Bone metastasis
Modern imaging
detection - response

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Cliniques universitaires
SAINT-LUC
UCL BRUXELLES

Targets of the course

- *Reminder on BONE METASTASES*
- *Limits of techniques available until recently*
- *Highlight emerging techniques*
- *Get familiar with their observations*
- *Understand their roles*
  - *For lesion detection*
  - *For response evaluation*
- *Be ready facing suspicion of COMPLICATIONS*

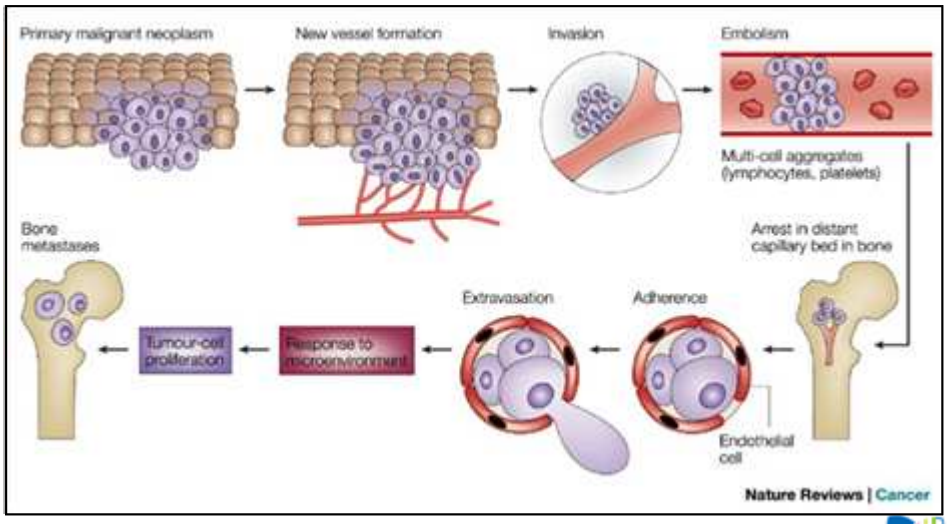
Bone metastases

- Most frequent bone tumors (70% malignant tumors)
- Hematogenic >> Contiguity (primary, nodes)
- Red marrow containing areas
- Mix of osteolysis and osteosclerosis but with dominant patterns

Bone mestastasis: pathophysiology

- Mechanism of dissemination
- Bone « landing »
- Local effects on bone
- Different phenotypes: sclerotic/lytic
- Big providers

Metastases = tumor spread at distance

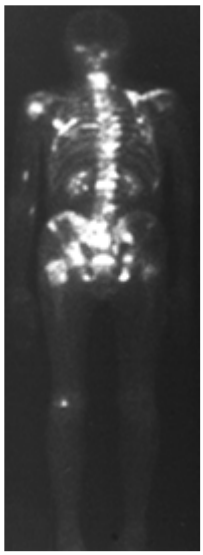


G. Mundy et al. Nature Reviews Cancers, 2, 586, 2002

"When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil. …."

— Stephen Paget – 1889

"Anatomical" osteotropism

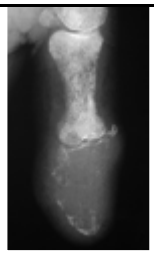


Red Marrow distribution

Bone mestastasis: locations

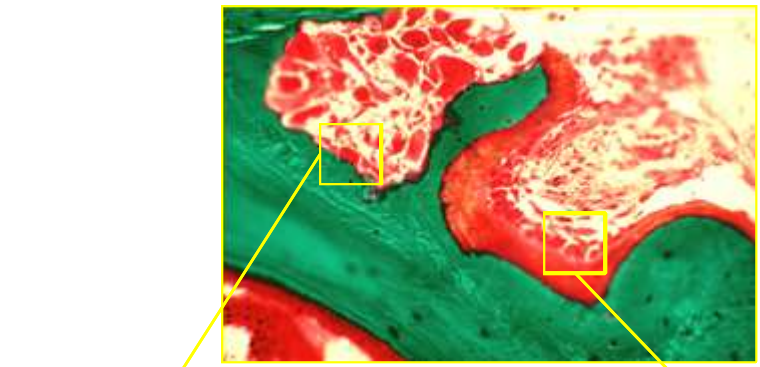
- Spine 80 %
- Pelvis 60 %
- Ribs 30 %
- Skull 10 %
- Long bones
- Distal skeleton

Acrometastasis: primary

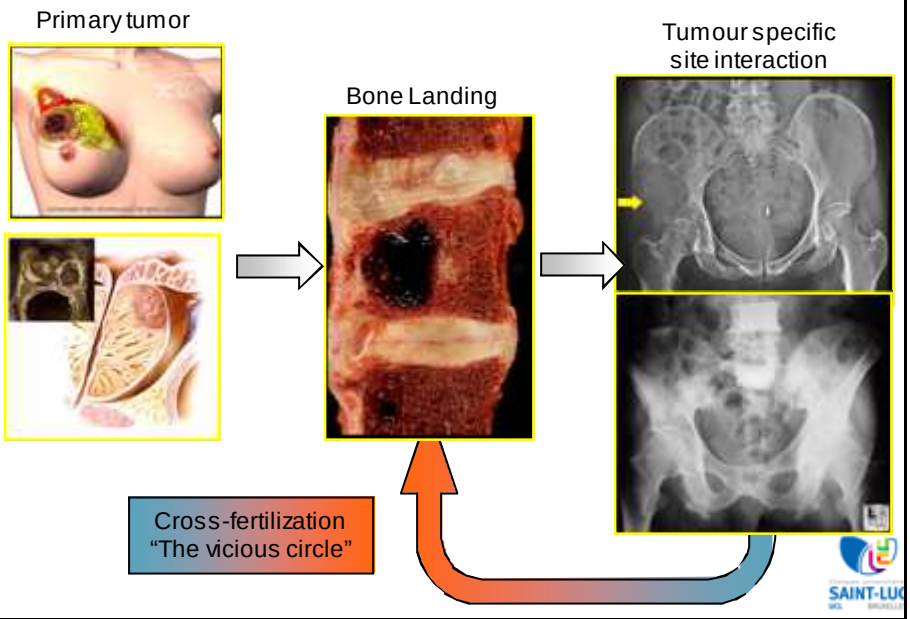


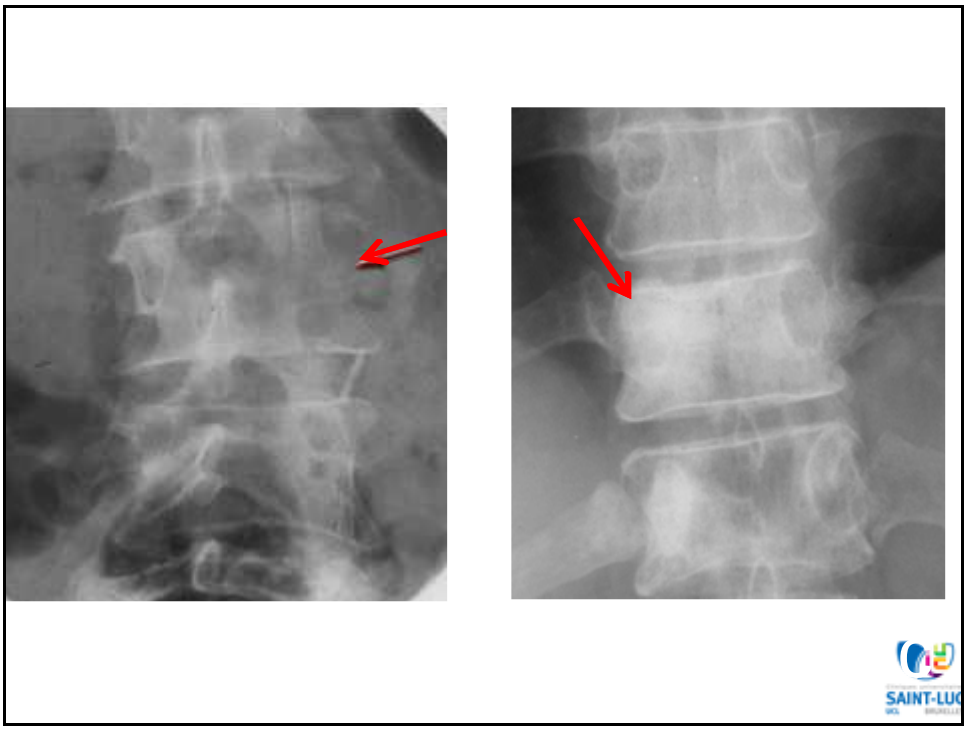
- Superior limb Lung, breast, kidney… œsophagus, colon, rectum, prostate, utérus, ostéosarcome)
- Inferior limb Pelvic cancer : bladder, colo-rectal, uterus…; Lung

Bone Remodeling



Basic mechanisms






G

Bone mestastasis: « phenotypes »

- Predominantly osteoblastic
  Prostate, carcinoid, medulloblastoma,…
- Predominantly osteolytic
  Renal cell, thyroid, melanoma squamous cell…
- Mixed
  Breast, GI, …

Bone metastases : primary

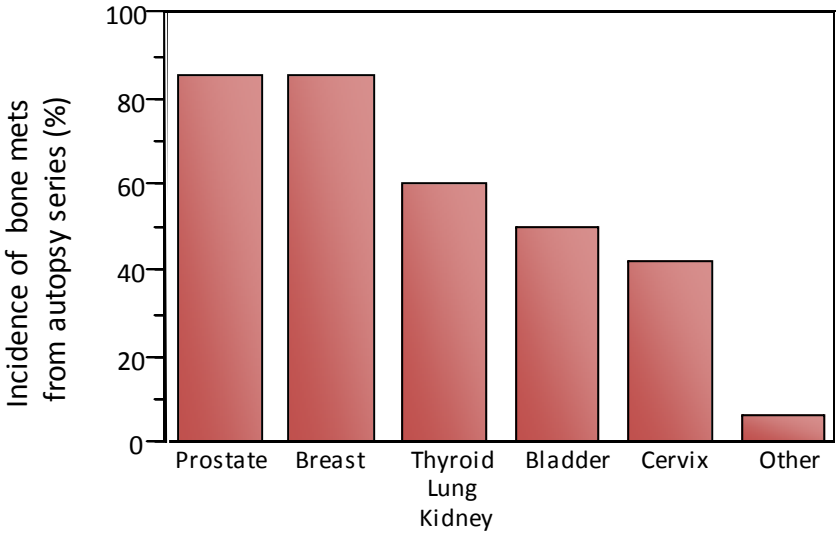
Adults: Breast (70% of BM in female)
Prostate (60% of BM in male)
Lung, Thyroid, Kidney, GI, Gyneco,…

Children: neuroblastoma, Ewing, osteosarcoma, malignant soft tissue tumors

Revealing the disease (20% of cases)
Solitary : renal, thyroid, HCC, lung, breast

Unknown primary: 4 % of cases

Big providers

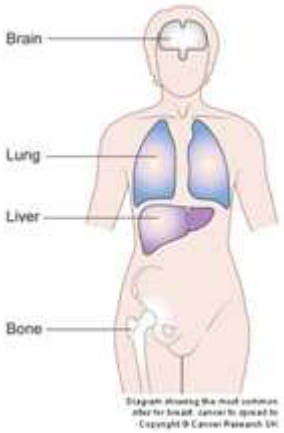


350 000 patients die each year in the US with bone metastases (Mundy Nat Rev Cancer 2

Metastatic dissemination in breast cancer

- Bone : most common metastatic site
- First in substantial proportion of patients
- 85 % other locations (visceral)
- Bone lesions detection and evaluation

of response: cardinal in patients with bone predominant or exclusive metastatic disease



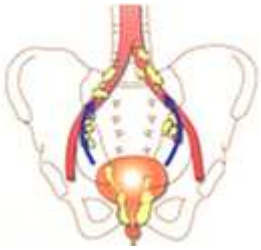
Coleman RE, Rubens RD (1987) The clinical course of bone Metastases from breast cancer. Br J Cancer 55: 61–66.

Hortobagyi GN (1991) Bone metastases in breast cancer patients. Semin Oncol 18: 11– 15

Hamaoka T, et al. Bone imaging in metastatic breast cancer. JCO 2004;22,2942-2953

Metastatic dissemination in prostate cancer

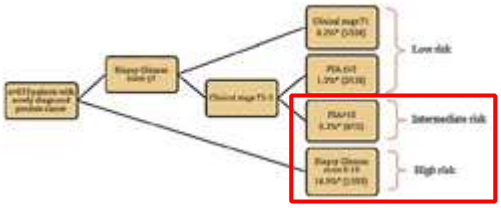
- 1589 Pca patients from a series of 19,316 autopsies in men> 40 years conducted between 1967 and 1995 at the Institute of Pathology of the University of Basel 90 % of bone mets
- Bones (63%) > Nodes (36%) >> Visceral (6%)



Bubendorf L et al. Hum Pathol. 2000 May;31(5):578-83.
Yossepowitch O. Eur Urol 2007

Who needs a metastatic work-up ? PROSTATE

- EAU[1]
  - Gleason ≥ 7(4+3)
  - ≥T3
  - PSA ≥ 20ng/ml
  - Symptomatic patients
- AUA[2] et AJCC :
  - Gleason >7
  - PSA >20ng/ml
- NCCN[3]
  - T1-cT2 with PSA>20 ng/ml
  - Gleason ≥8
  - T3 ouT4
- Briganti[4]
  - Gleason ≤ 7; T2-T3; PSA > 10 ng/ml
  - Gleason 8-10



(1) http://www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf
(2) http://www.auanet.org/education/guidelines/prostate-cancer.cfm,
(3) https://subscriptions.nccn.org/gl_login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/prostate.
(4) Briganti et al., European Urology 57 (2010), 551-558

BONE METASTASES

Detection

TECHNIQUES

- X-rays
- CT

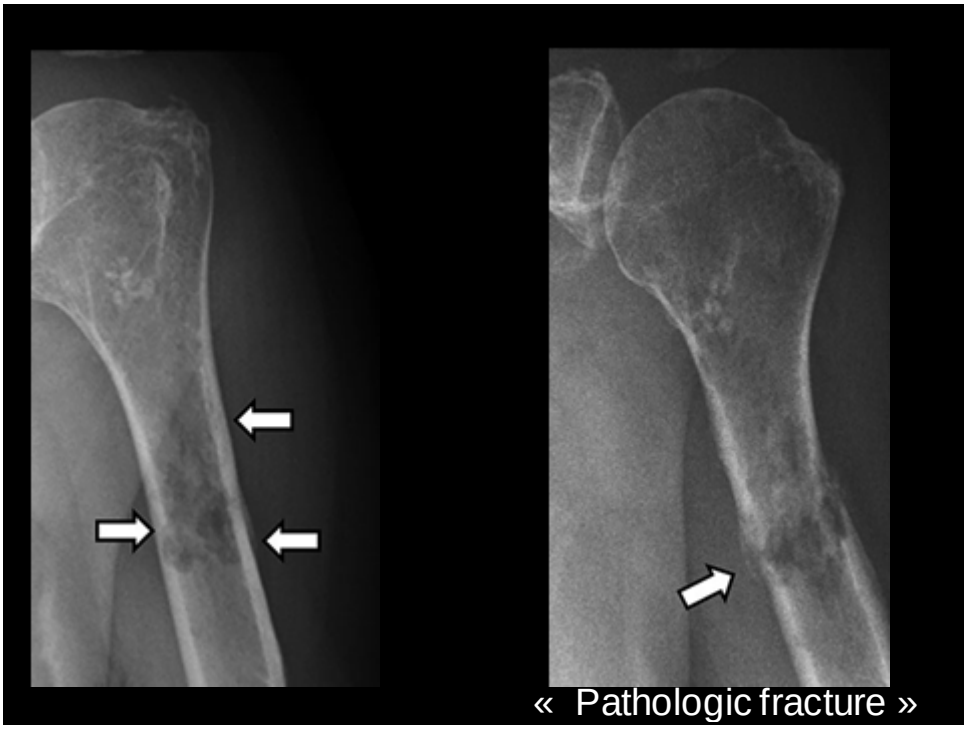
- Bone scintigraphy
- SPECT

- MRI
- PET (CT)

Radiographs (x-rays)

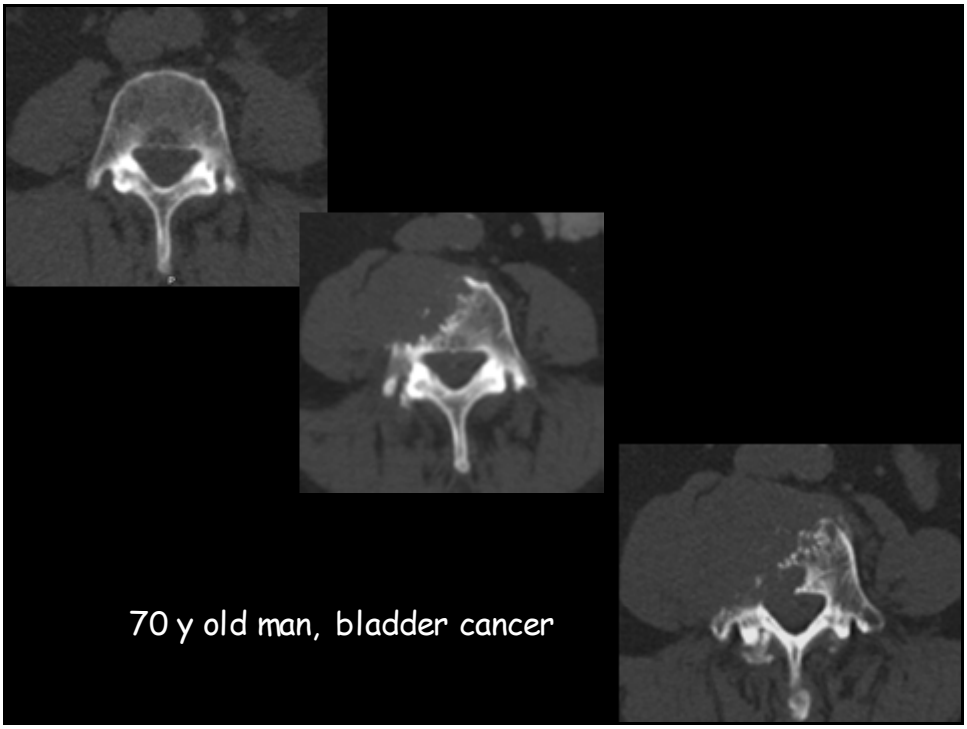
- Historical, available, low cost
- Irradiating
- No place in screening
- Limited sensitivity (>30%destruction); delay
- First line in symptomatic patient
- Second line in screening (after bone scinti)

Hamaoka T, et al. Bone imaging in metastatic breast cancer. JCO 2004;22,2942-2953

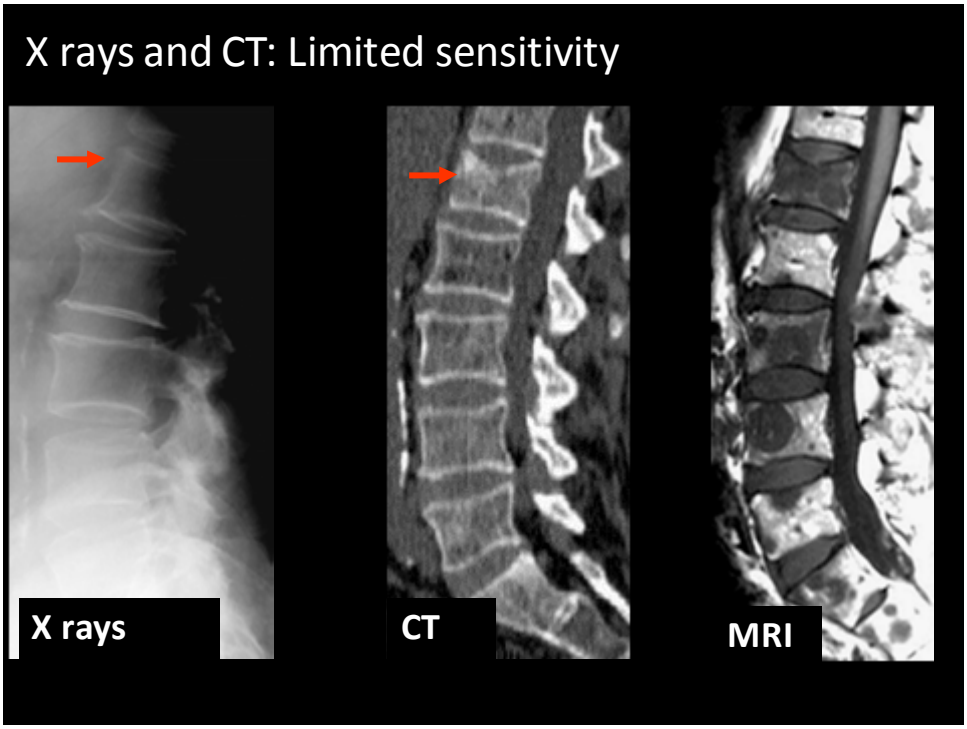


CT (computed tomography)

- Irradiating
- Limited coverage
- Not a bone screening tool
- ….but often available (visceral screening…)
- So offers a window to bone !!!



X rays and CT: Limited sensitivity



Bone scintigraphy (bone scan)

- Tc 99m bisphosphonate
- Historical (1960's), available, low cost
- Whole body
- But limited sensitivity (lytic, …)
- Limited specificity (osteoblastosis)
- Frequently requires X-Rays, CT or MRI
- Late for bone lesion detection
- Late and non reliable for response assessment

Loeffler RK, et al. Limitations of bone scanning in clinical oncology. JAMA 1975;234,1228-1232)

Localization of Technetium-99m Methylene Bisphosphonate in Bone Using Micro-autoradiography

TA. Einhorn. Journal of Orthopedic Research 4:180-187, 1986

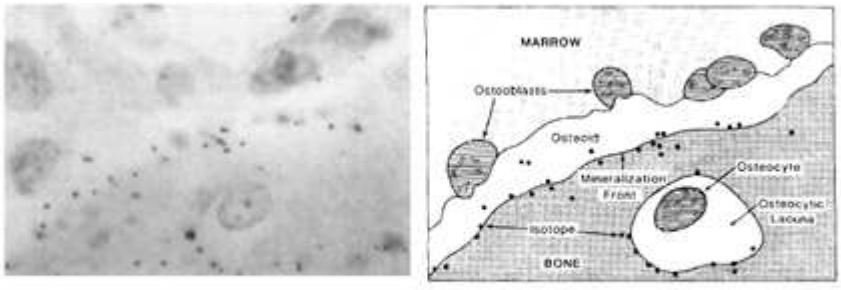
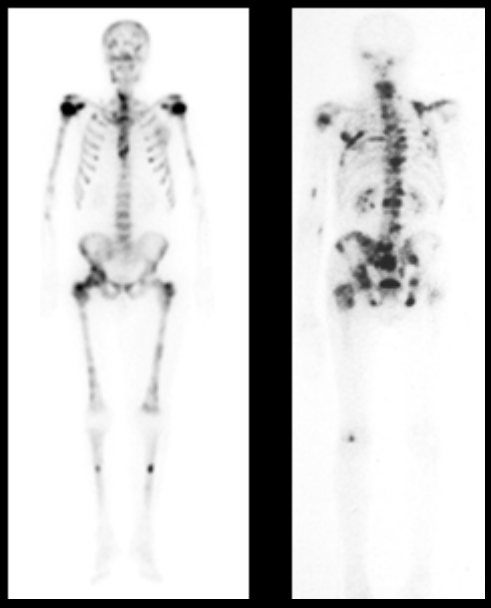
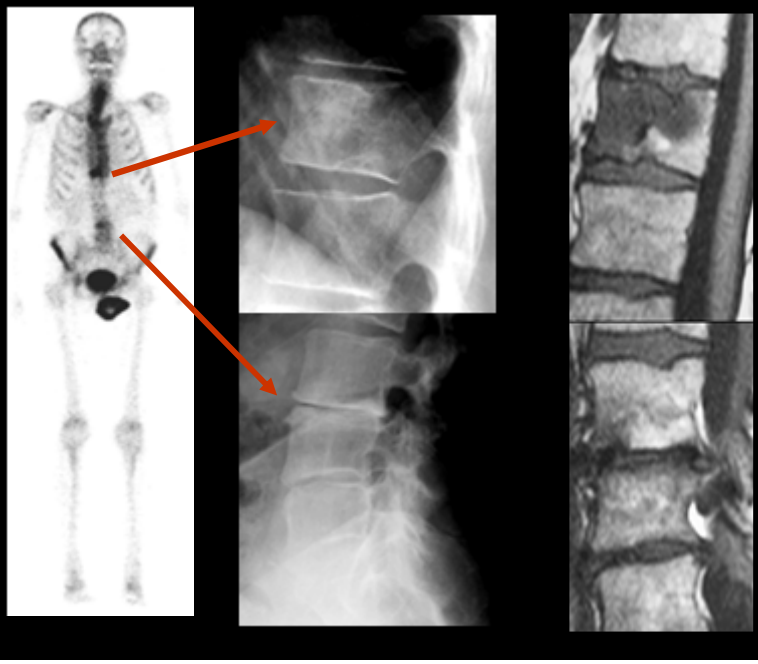


FIG. 4. (A) High-power microautoradiograph showing localization of [^{99m}Tc]MDP to the mineralization front of bone as well as to the border of an osteocytic lacuna. The silver granules that have been precipitated at these sites indicate the uptake of isotope at the osteoid–mineralized bone interface. The silver grains precipitated within the substance of the osteoid may indicate the onset of mineralization in that region or could be due to artifactual displacement in the emulsion during preparation of the slide (hematoxylin and eosin, microautoradiograph, ×512). **(B)** Schematic representation of the histology viewed in **A.**

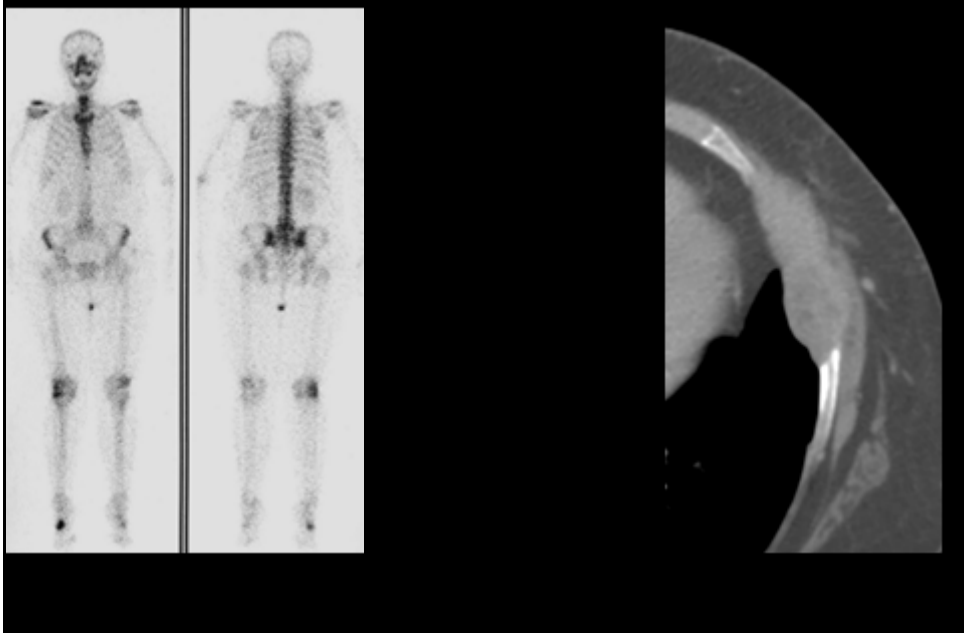
Prostate cancer



Bone scan: lack of specificity



Bone scan: lack of sensitivity



MRI: alternative to BS to detect bone mets

	Authors	Journal	Year/Issue/Pages	Number of patients
AS	Daffner	AJR Am J Roentgenol	1986;146:353-358	80
AS	Avrahami	J Comput Assist Tomogr	1989;13:598-620	40
AS	Algra	Radiographics	1991;11:219-232	71
AS	Fujii	Br J Urol	1995;39:207-209	36
WB	Eustace	AJR Am J Roentgenol	1997;169:1655-1661	25
AS	Traill	Clin Radiol	1999;54:448-451	200
AS	Freedman	Adult Urology	1999;50:321-329	19
WB	Steinborn	J Comput Assist Tomogr	1999;123-129	18
WB	Daldrup-Link	AJR Am J Roentgenol	2001;177:229-236	39
AS	Taoka	AJR Am J Roentgenol	2001;177:519-524	74
AS	Ghanem	Eur J Radiol	2002;43:256-261	20
WB	Lauenstein	Radiology	2004;233:139-148	51
WB	Engelhard	Eur Radiol	2004;14:99-105	22
WB	Nakanishi	Magn Reson Med Sci	2005;4:11-17	16
AS	Lecouvet	J Clin Oncol	2007;25:3281-3287	66
WB	Gutzeit	Skel Radiol	2010;39:333-343	36
WB	Lecouvet	Eur Urol	2012;62:68-75	100

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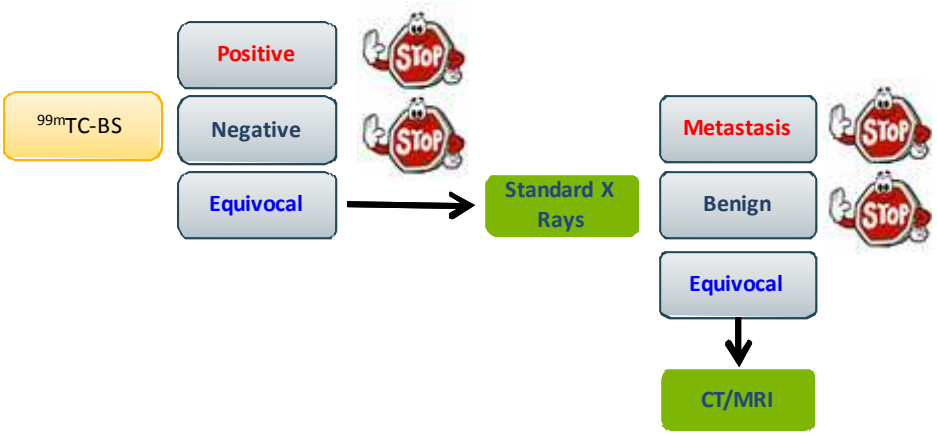
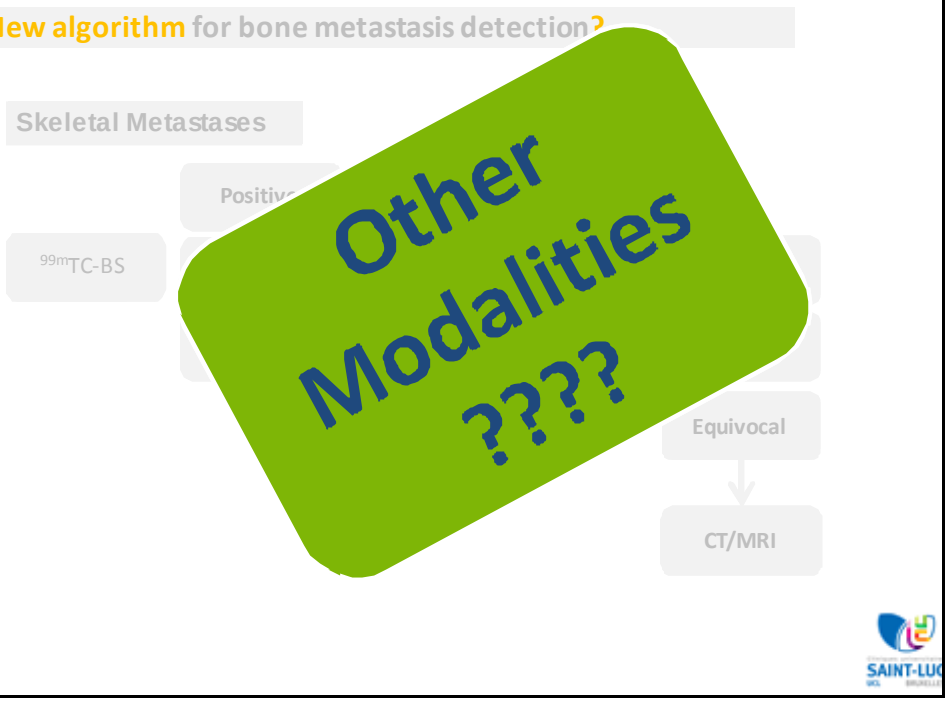
Standard algorithm for bone metastasis detection



New algorithm for bone metastasis detection?

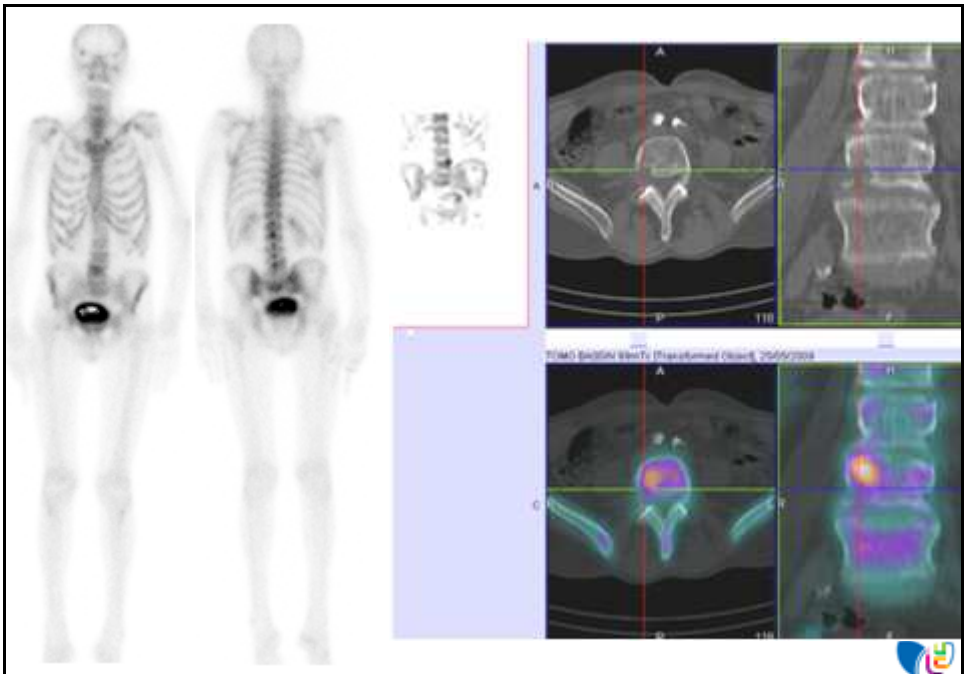


Bone SPECT

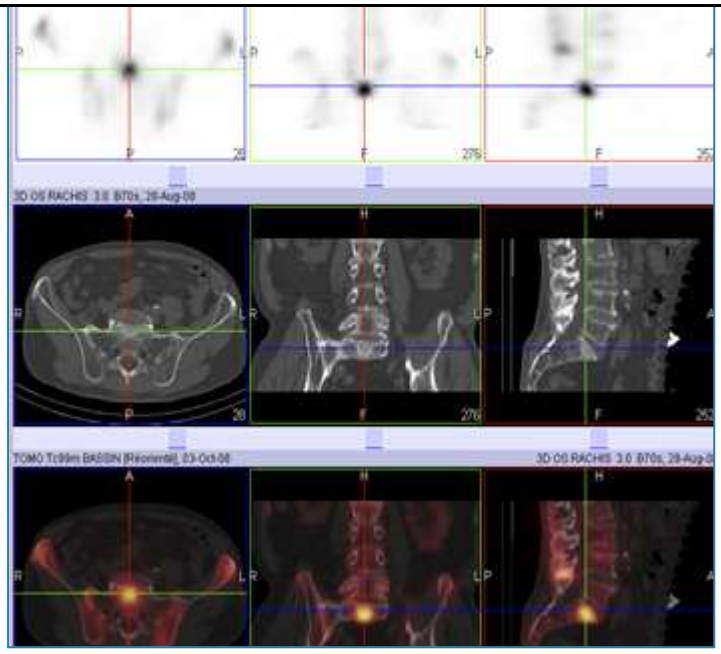
- Bisphosphonate Tc-99m
- From planar (Bone scintigraphy) to 3D
- Mainly increases specificity
- Often coupled with CT (anat)→ "hybrid" imaging
- Limited anatomic coverage

Han LJ, et al. Comparison of bone SPECT and planar imaging in the detection of vertebral metastases. In patients with back pain. EJNM 1998; 23,635-638)

Romer W, et al. SPECT-guided-CT for evaluating foci of increased bone metabolism clasified as indeterminate on SPECT in cancer patients. JNM 2006;47, 1102-1106).



Images from Dr P BOURGUET, Nantes, France



SPECT-CT (99mTc)

Images from Dr F Paycha, Colombes, France

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Imaging strategies for bone metastases

Tumour cells in the bone marrow

MRI, PET

Activation osteoclasts / osteoblasts

Bone remodelling and lesions

Bone scan, SPECT

X rays, CT

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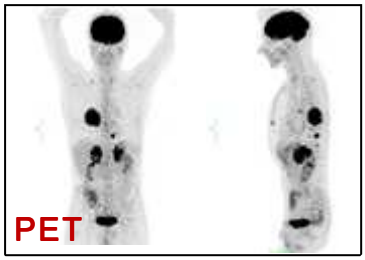
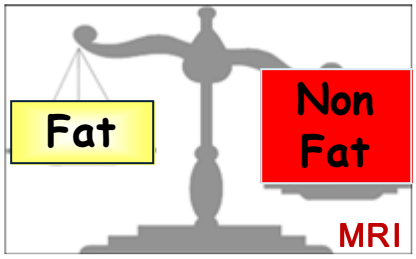
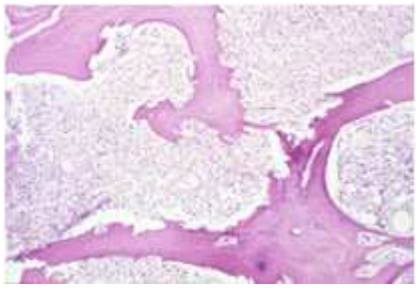
PET and MRI: marrow imaging



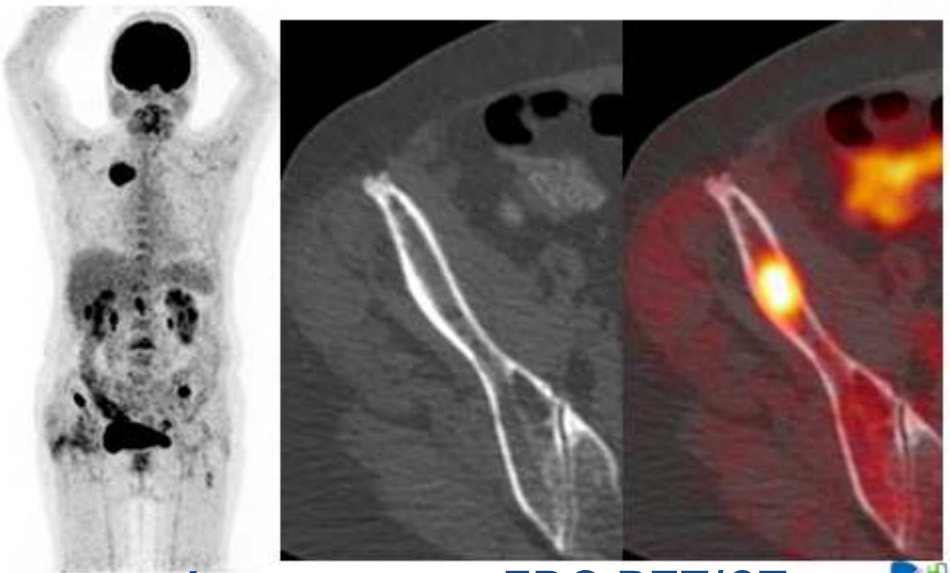




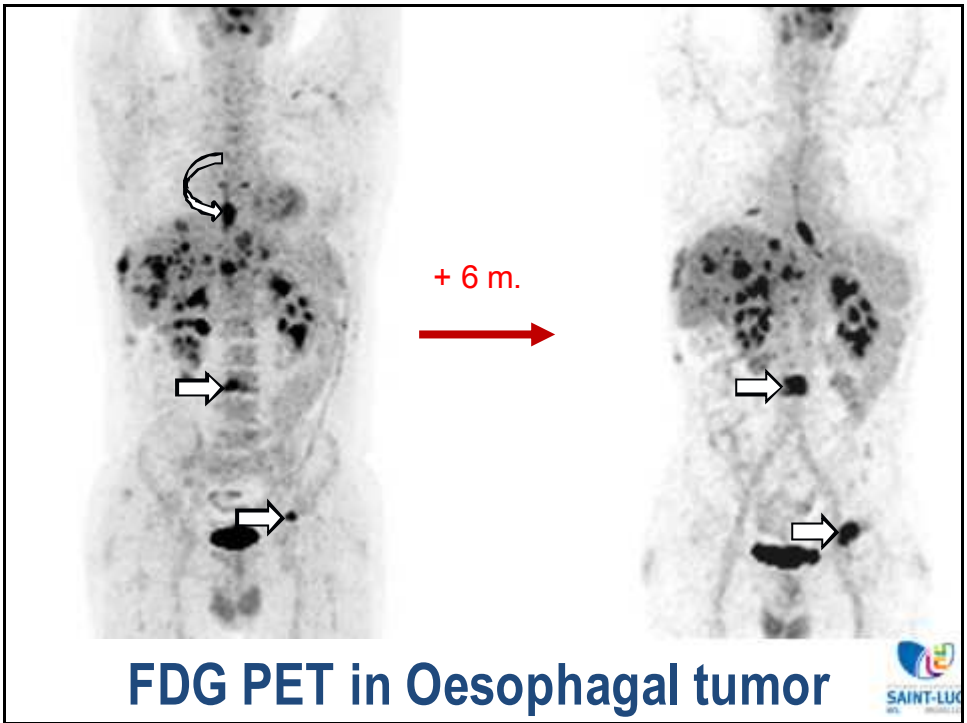
PET-Scan, PET-CT

- Metabolic ≠ morpho.
- « Whole body staging »:diagnosis AND stage
- Response assessment
- Non universal markers : «cancer-dependent»
  - –18 FDG : lung, lymphoma, breast?
  - –11C/18F Choline, 11C/18F Acetate : prostate
  - –18 Na-F: super bone scan
- Better in lytic than blastic metastases
- Cost, availability?

Hamaoka T, et al. Bone imaging in metastatic breast cancer. JCO 2004;22,2942-2953



Lung cancer: FDG PET/CT

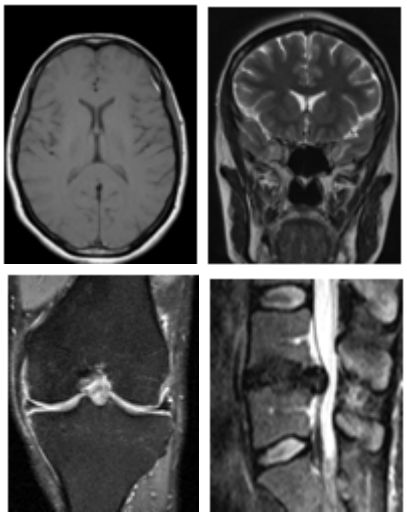


FDG PET in Oesophagal tumor

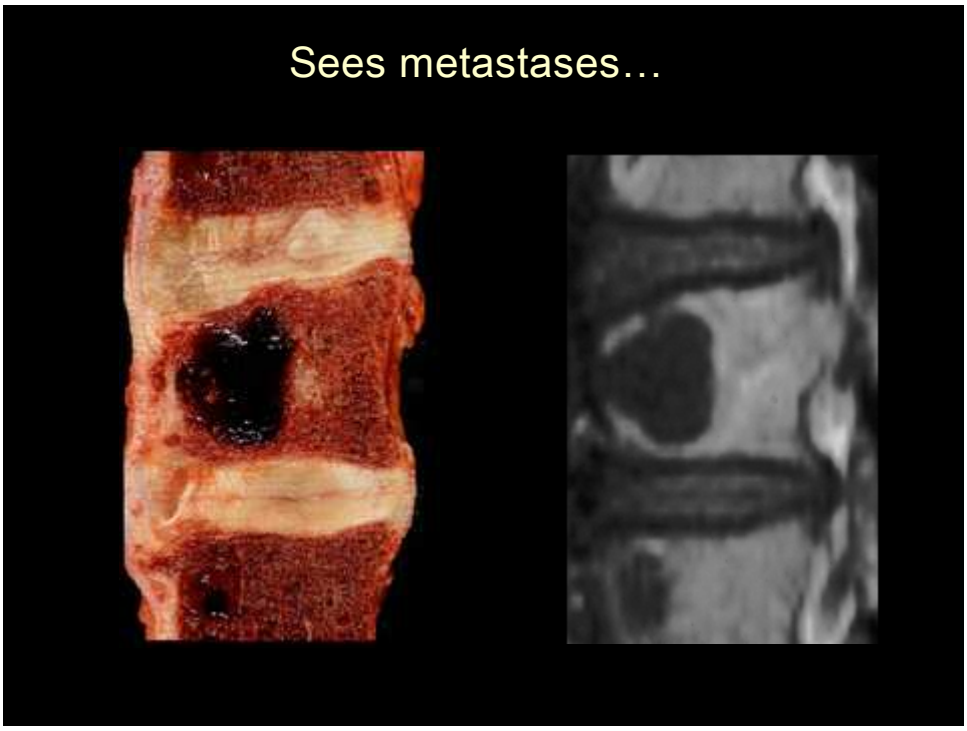
Choline PET in prostate cancer

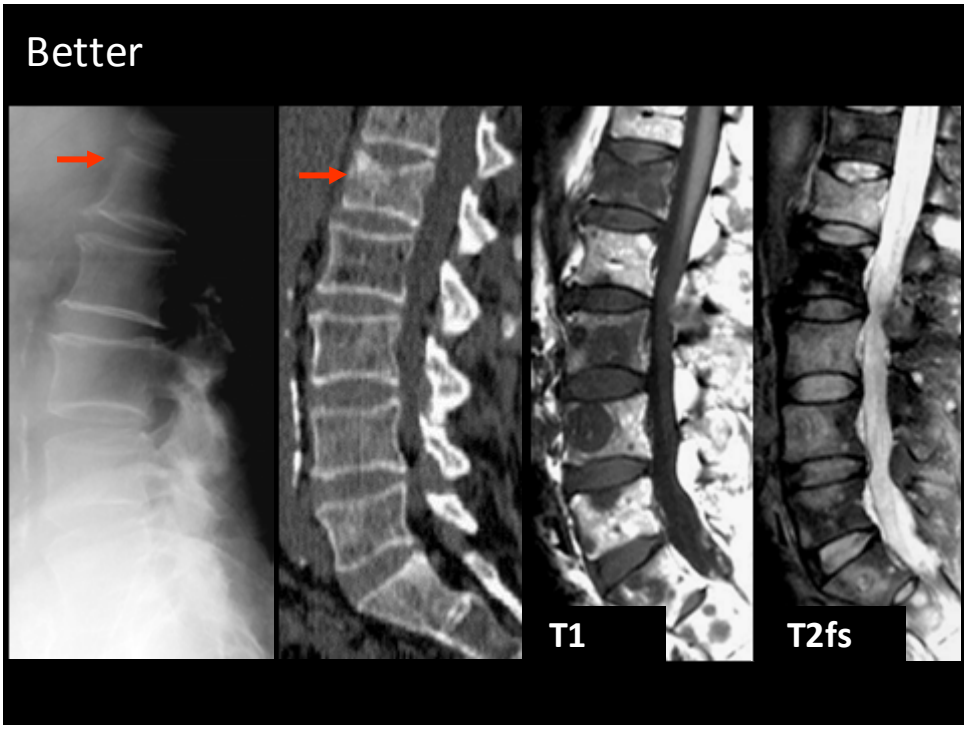
From JN Talbot, Hop. Tenon, Paris

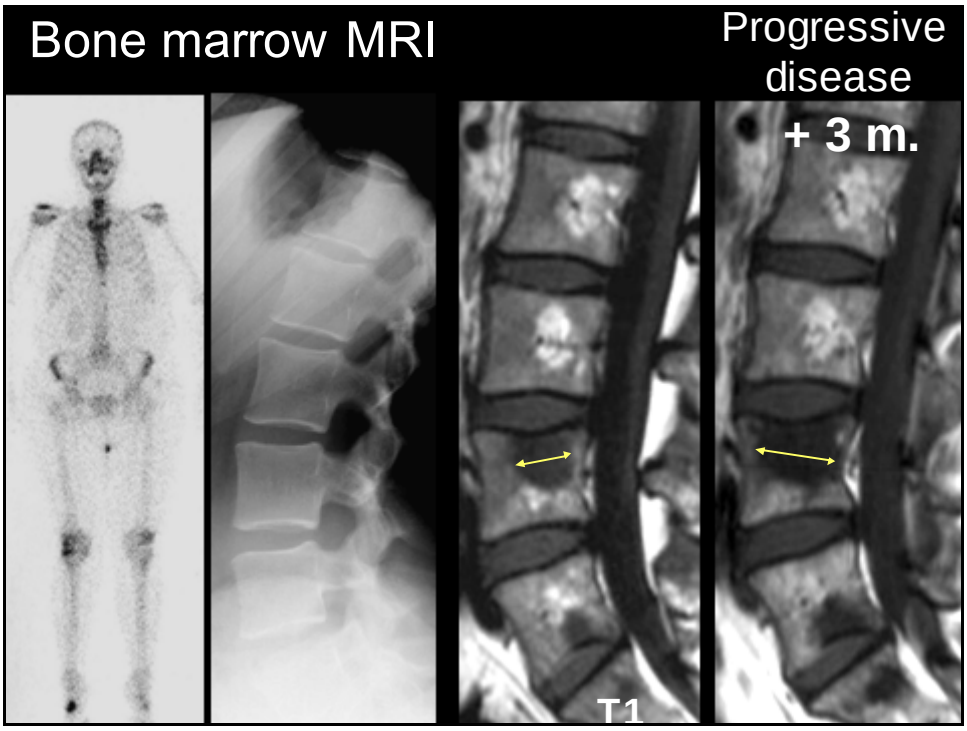
MRI

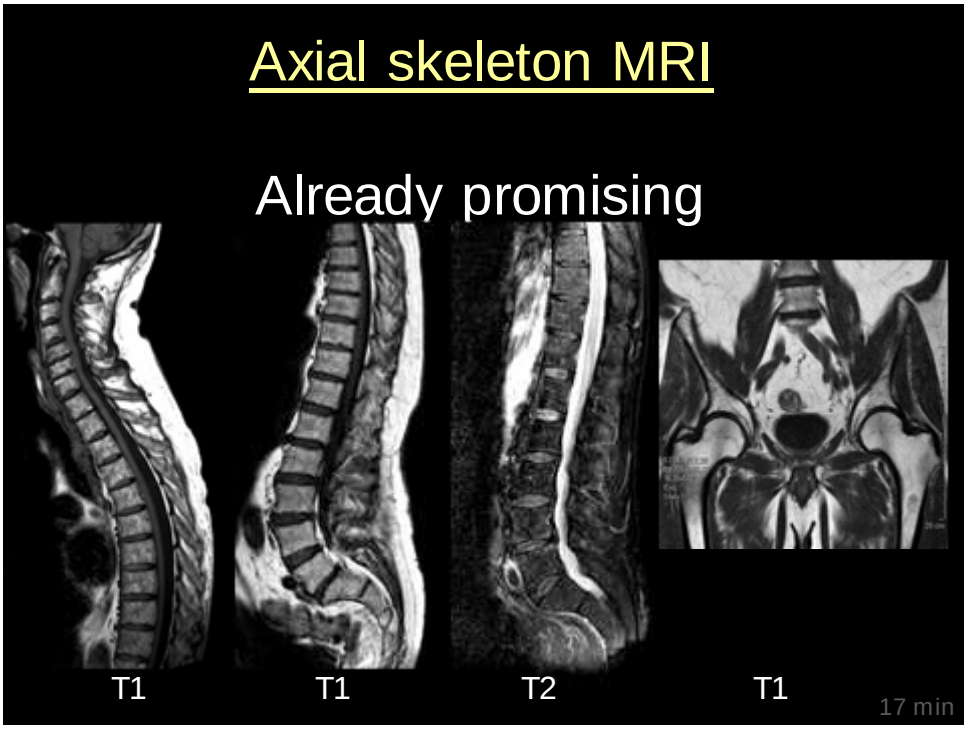


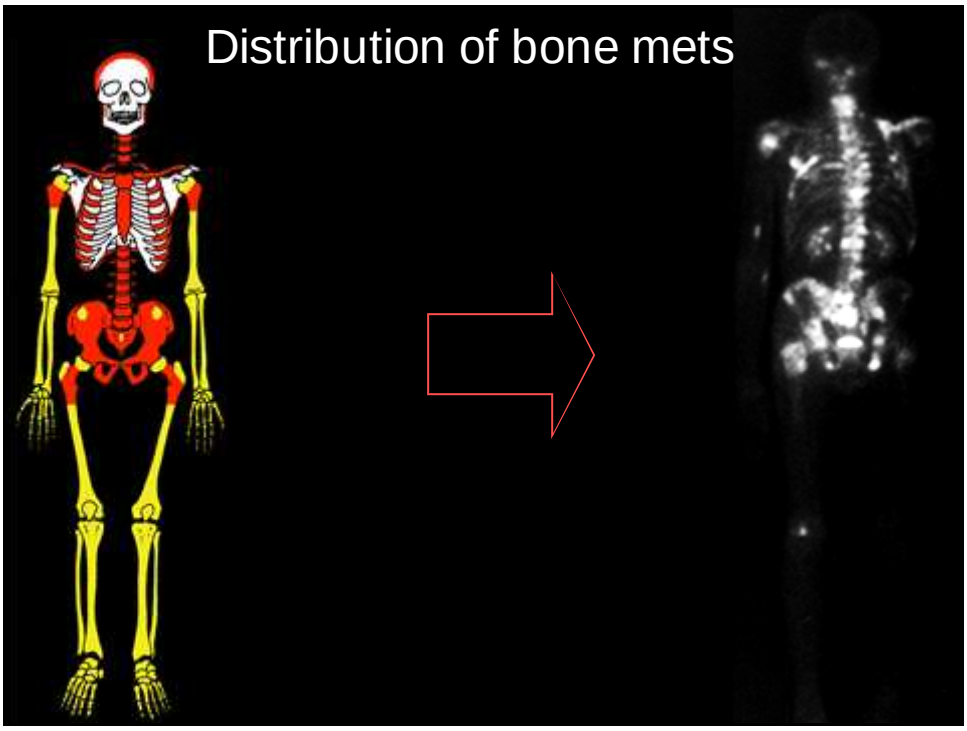
New application…

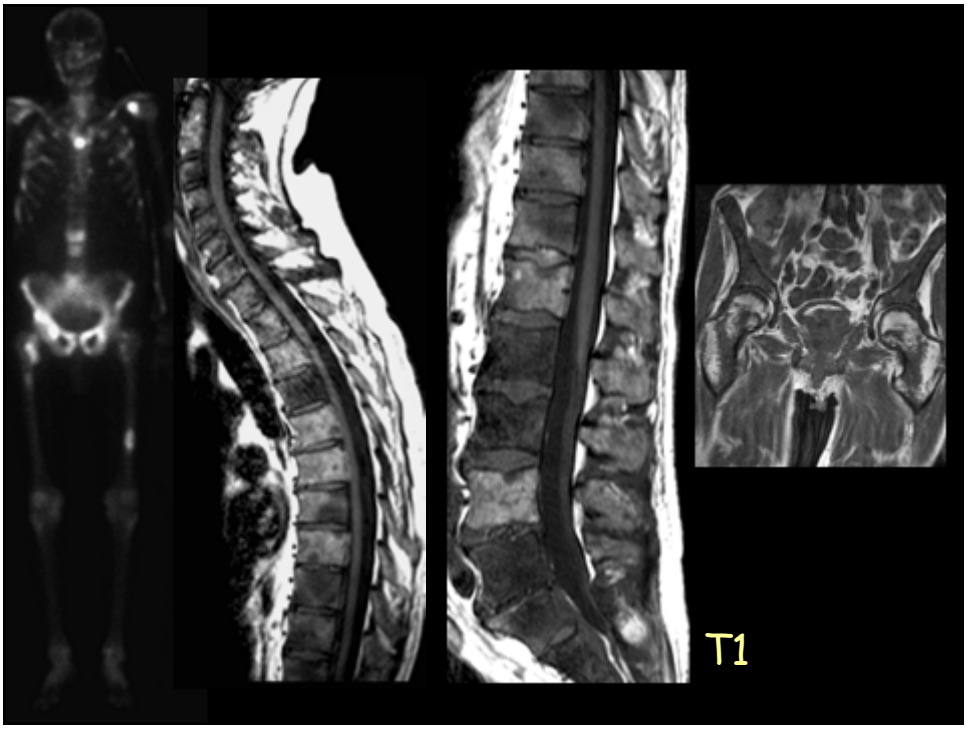

Sees metastases…


Better
T1
T2fs


Bone marrow MRI
Progressive disease
+ 3 m.
T1


Axial skeleton MRI
Already promising
T1
T1
T2
T1
17 min

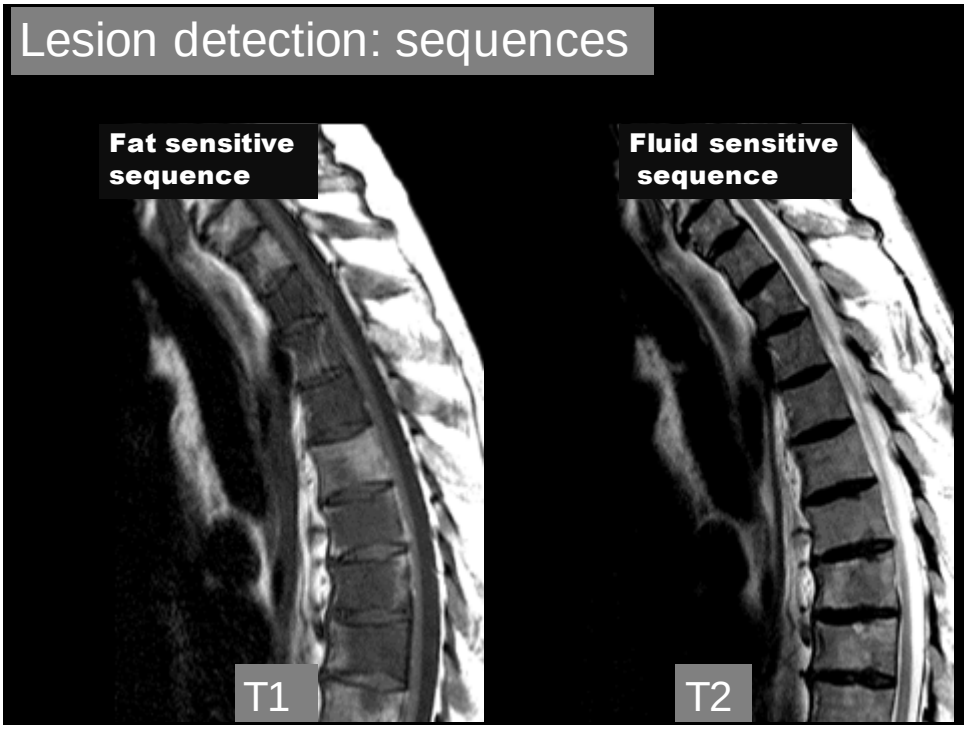

Distribution of bone mets

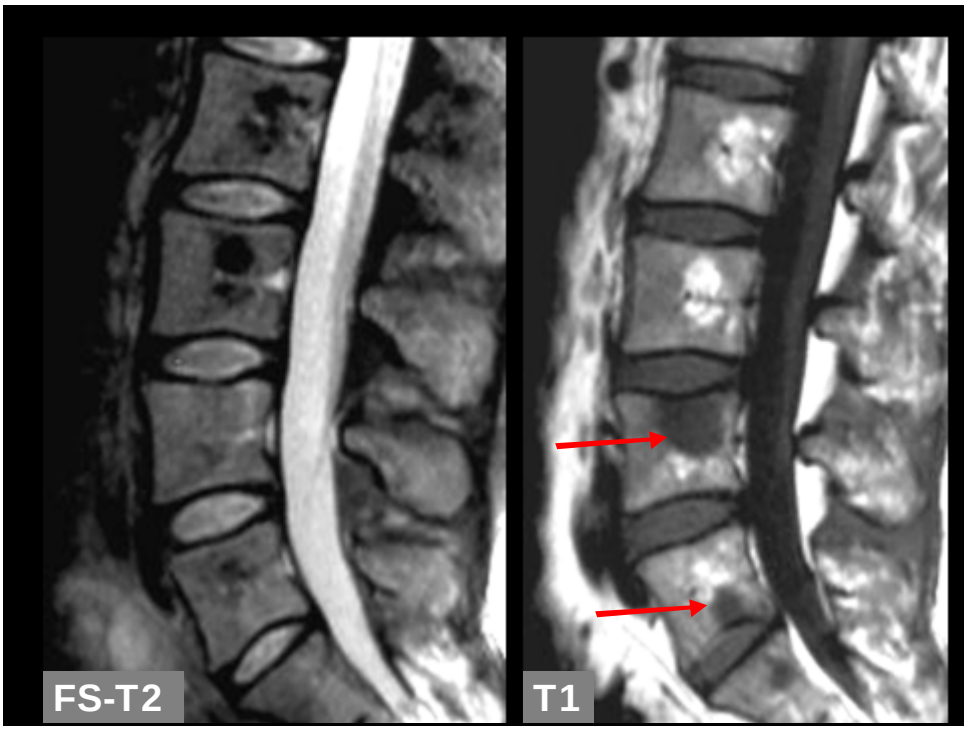

T1

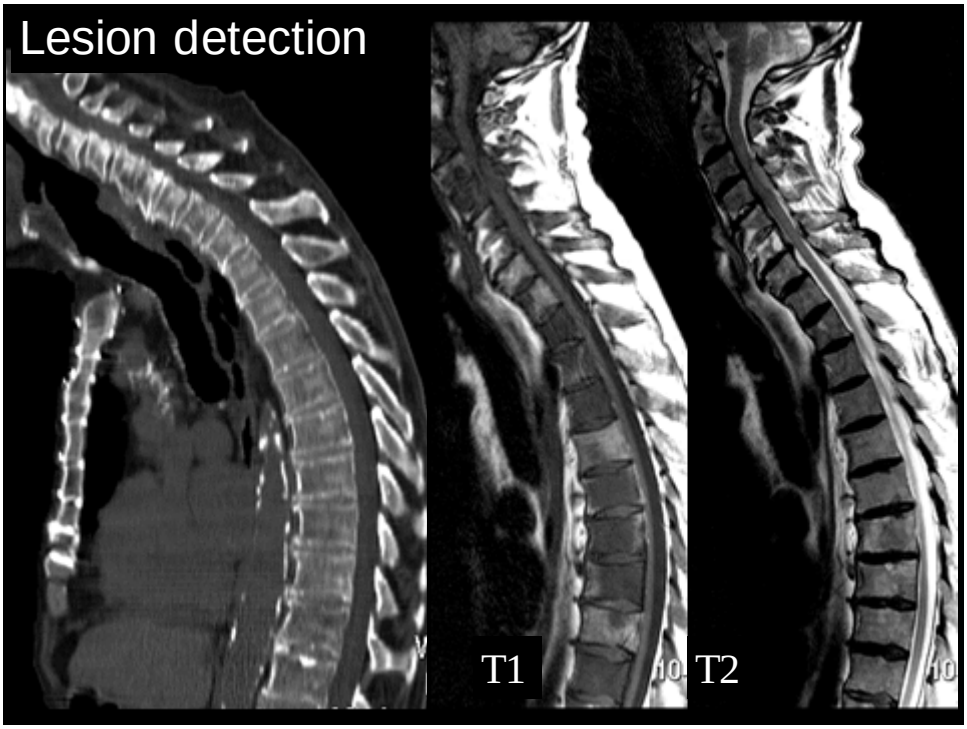

T1

BONE METASTASES
MRI TECHNIQUE

Lesion detection: sequences

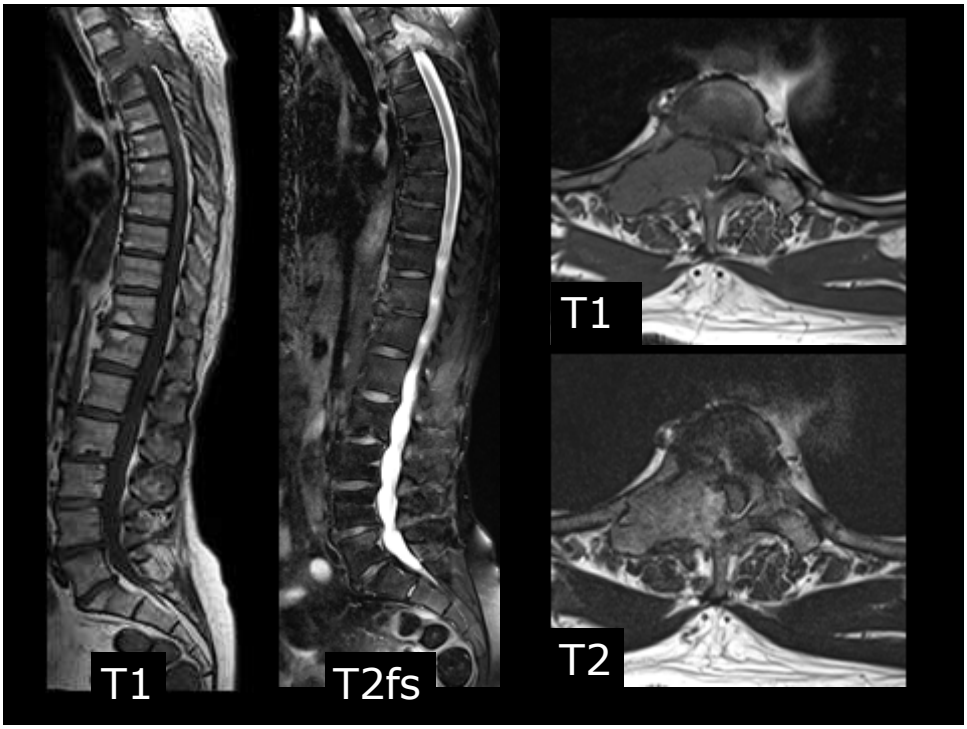


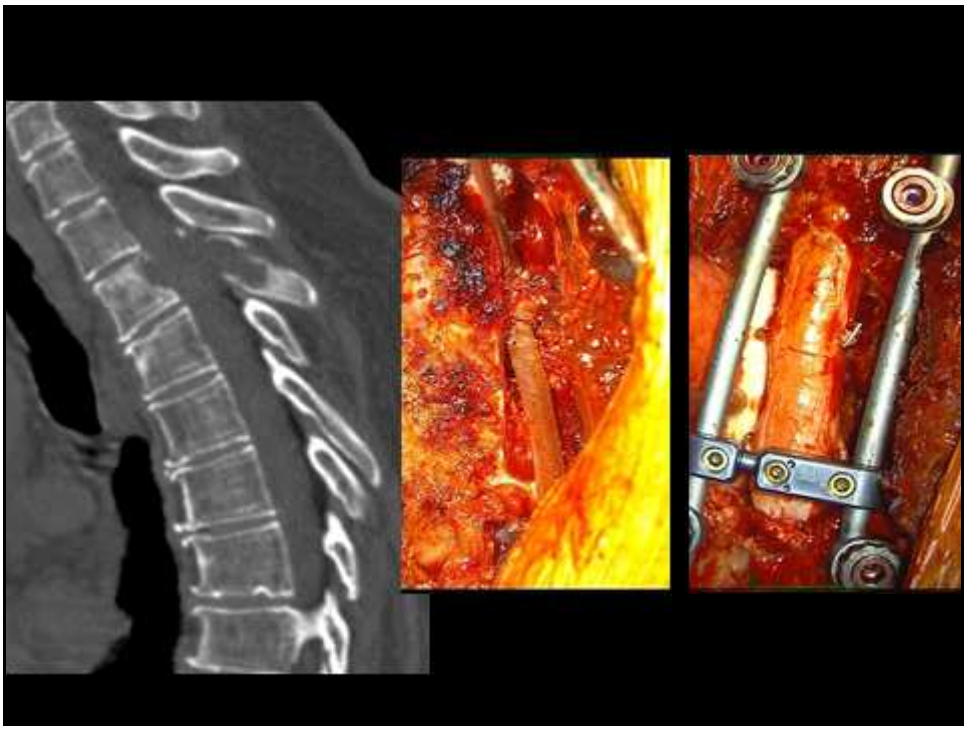

FS-T2
T1

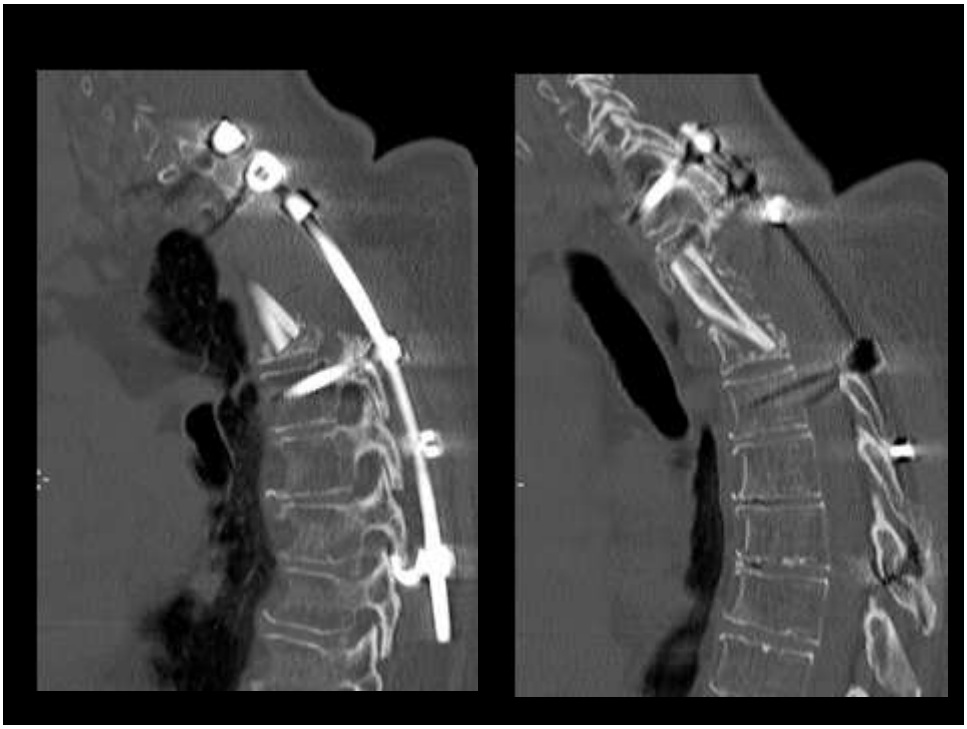

Lesion detection
T1
T2

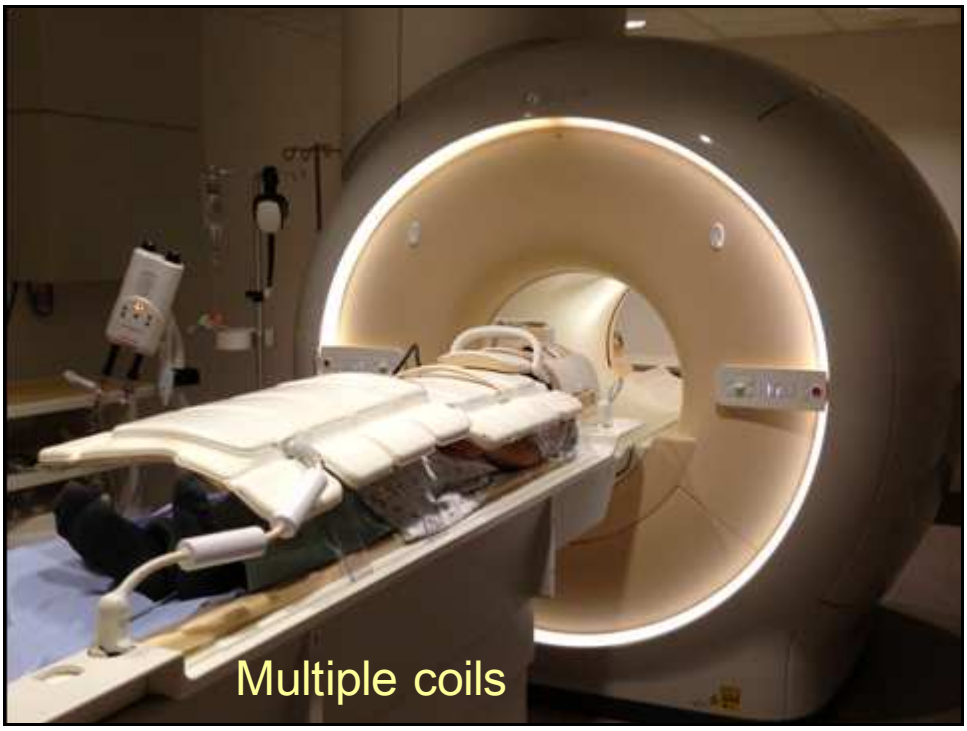
T1: MOELLE OSSEUSE (→ métas).

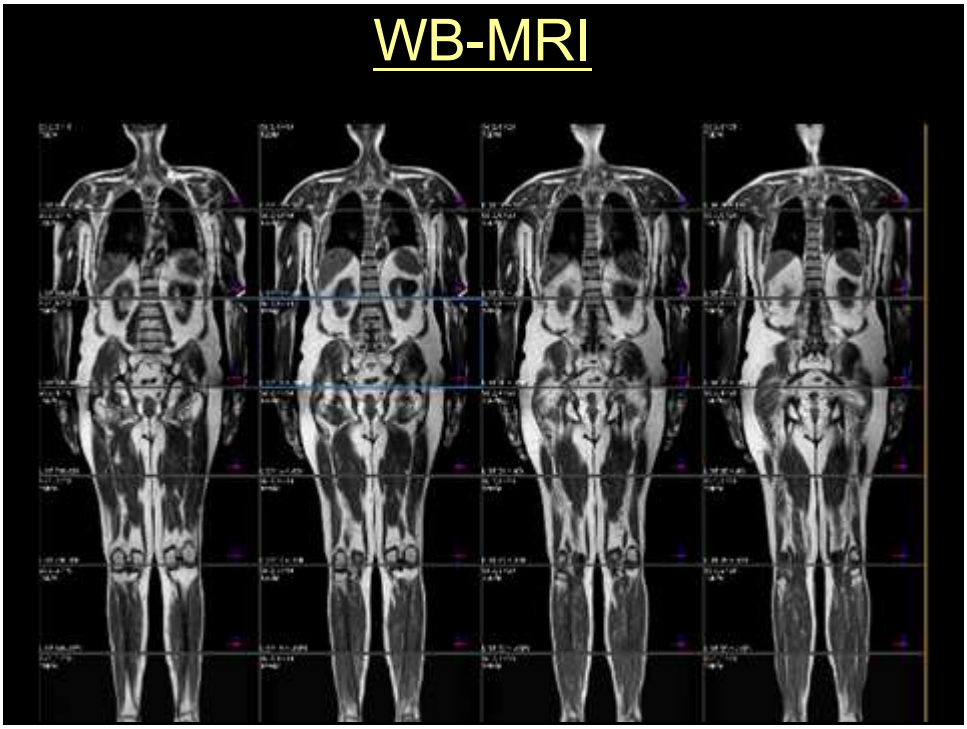
T2 : MOELLE EPINIERE(→ effet de masse)

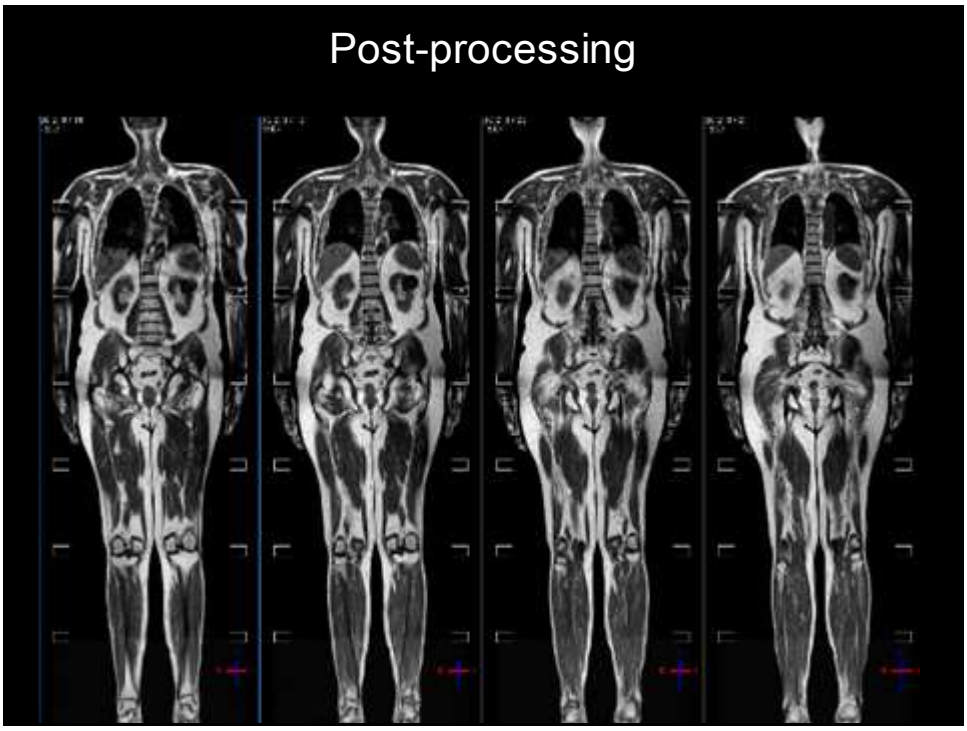


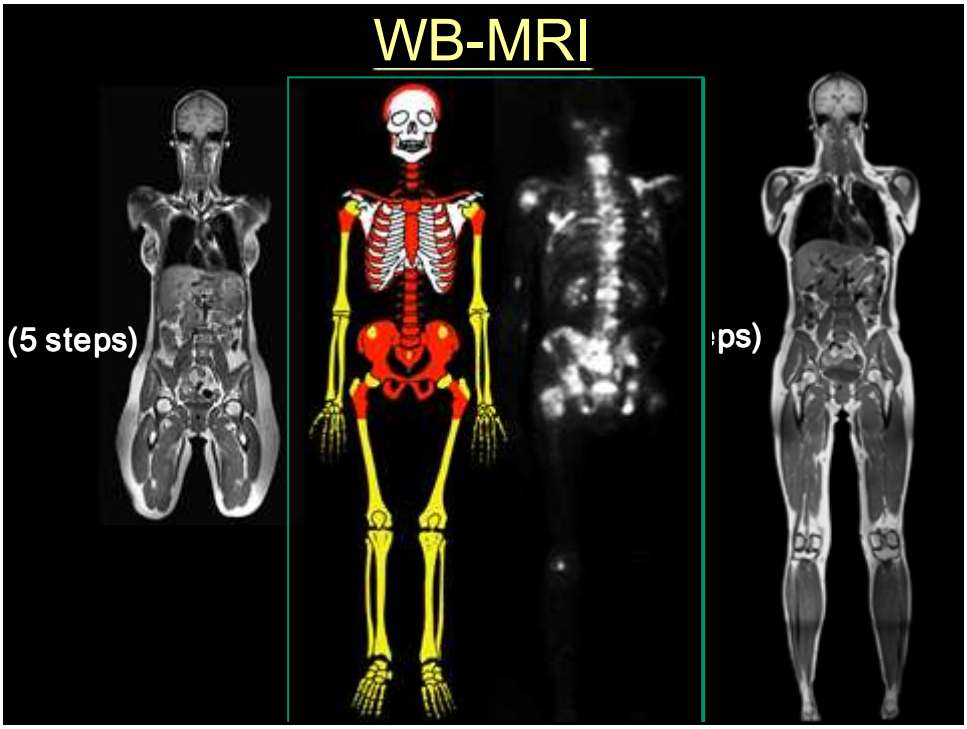


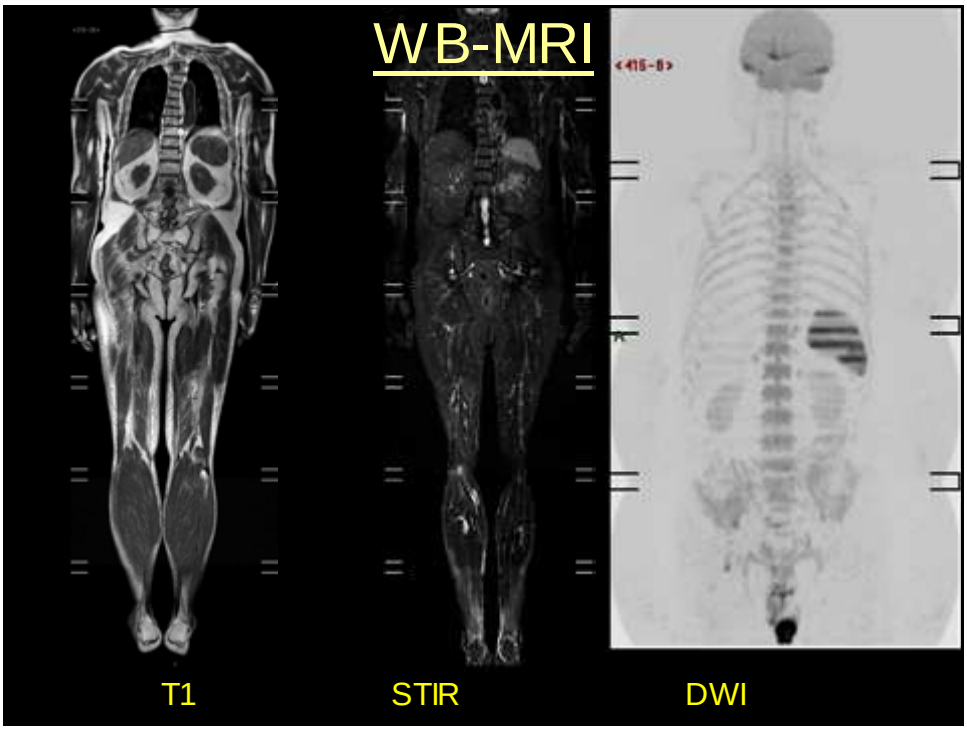


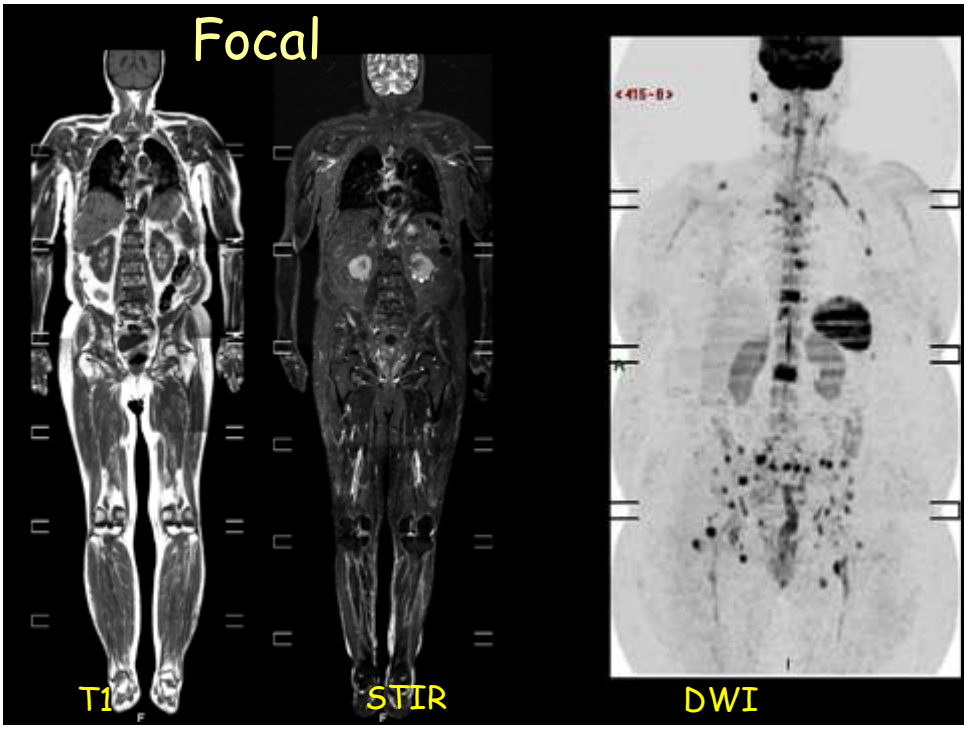

Multiple coils

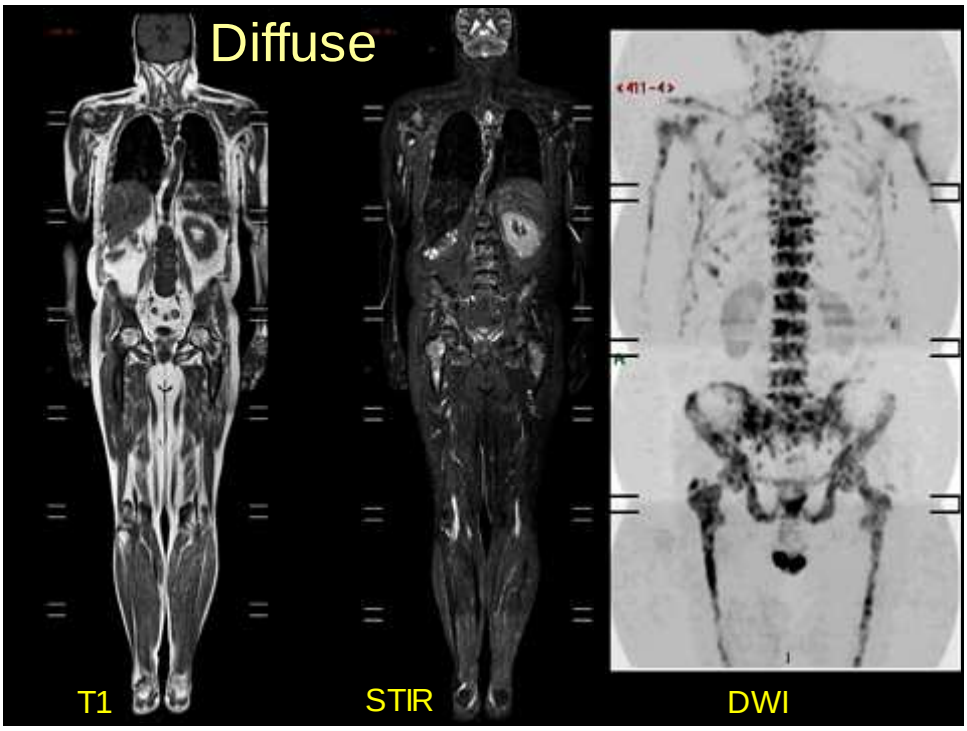

WB-MRI

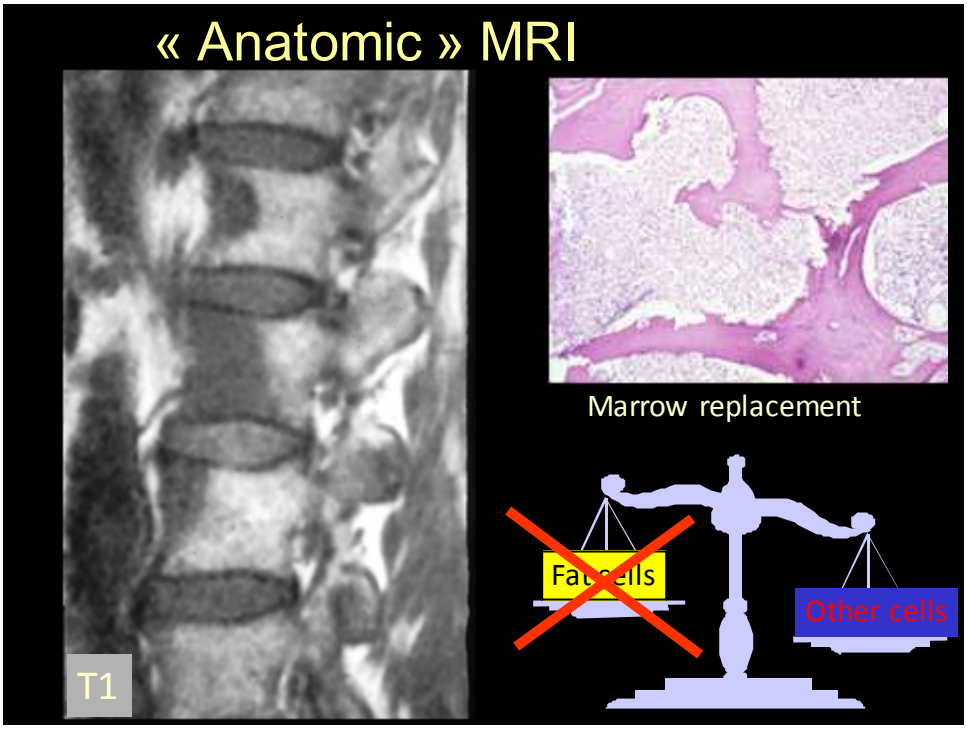

Post-processing


WB-MRI
(5 steps)

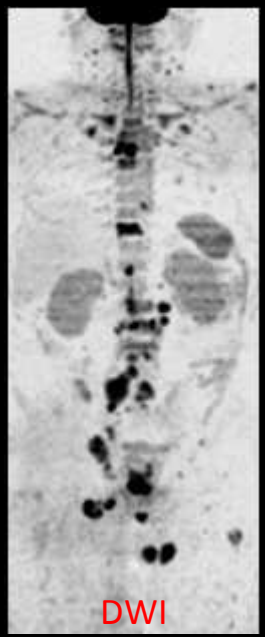

WB-MRI
T1
STIR
DWI

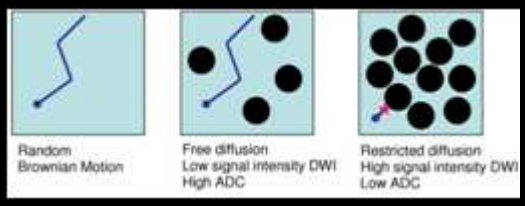

Focal
T1
STIR
DWI


Diffuse
T1
STIR
DWI

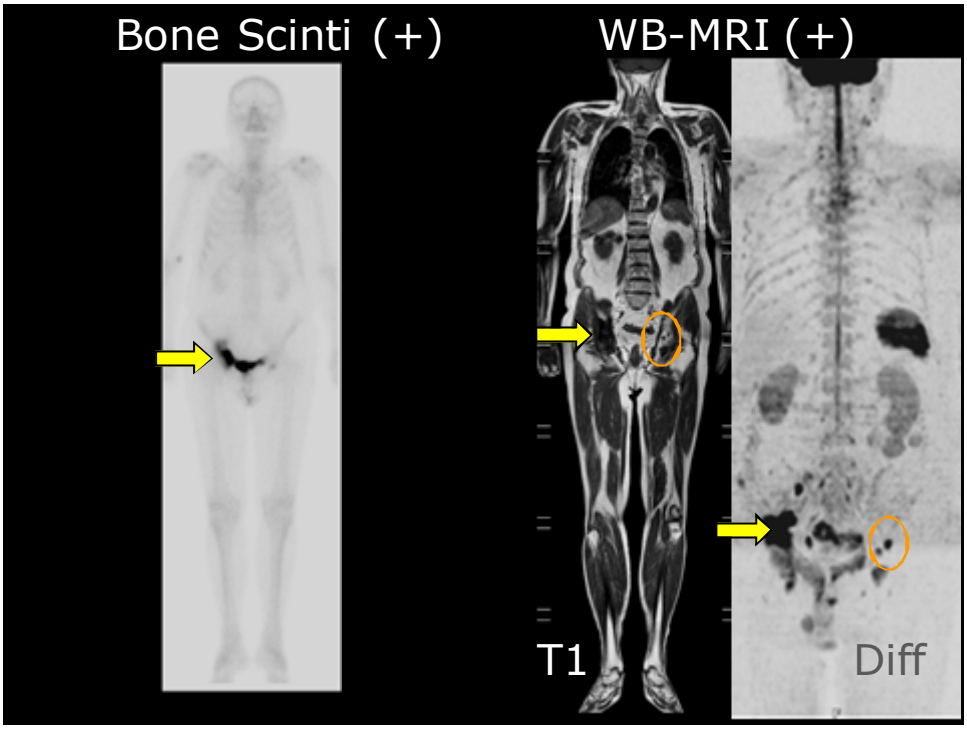

« Anatomic » MRI
T1
Marrow replacement
Fat cells
Other cells

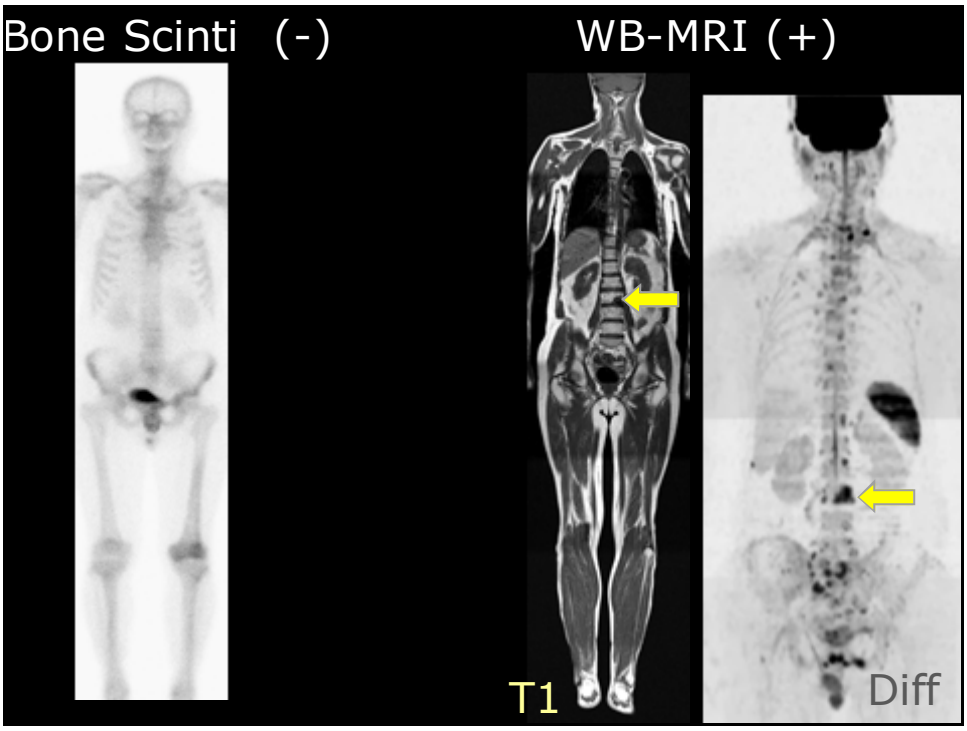
« Diffusion-weighted » MRI

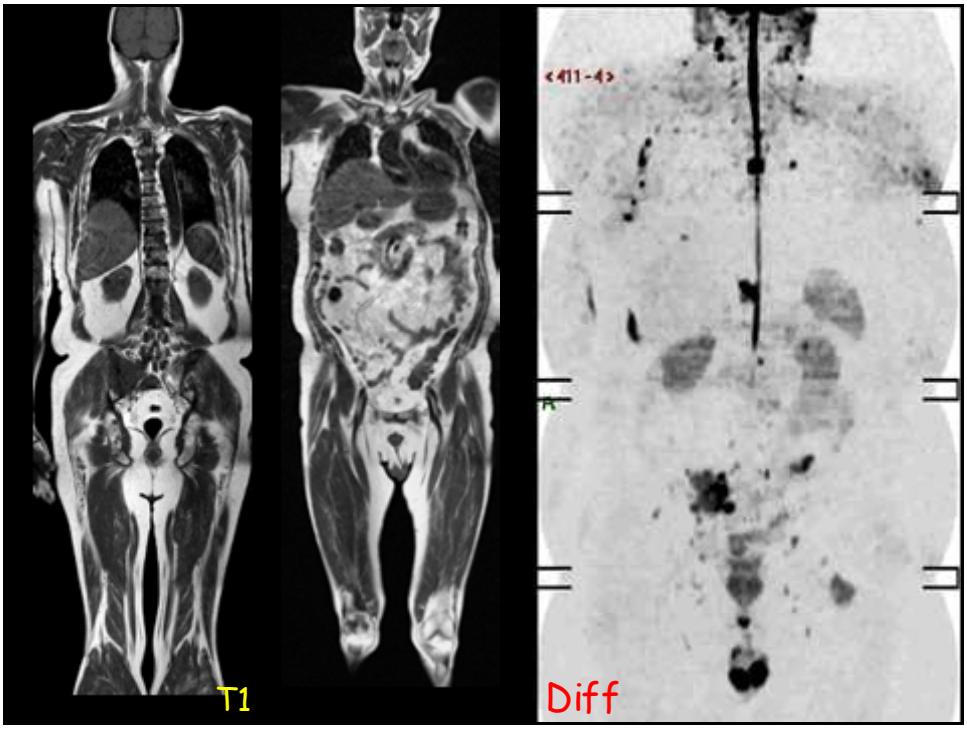


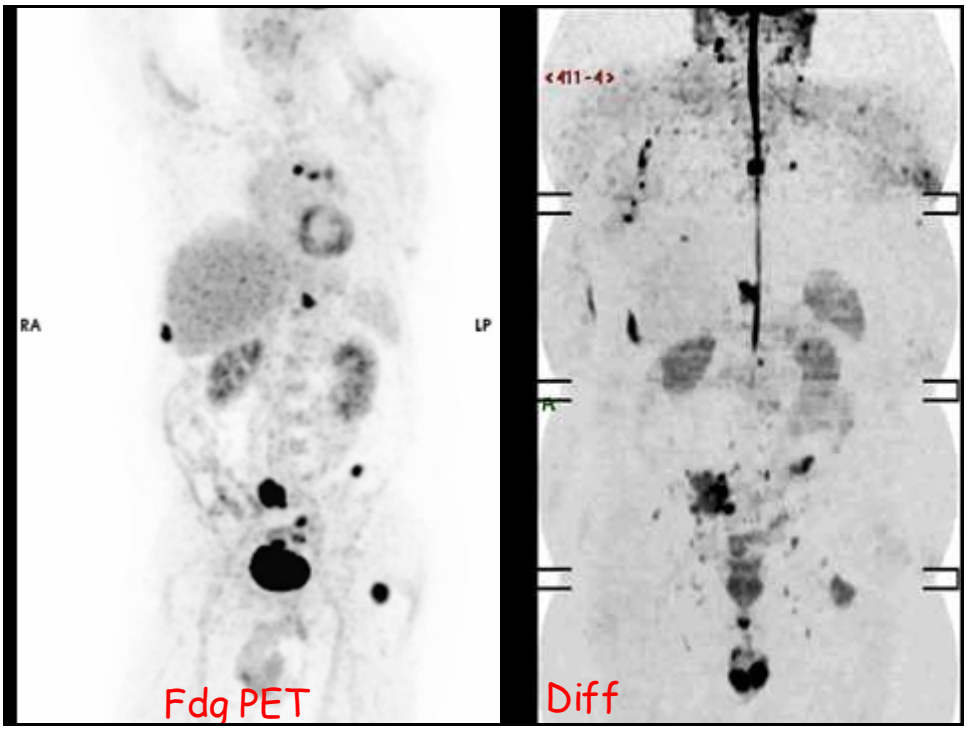


O'Flynn EA, DeSouza NM
Functional magnetic resonance: biomarkers of response in breast cancer
Breast Cancer Res. (2011)




Bone Scinti (-)
WB-MRI (+)
T1
Diff


T1
Diff



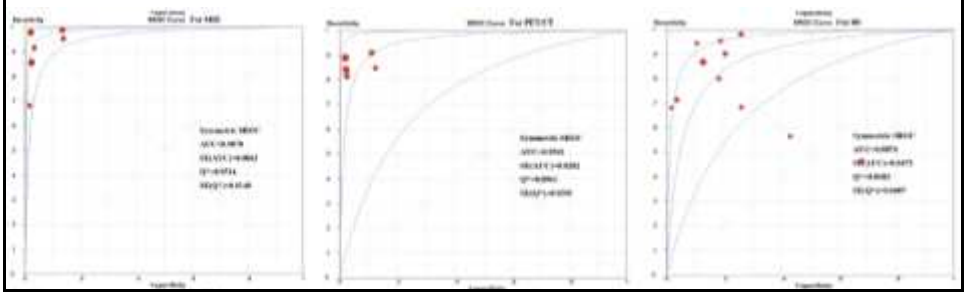
Diagnosis of bone metastases: a meta-analysis comparing ^{18}FDG PET, CT, MRI and bone scintigraphy. Yang H-L, et al Eur Radiol 2011;21:2604–17.

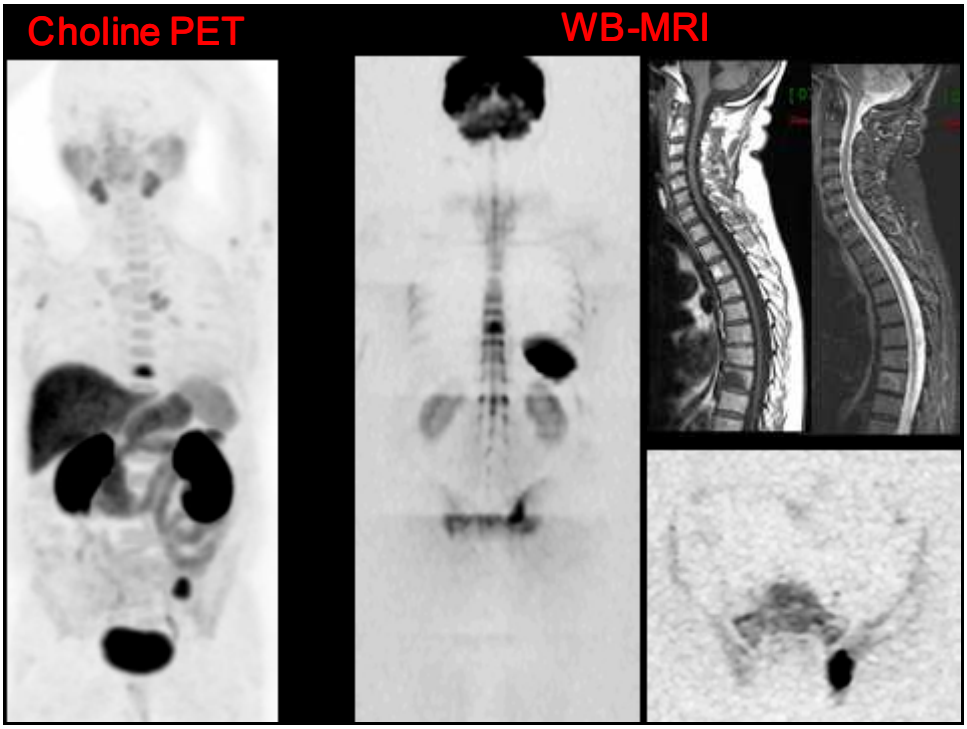
	MRI	PET/CT	BS
Sensitivity	91%	90%	86%
Specificity	95%	97%	81%

67 articles
145 studies
15221 patients.

Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of **bone metastases** in patients with prostate cancer: a meta-analysis
Shen G et al. Skel Radiol 2014

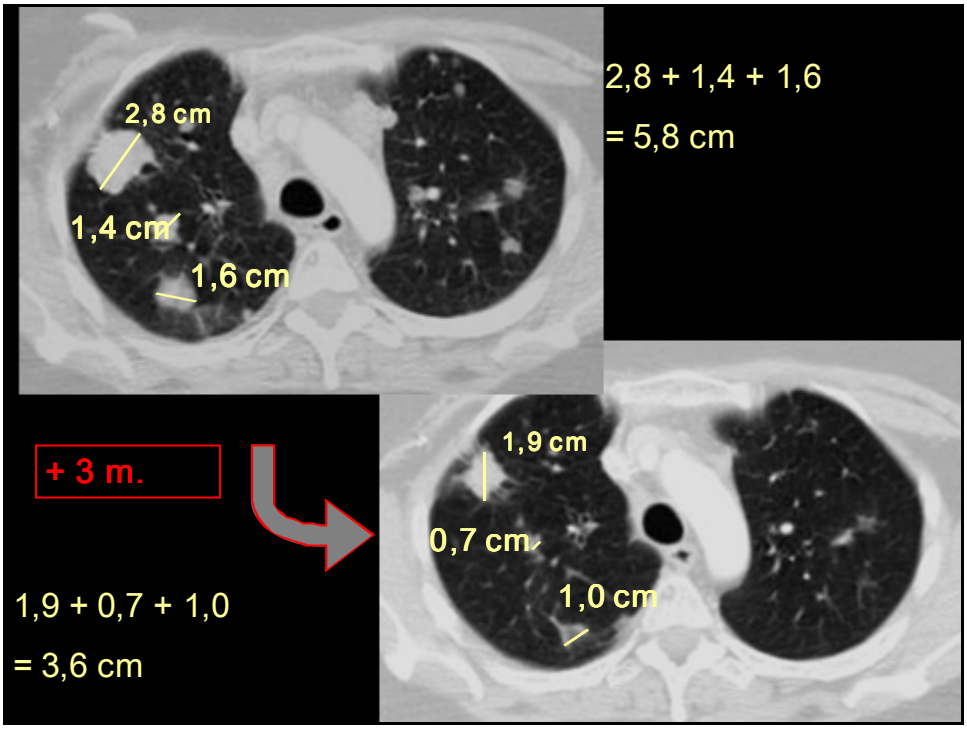
	MRI	PET/CT	BS
Sensitivity	95%	87%	79%
Specificity	96%	97%	82%
AUC	99%	95%	89%





BONE METASTASES

Response



« Bone metastases are not measurable »

…The assessment of response is impossible

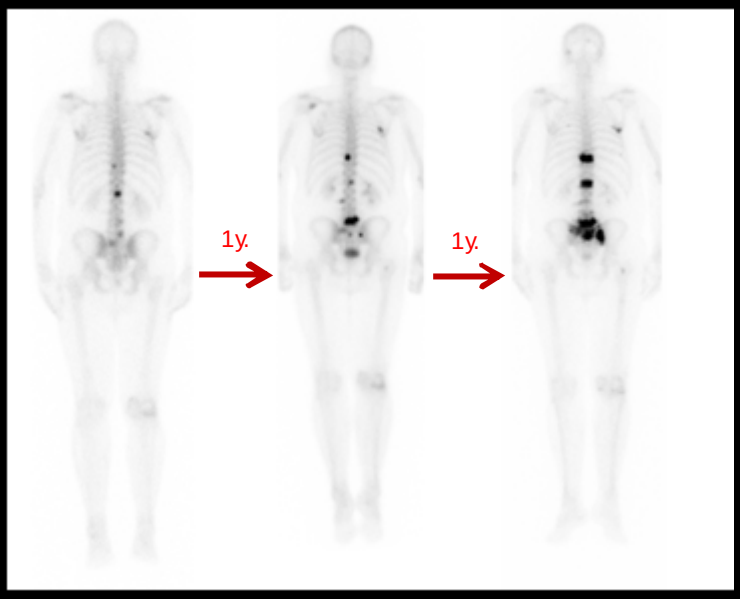
in patients with bone lesions only…

Therasse P, et al

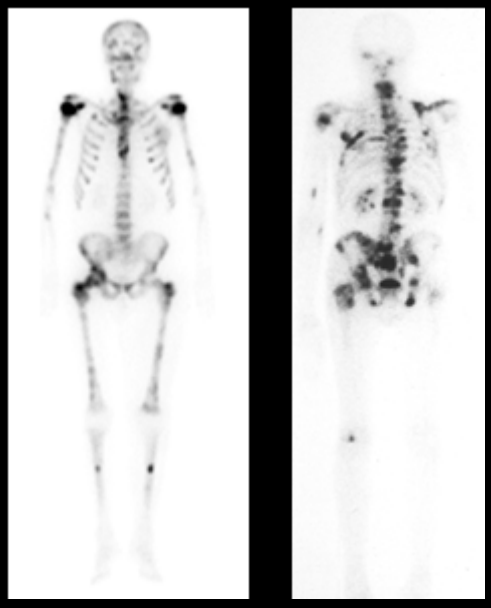
RECIST Guidelines

J Natl Cancer Inst. 2000 2;92:205-16

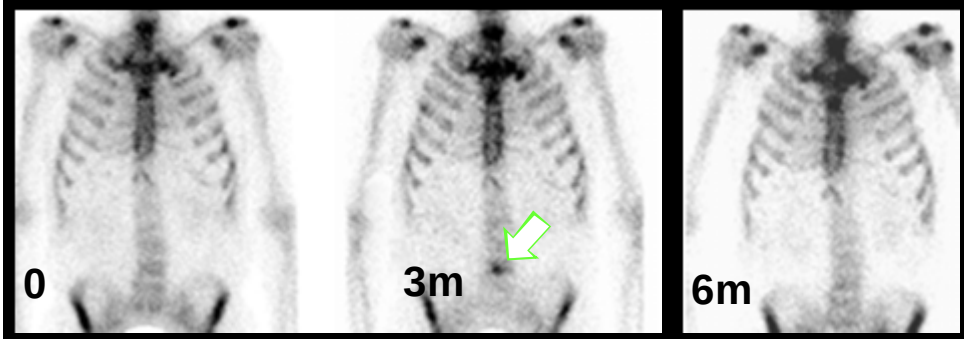
Bone scan: non ambiguous progression



Bone scan: measurements ?

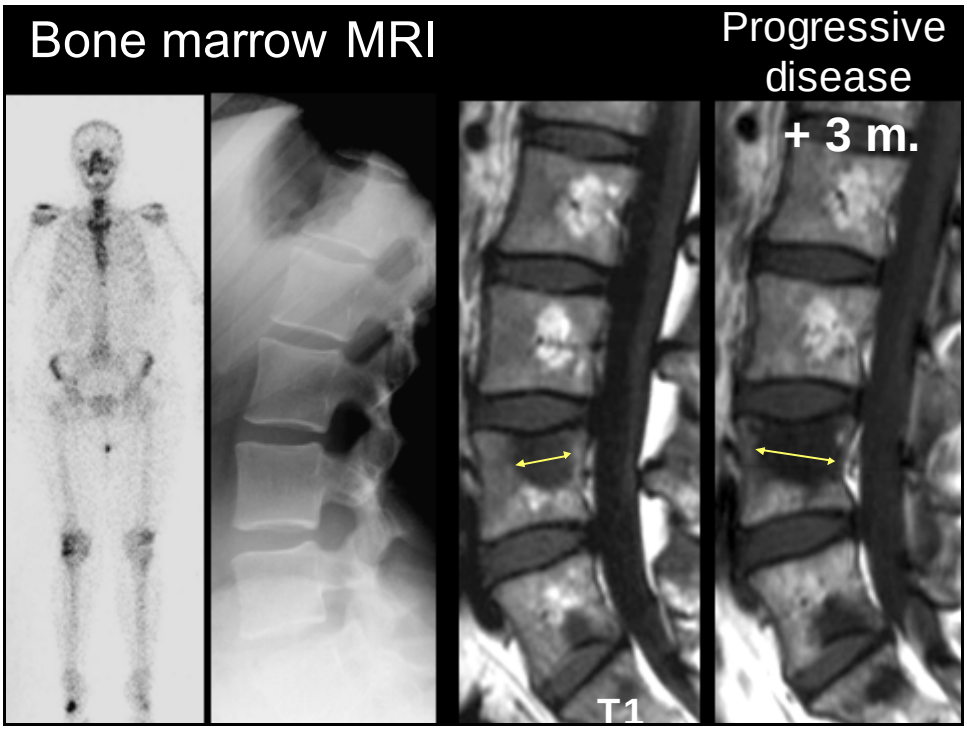


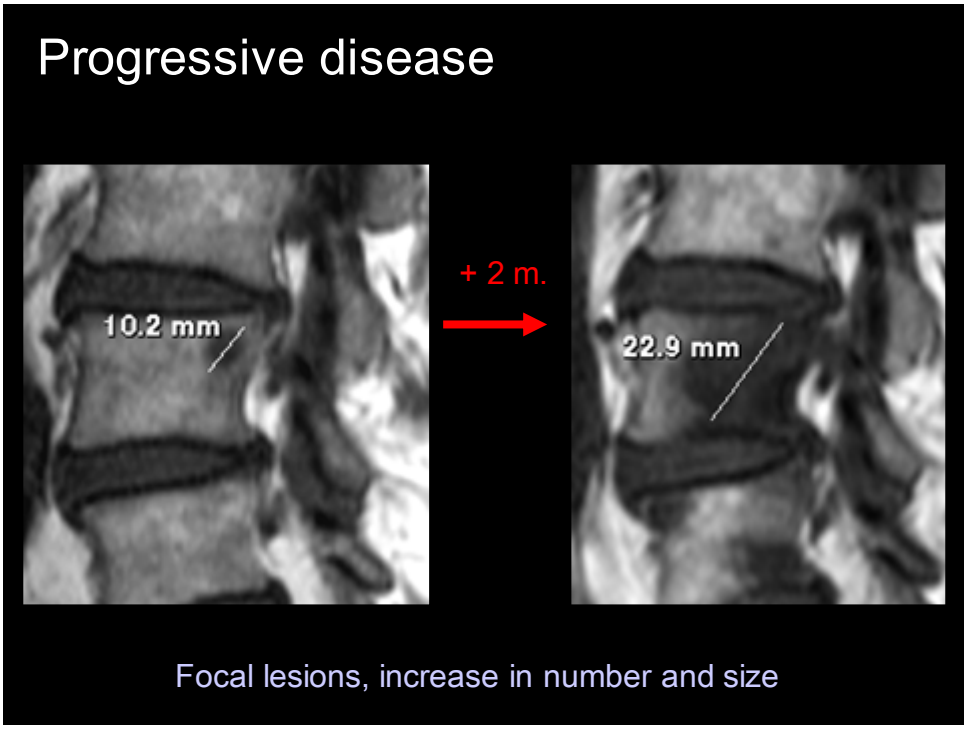
Bone scan: confusing findings

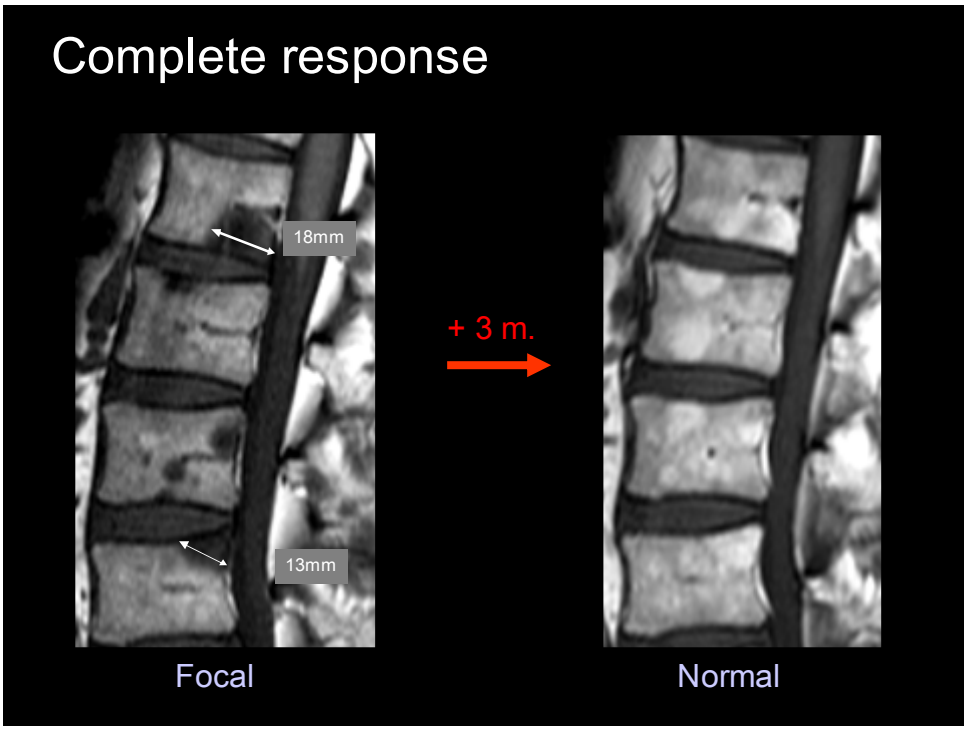


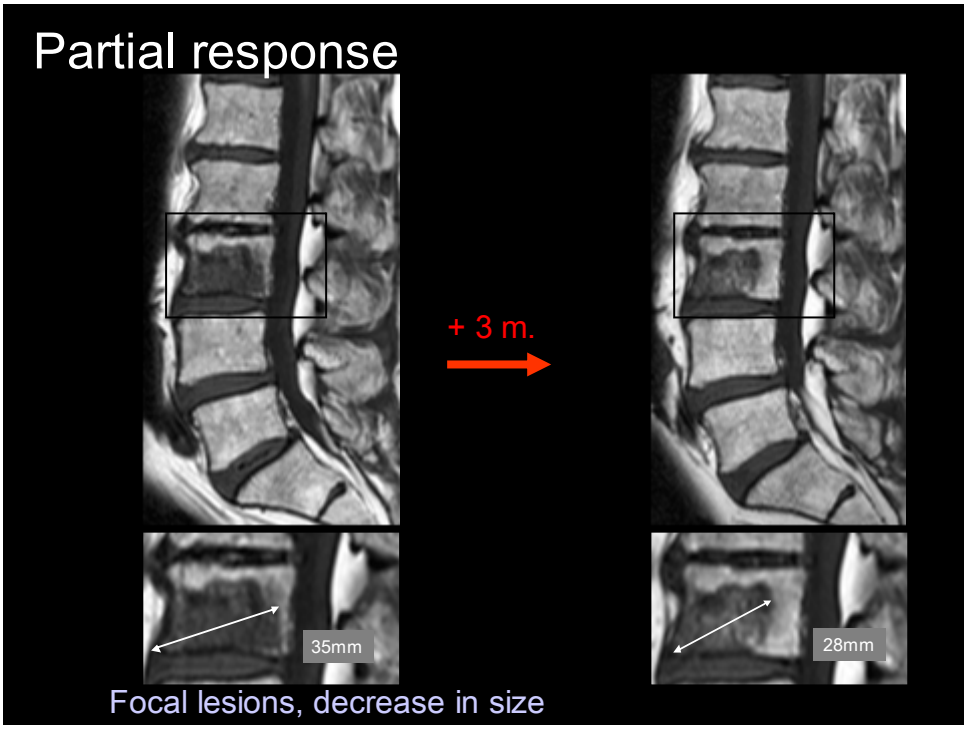
FLARE PHENOMENON= false progression

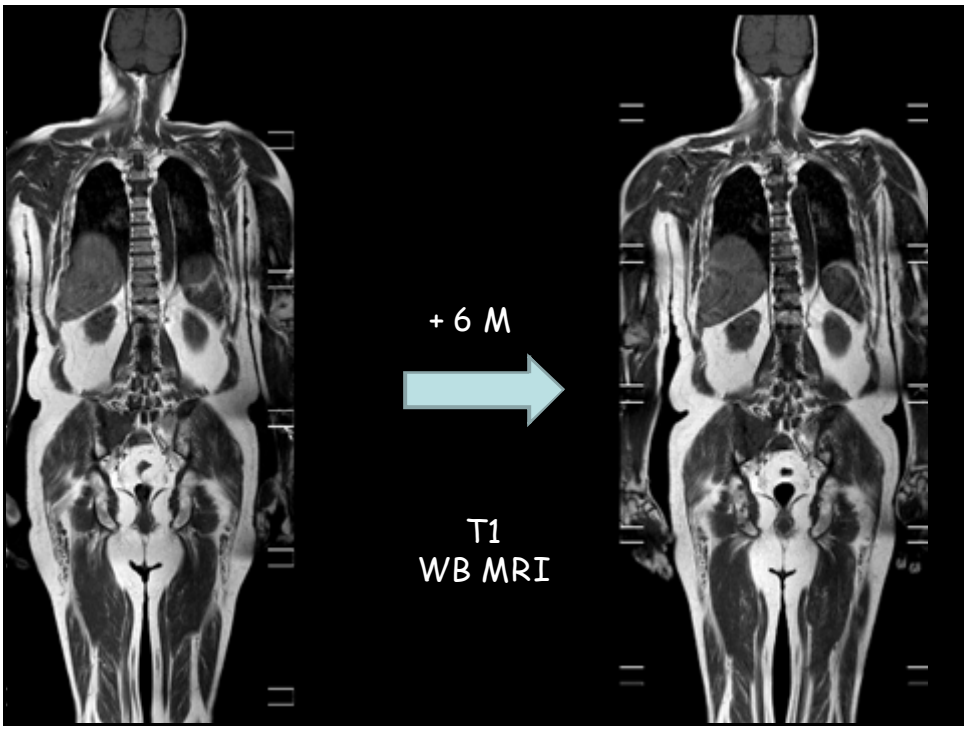
- increase in osteoblastic activity // response
- transient ↗ in apparent lesion nb and size
- followed by regression

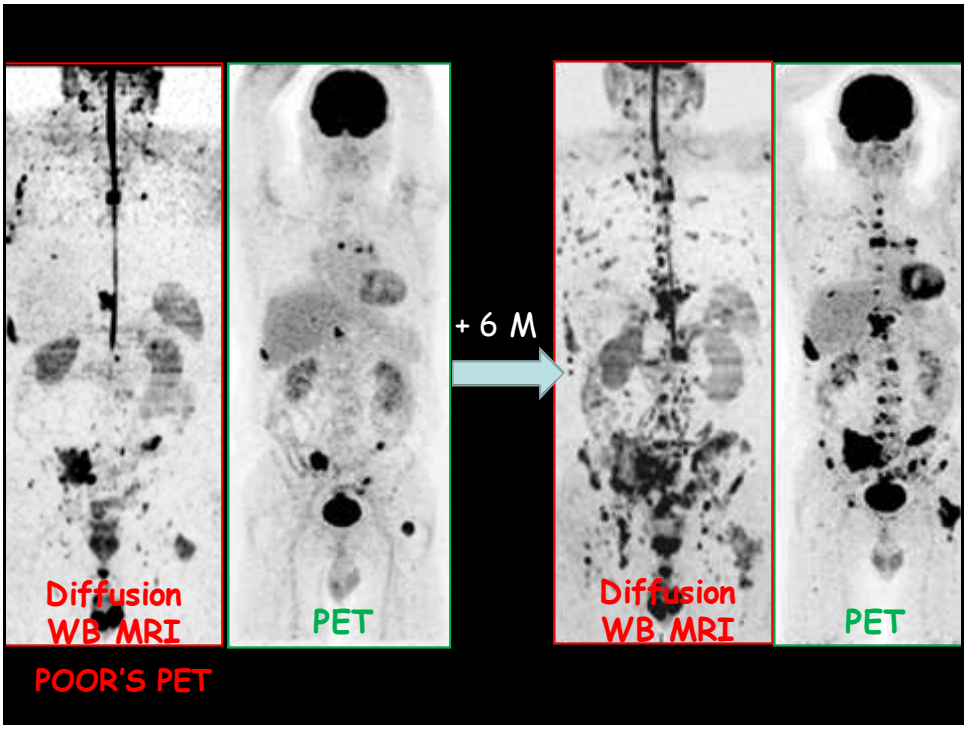

Bone marrow MRI
Progressive disease
+ 3 m.
T1


Progressive disease
10.2 mm
+ 2 m.
22.9 mm
Focal lesions, increase in number and size


Complete response
18mm
13mm
+ 3 m.
Focal
Normal


Partial response
+ 3 m.
35mm
28mm
Focal lesions, decrease in size


+ 6 M
T1
WB MRI

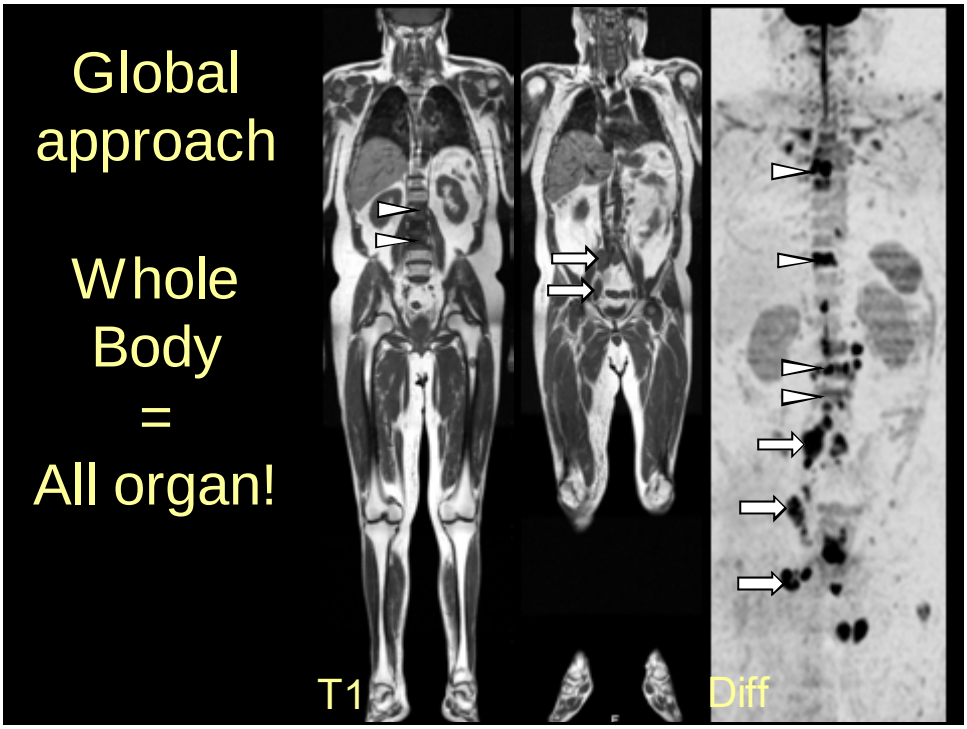

Diffusion
WB MRI
PET
+ 6 M
Diffusion
WB MRI
PET
POOR'S PET

« Bone metastases are ~~not~~ measurable »

Tombal B, Rezazadeh A, Therasse P, Van Cangh PJ, Vande Berg B, Lecouvet FE.
MRI of the axial skeleton enables objective measurement of tumor response on prostate cancer bone metastases. Prostate. 2005 Oct 1;65(2):178-87.

Brown AL, Middleton G, MacVicar AD, Husband JE.
T1-weighted MRI in breast cancer vertebral metastases: changes on treatment and correlation with response to therapy. Clin Radiol. 1998;53:493-501.

Ciray I, Lindman H, Aström KG, Bergh J, Ahlström KH.
Early response of breast cancer bone metastases to chemotherapy evaluated with MRI. Acta Radiol. 2001;42:198-206.

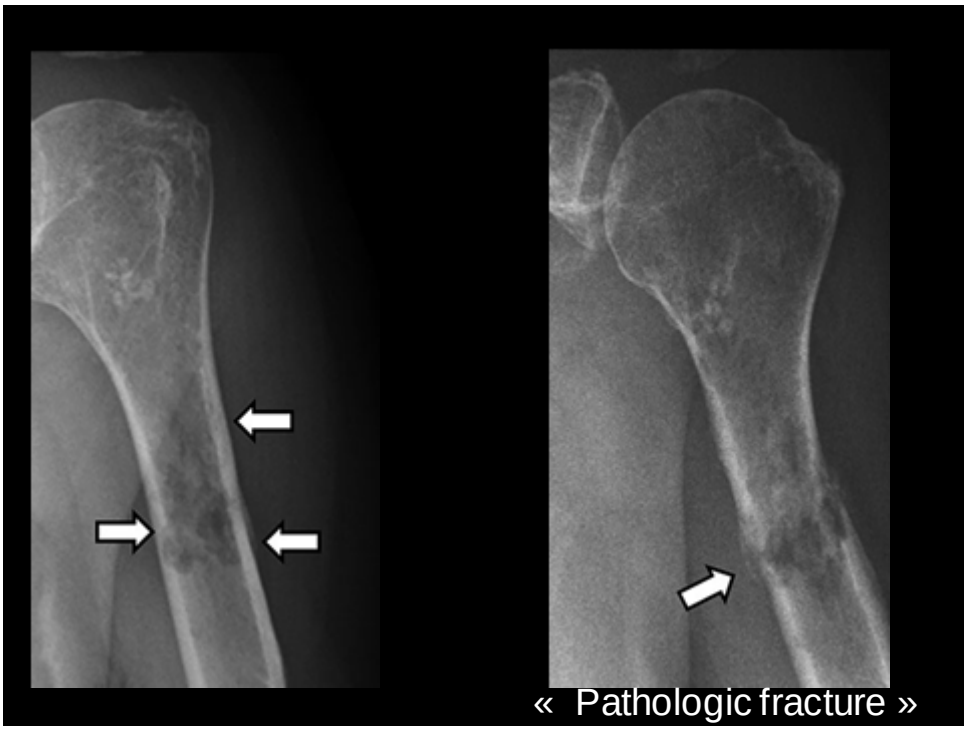


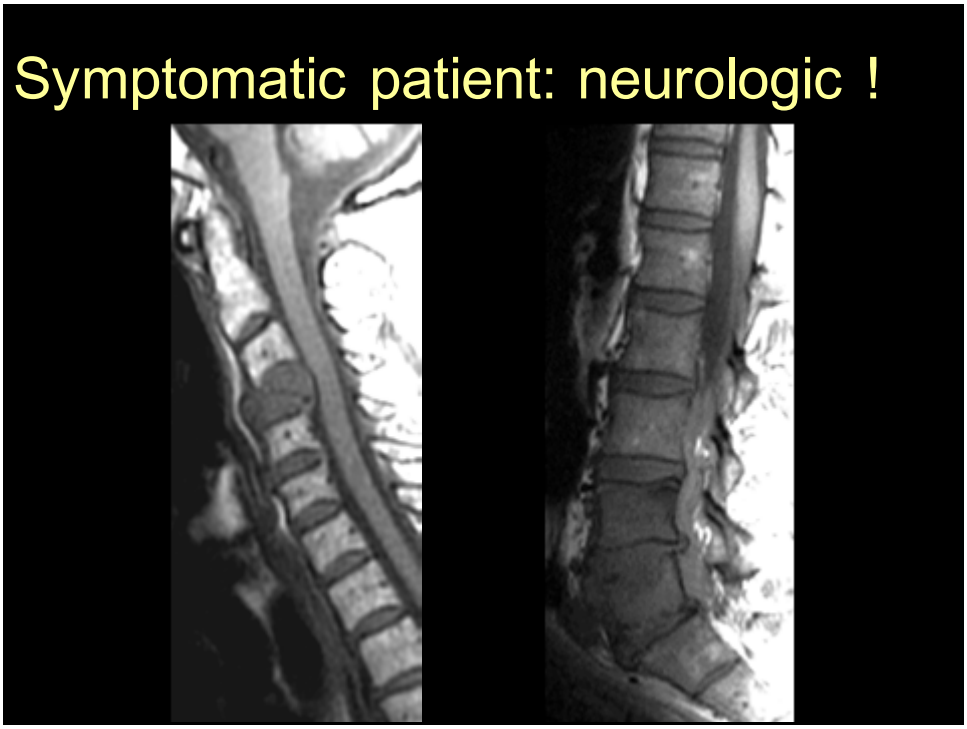
BONE METASTASES

Complications

Bone mestastasis: SYMPTOMATIC PATIENT

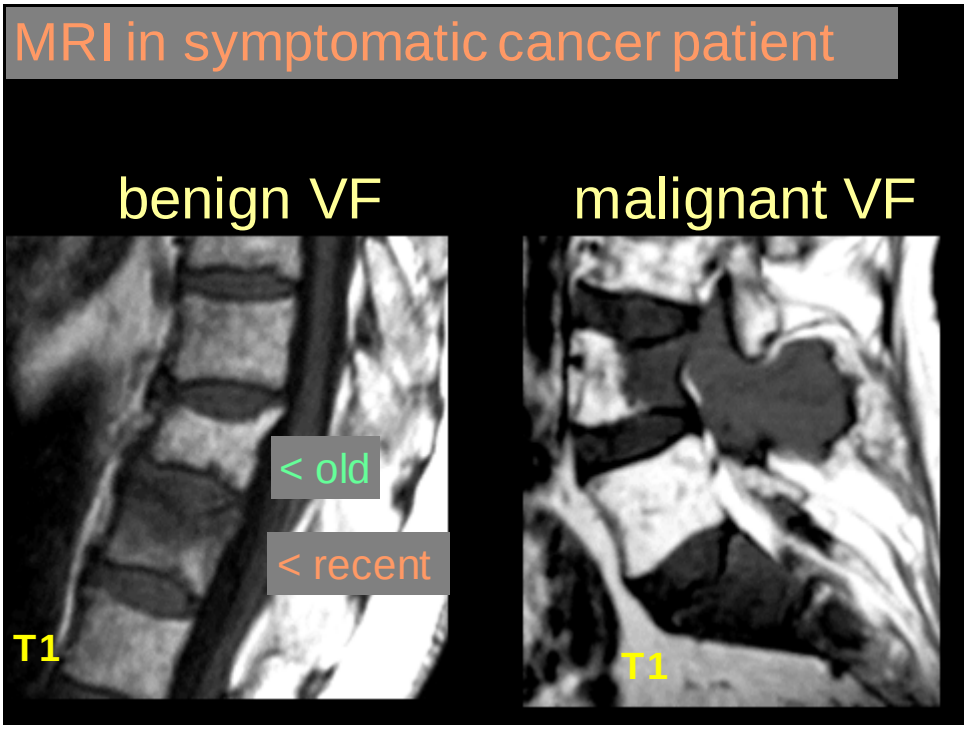
- Peripheral Skeleton : X-rays !
- Central skeleton: MRI !


« Pathologic fracture »

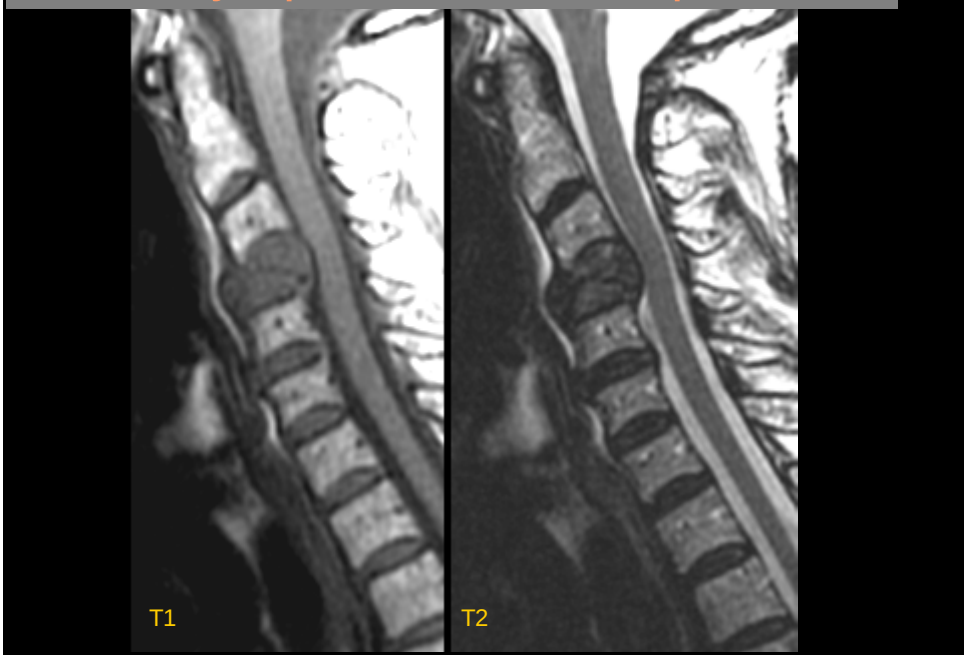

Symptomatic patient: neurologic !

BONE METASTASES

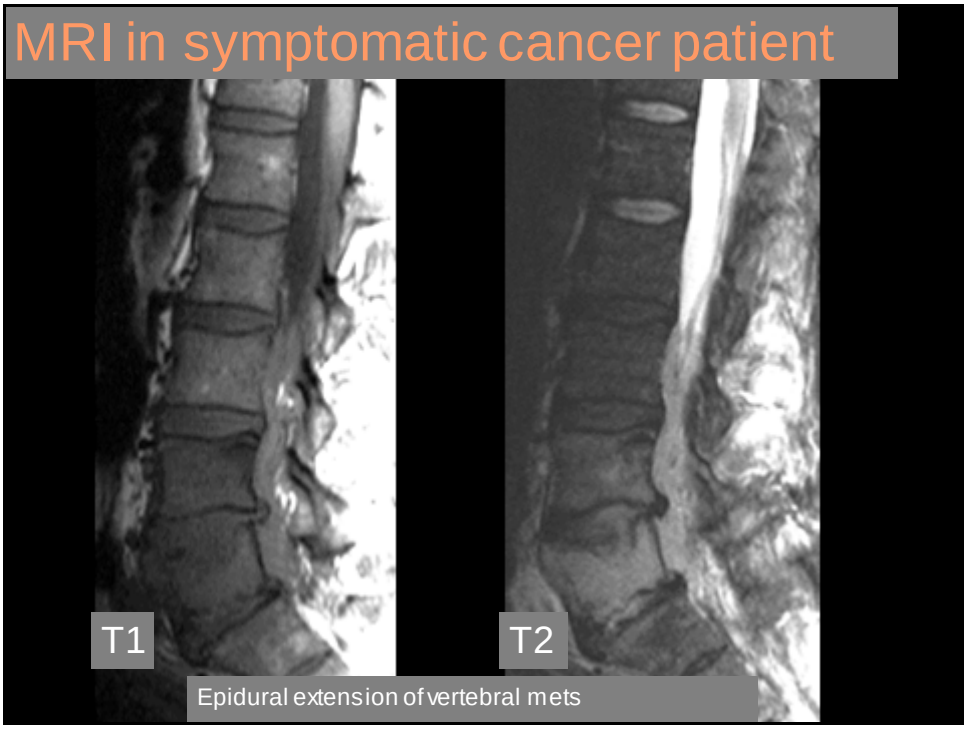
BENIGN Vs MALIGNANT VCF

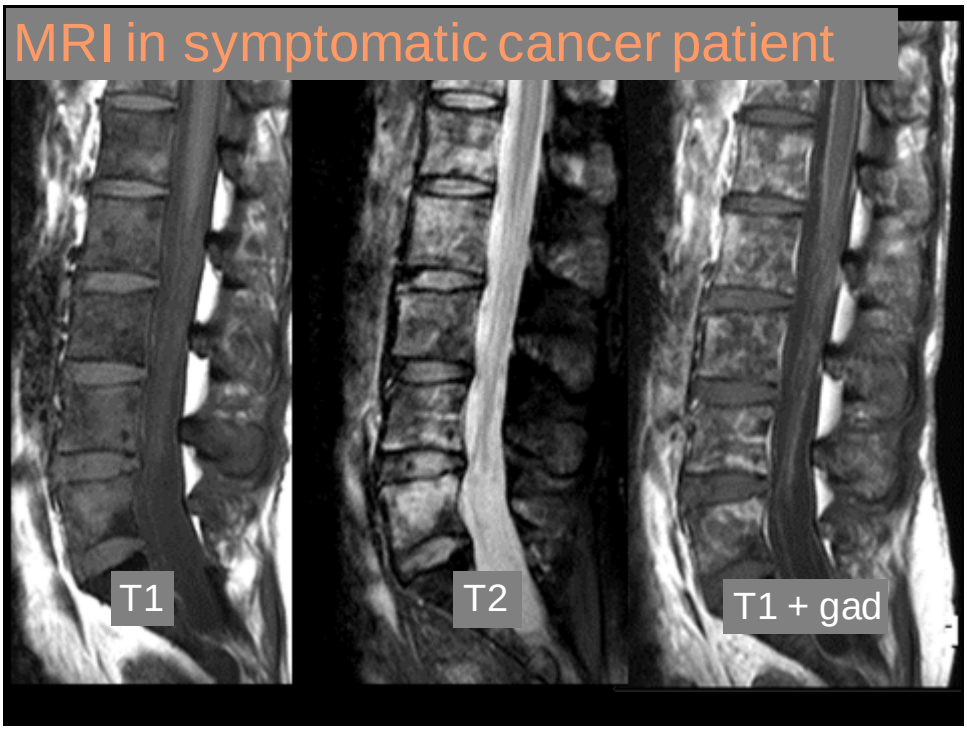


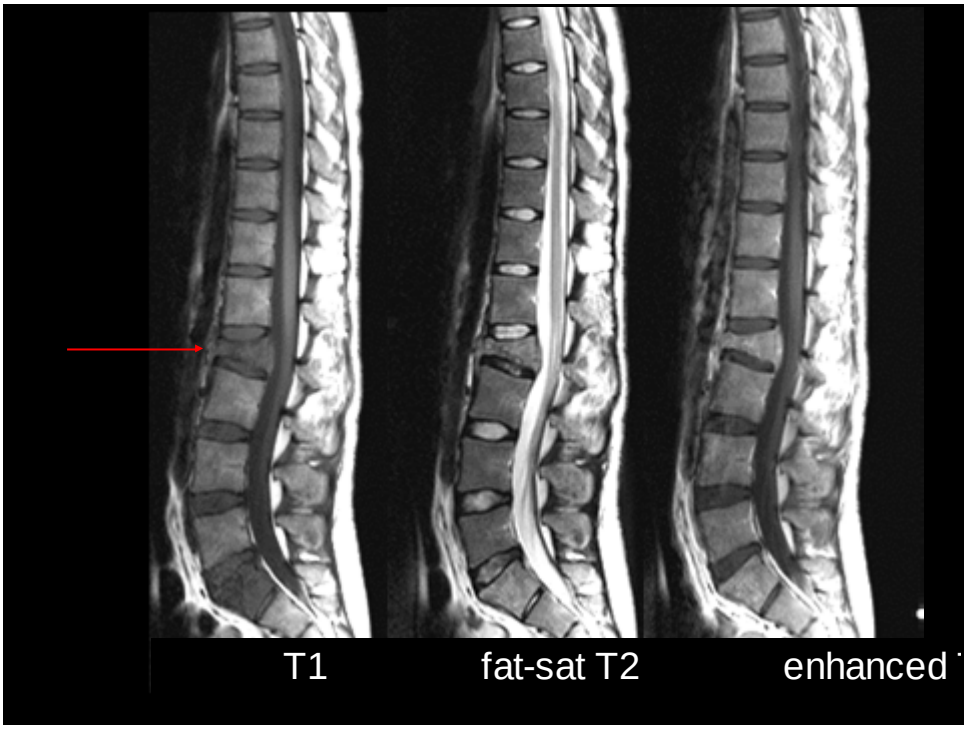
MRI in symptomatic cancer patient

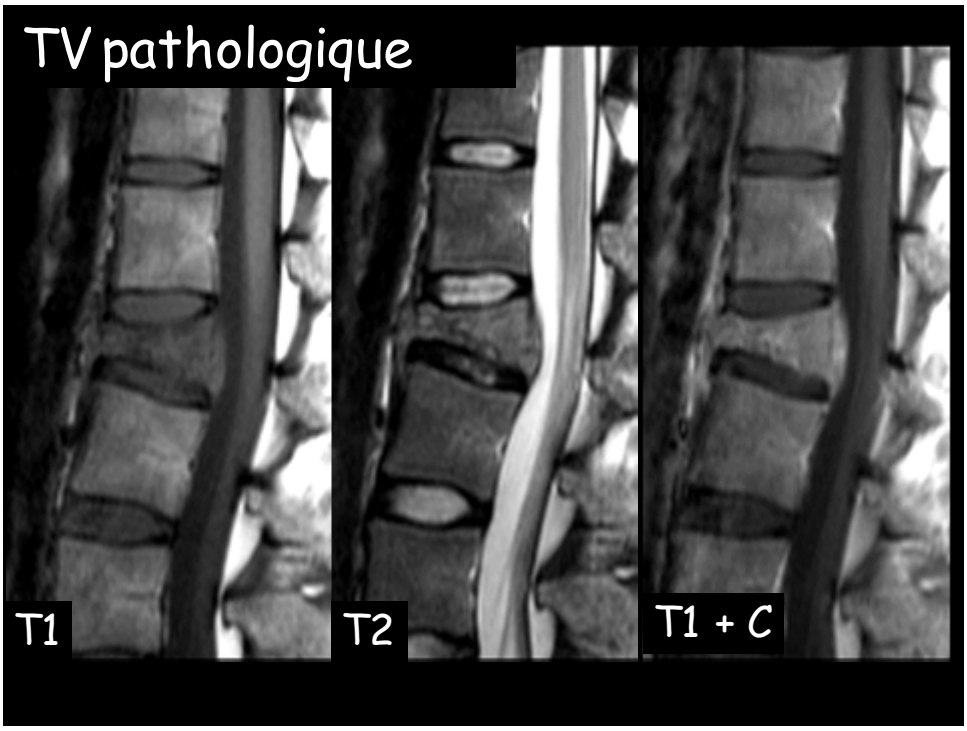


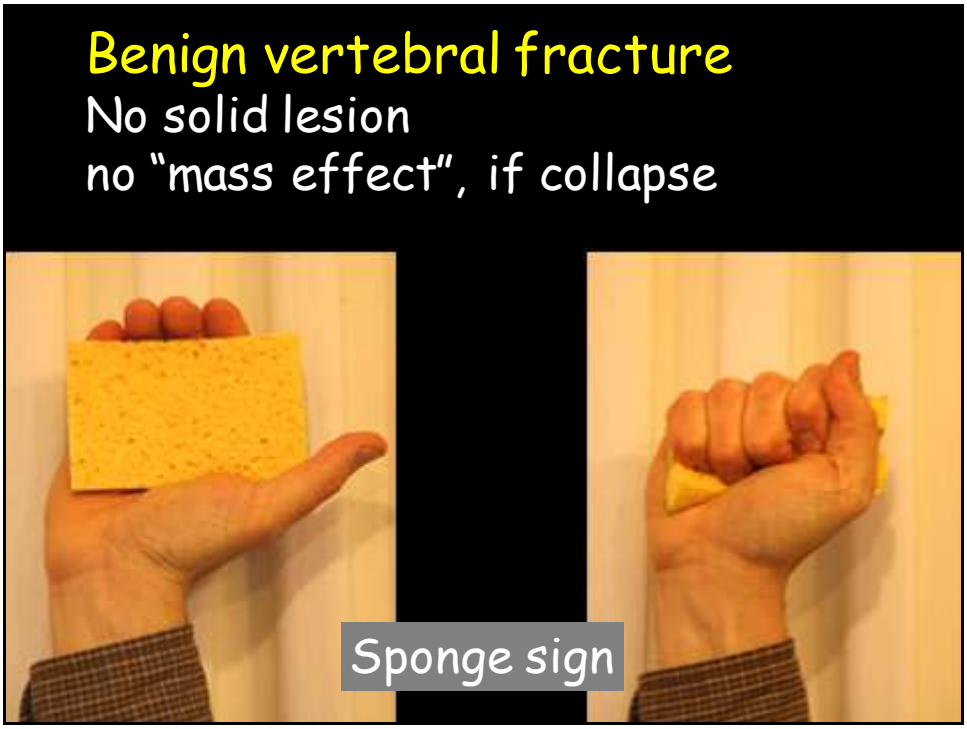
MRI in symptomatic cancer patient




MRI in symptomatic cancer patient
T1
T2
T1 + gad


T1
fat-sat T2
enhanced

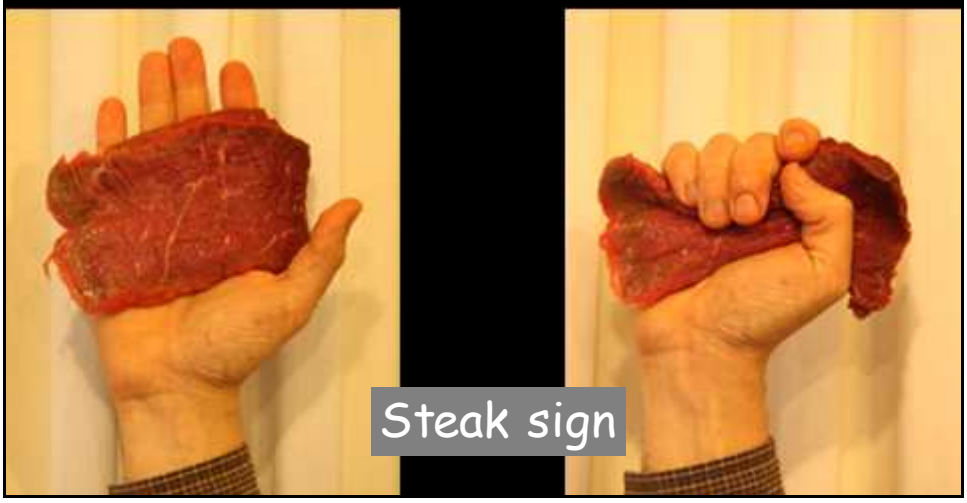

TV pathologique
T1
T2
T1 + C


Benign vertebral fracture
No solid lesion
no "mass effect", if collapse
Sponge sign

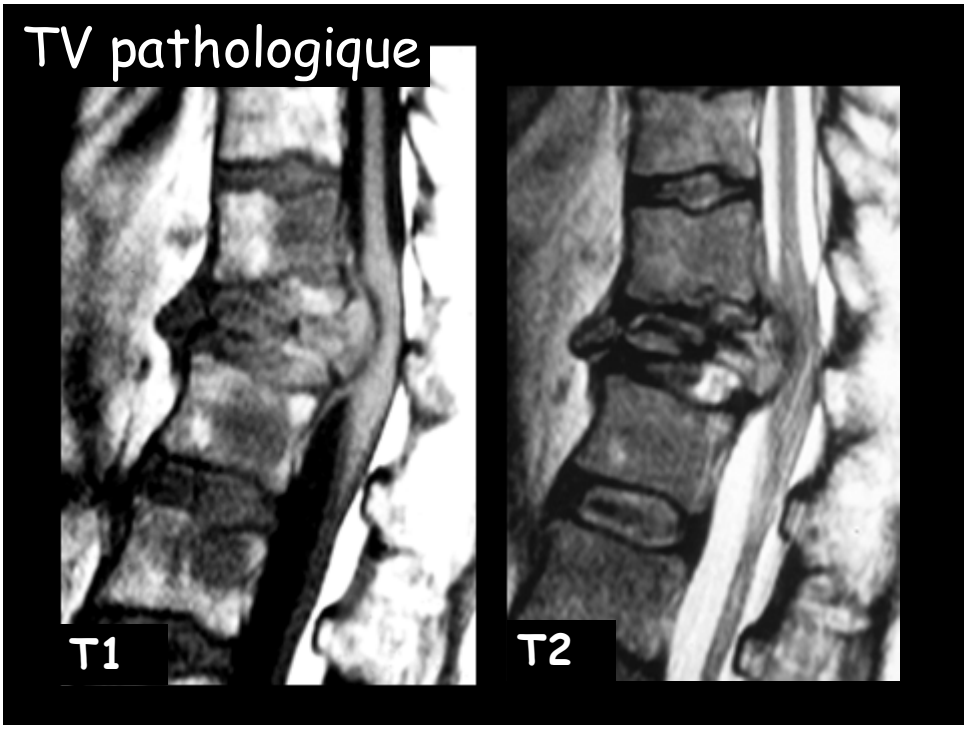
Malignant fracture

Superimposed "solid" lesion

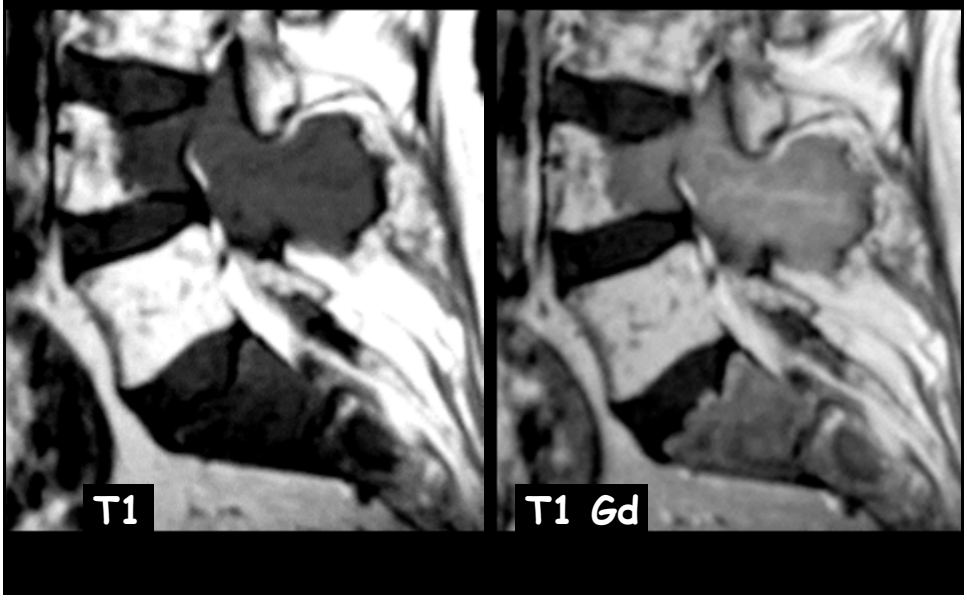
"mass effect", if collapse

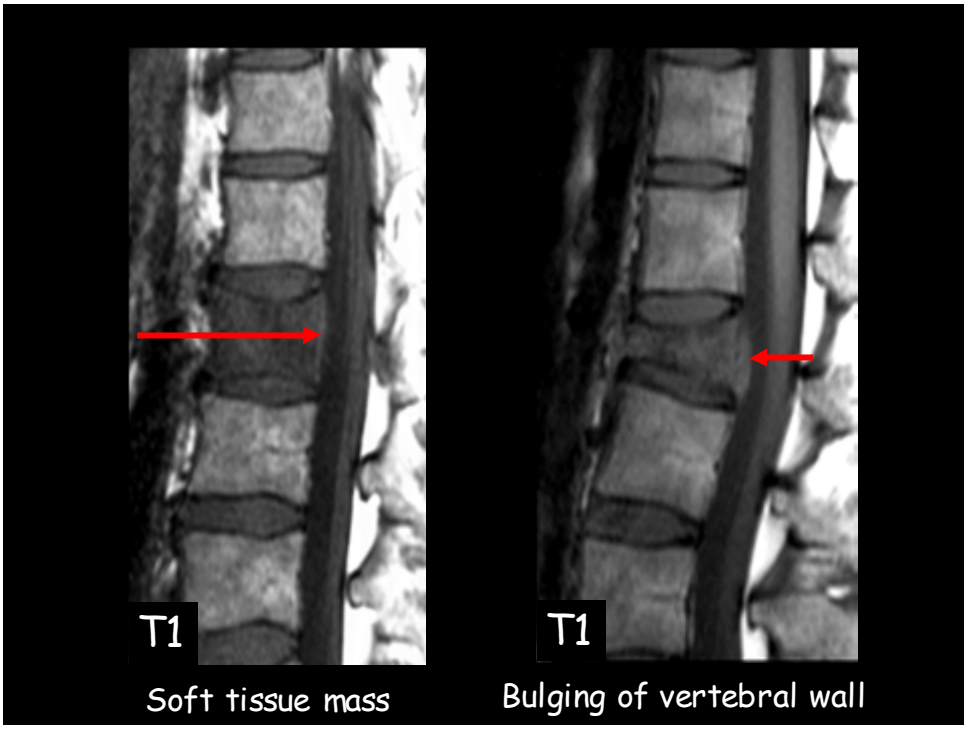


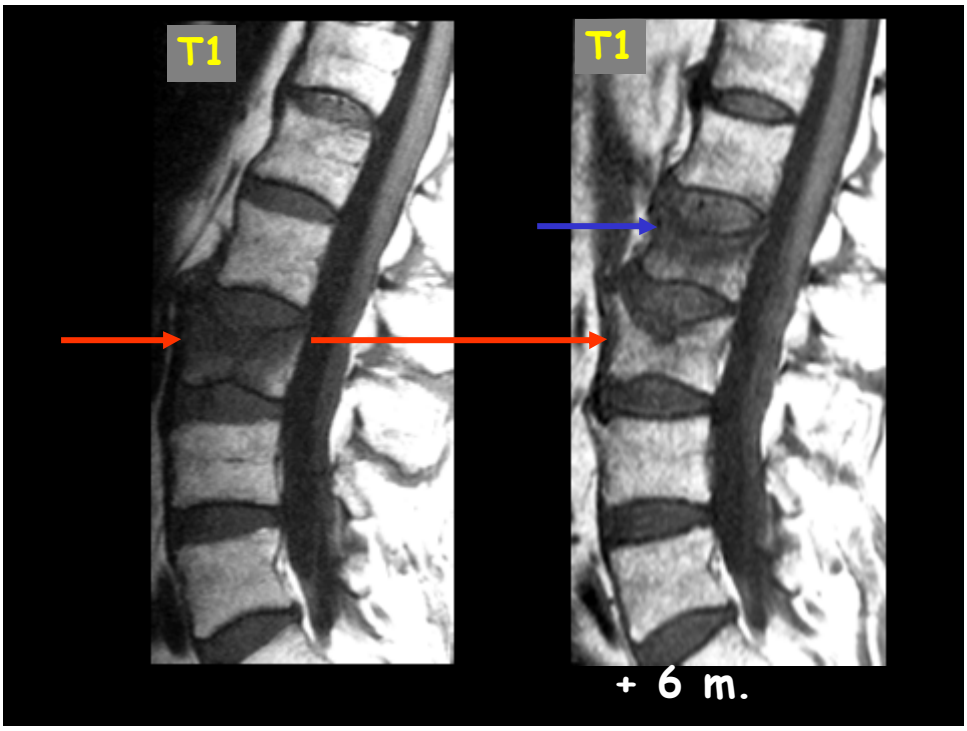
TV pathologique

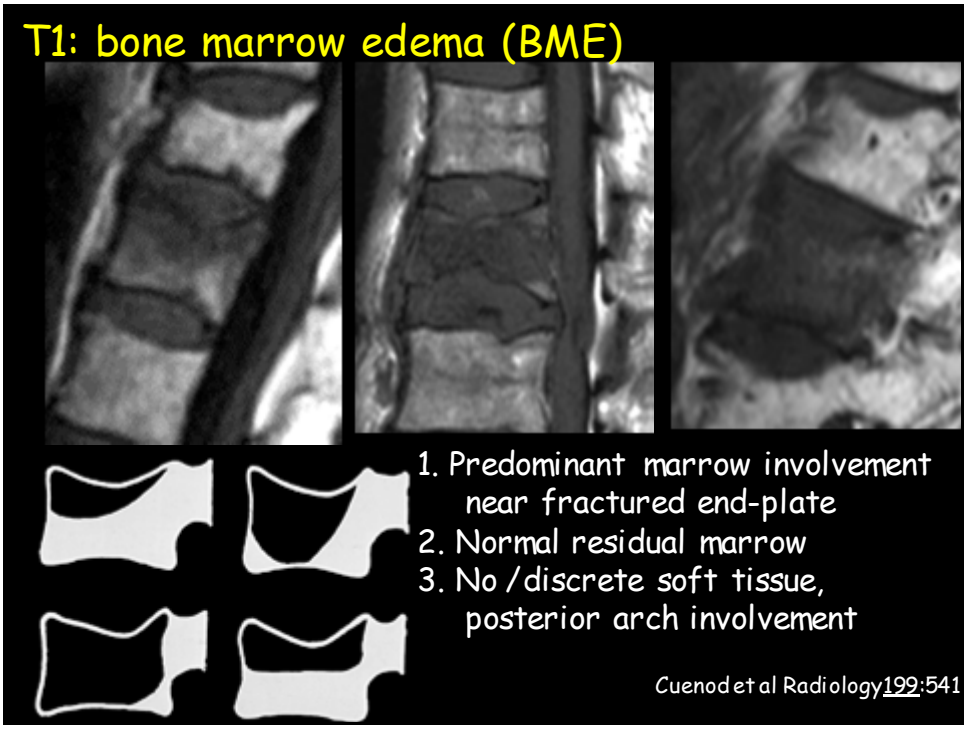


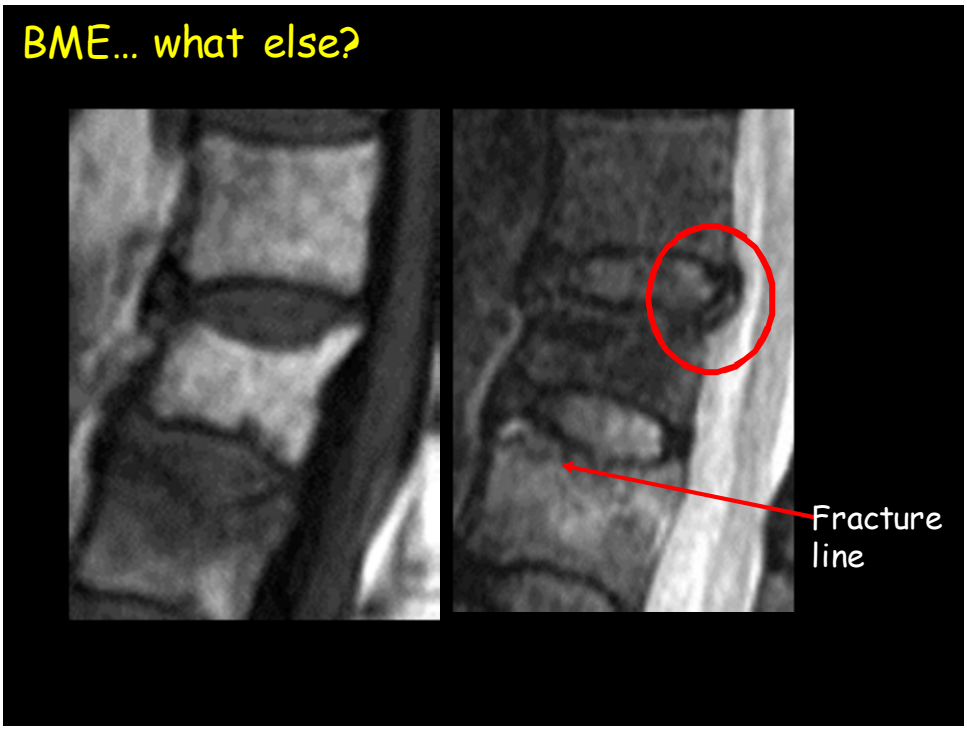
A distance de la fracture : arc postérieur



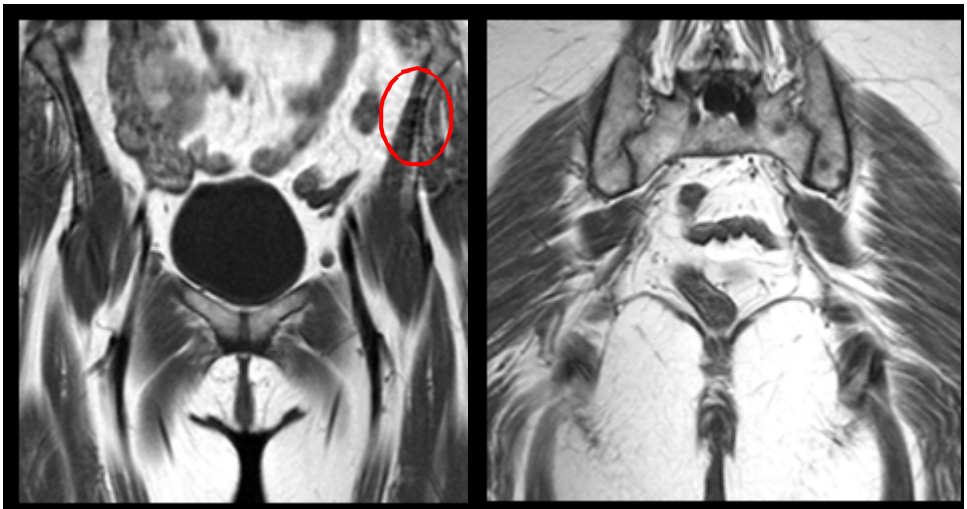



T1
T1
+ 6 m.


T1: bone marrow edema (BME)
1. Predominant marrow involvement near fractured end-plate
2. Normal residual marrow
3. No /discrete soft tissue, posterior arch involvement
Cuenod et al Radiology 199:541

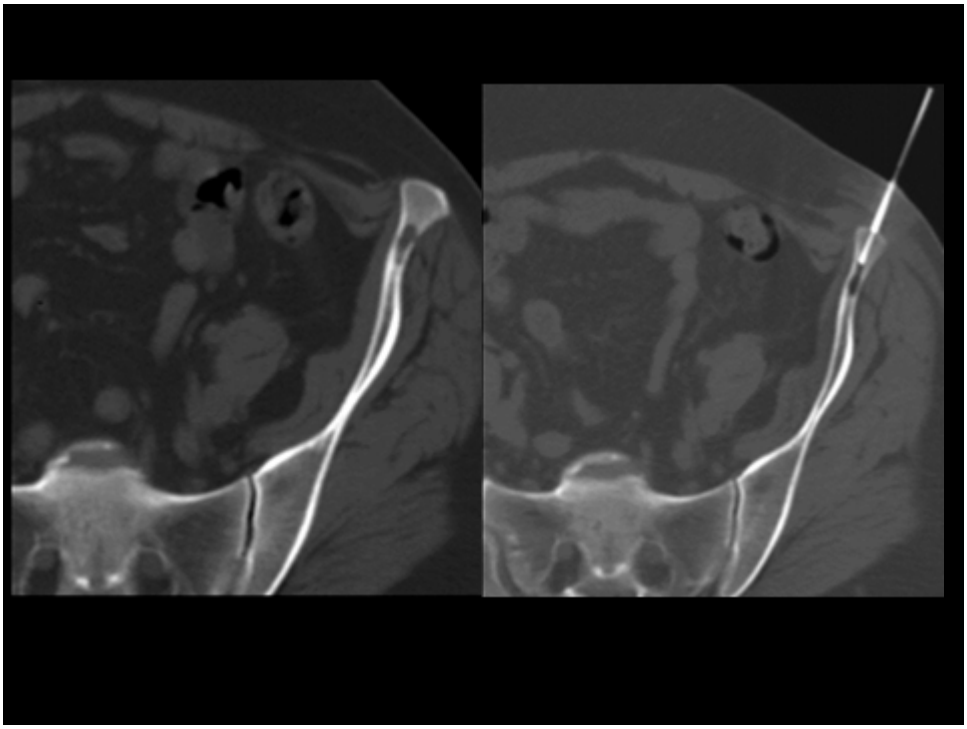

BME… what else?
Fracture line


42-year-old woman, history breast cancer, vertebral lesion to biops
T1
T2



Value of pelvis MR

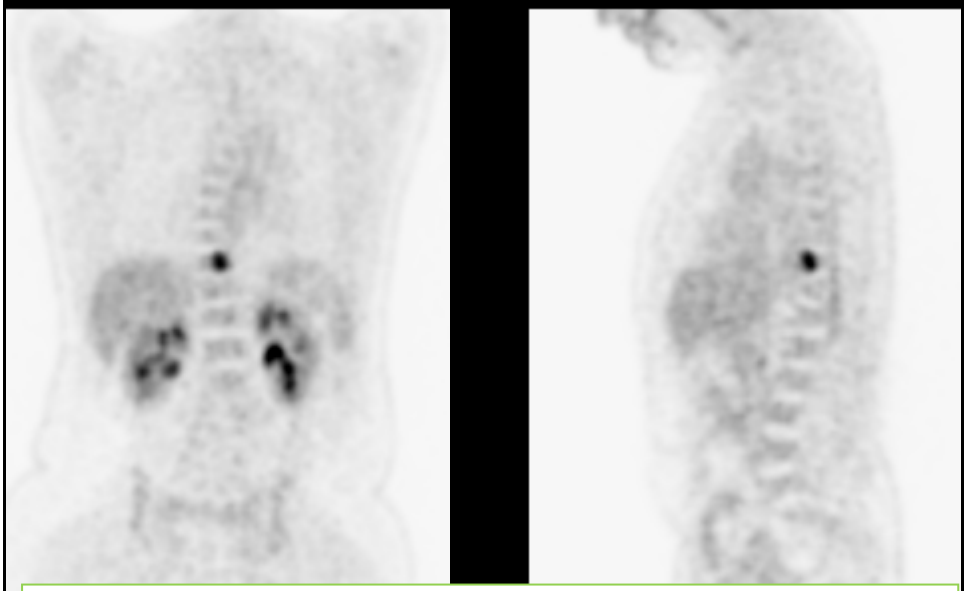
- **Large amount of red marrow (30%)**
- **Lesion with fracture risk**
- **Easy target for biopsy**



BONE METASTASES

Biopsy

48 y-old woman, colon AND breast cancer history



Unique lesion → met ? origin? receptors?