomiting, constipation, loss of appetite
- Cardiovascular symptoms: bradycardia, dysrhythmias, hypertension
- Kidney disease: kidney failure, kidney stones, nephrogenic diabetes insipidus

Treatment:

- Rehydration and
- bisphosphonate therapy

SYMPTOMS COMMONLY ASSOCIATED WITH BONE METASTASES (BM)

Conclusions

- In cancer patients a referred bone pain cannot be under evaluated in radiation oncology clinical practice.
- An accurate clinical assessment is mandatory during follow up.
- Radiological exams -often the only tools that allow a correct diagnosis- should be prescribed without hesitation to give a correct diagnosis and an appropriate therapy.
- Therapeutic choice should be personalized (surgery when necessary)
- A correct approach can improve QoL and sometimes survival of BM patients.

LA CULTURA SENZA TECNICA È UN'ARMA SPUNTATA,
LA TECNICA SENZA CULTURA È DISARMATA

ARTI DEL RACCONTO