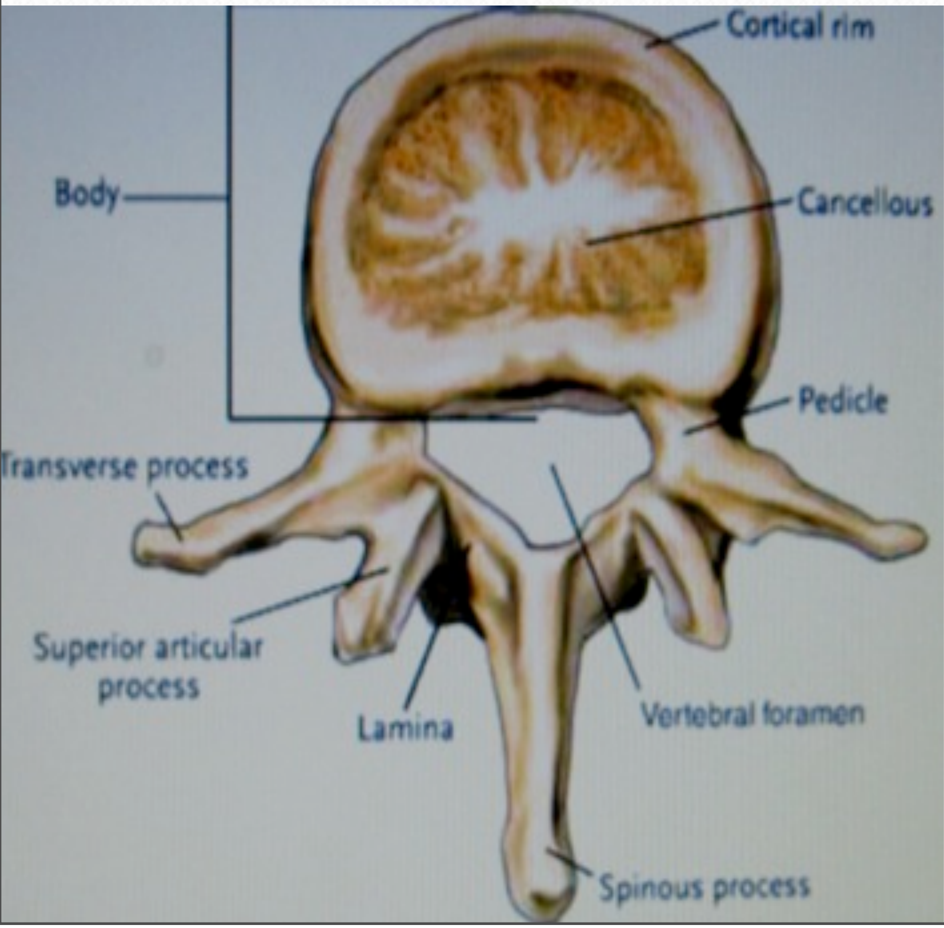
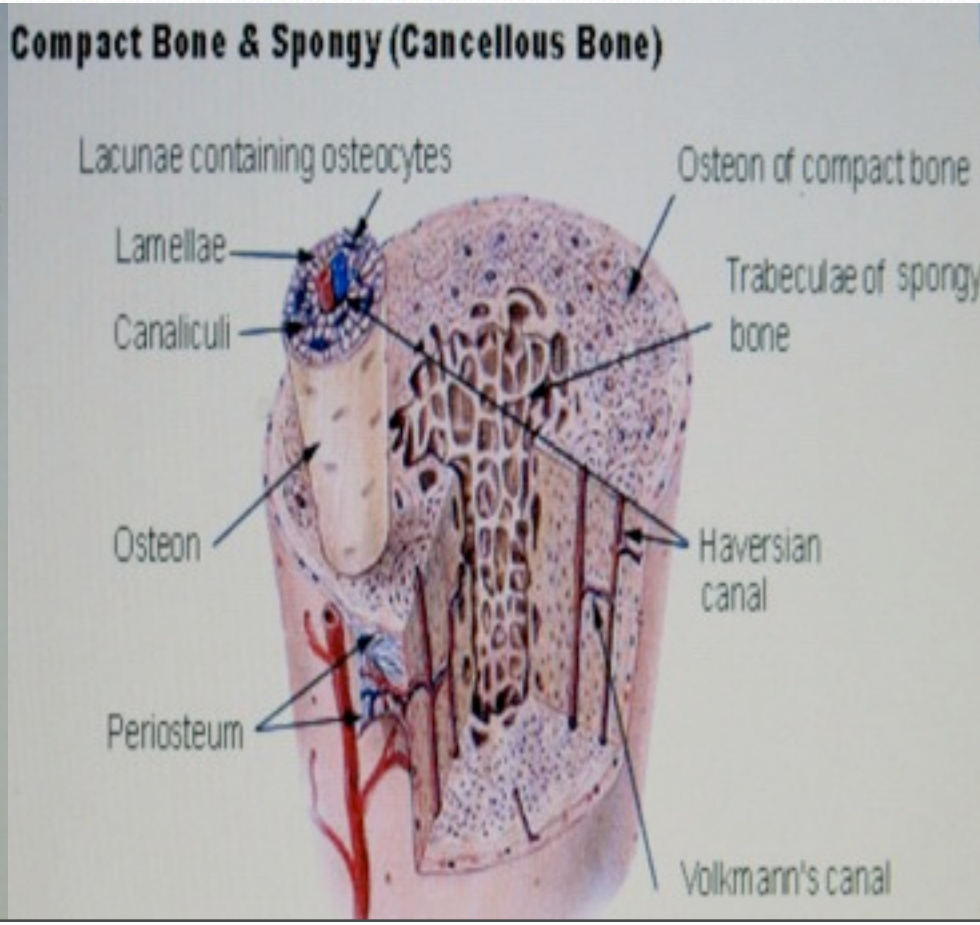
ISOTOPE BONE IMAGING

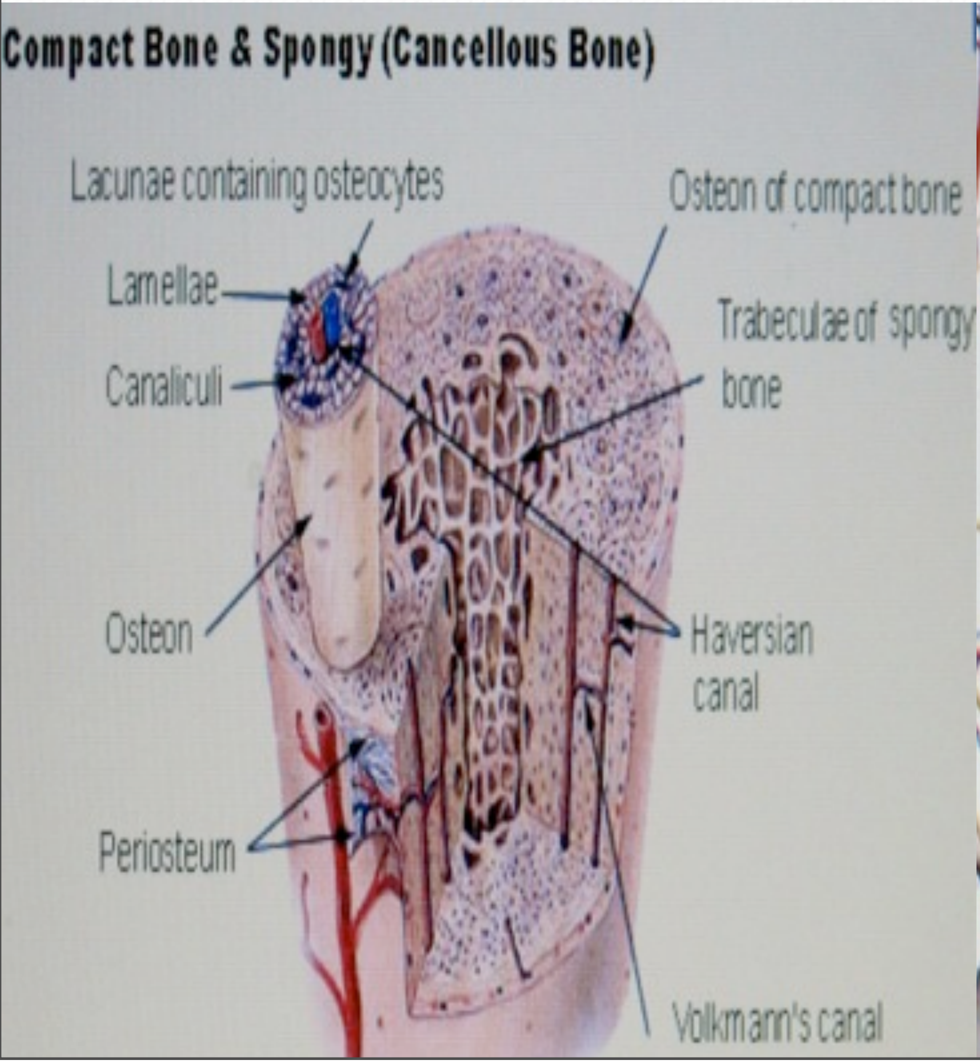
MARROW/CANCELLOUS



COMPACT/CELLULAR

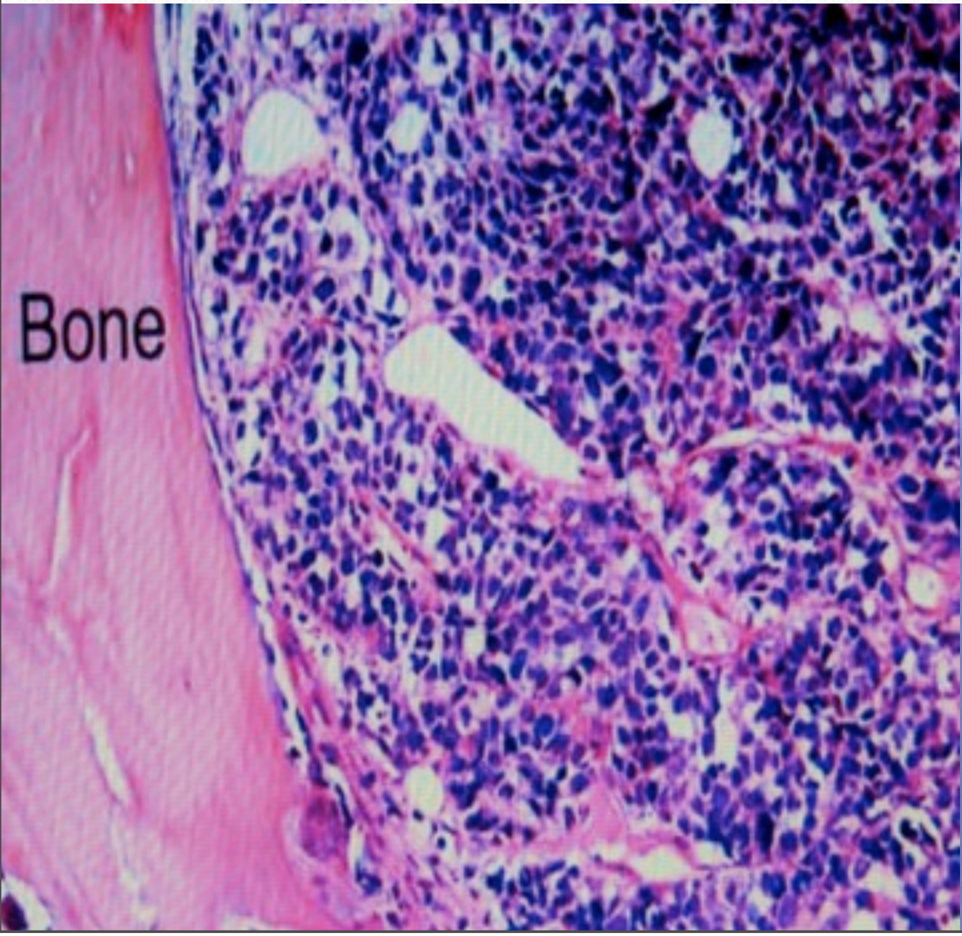


BONE BLOOD SUPPLY

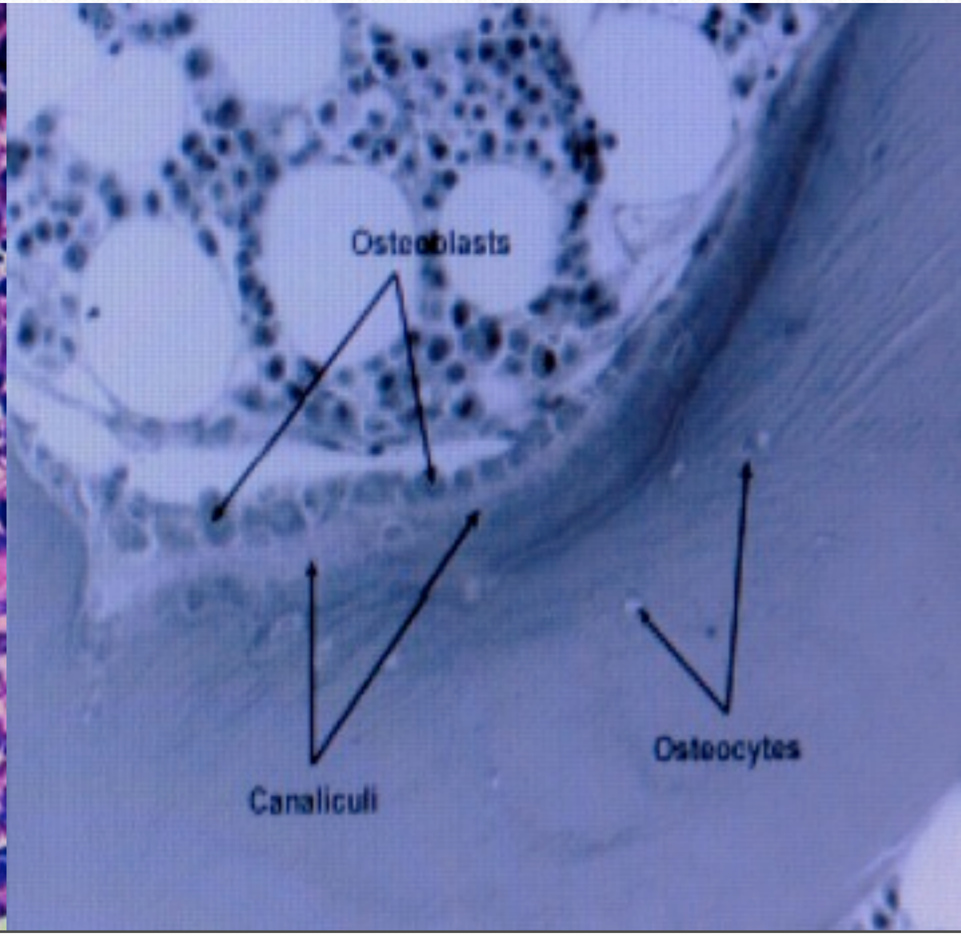


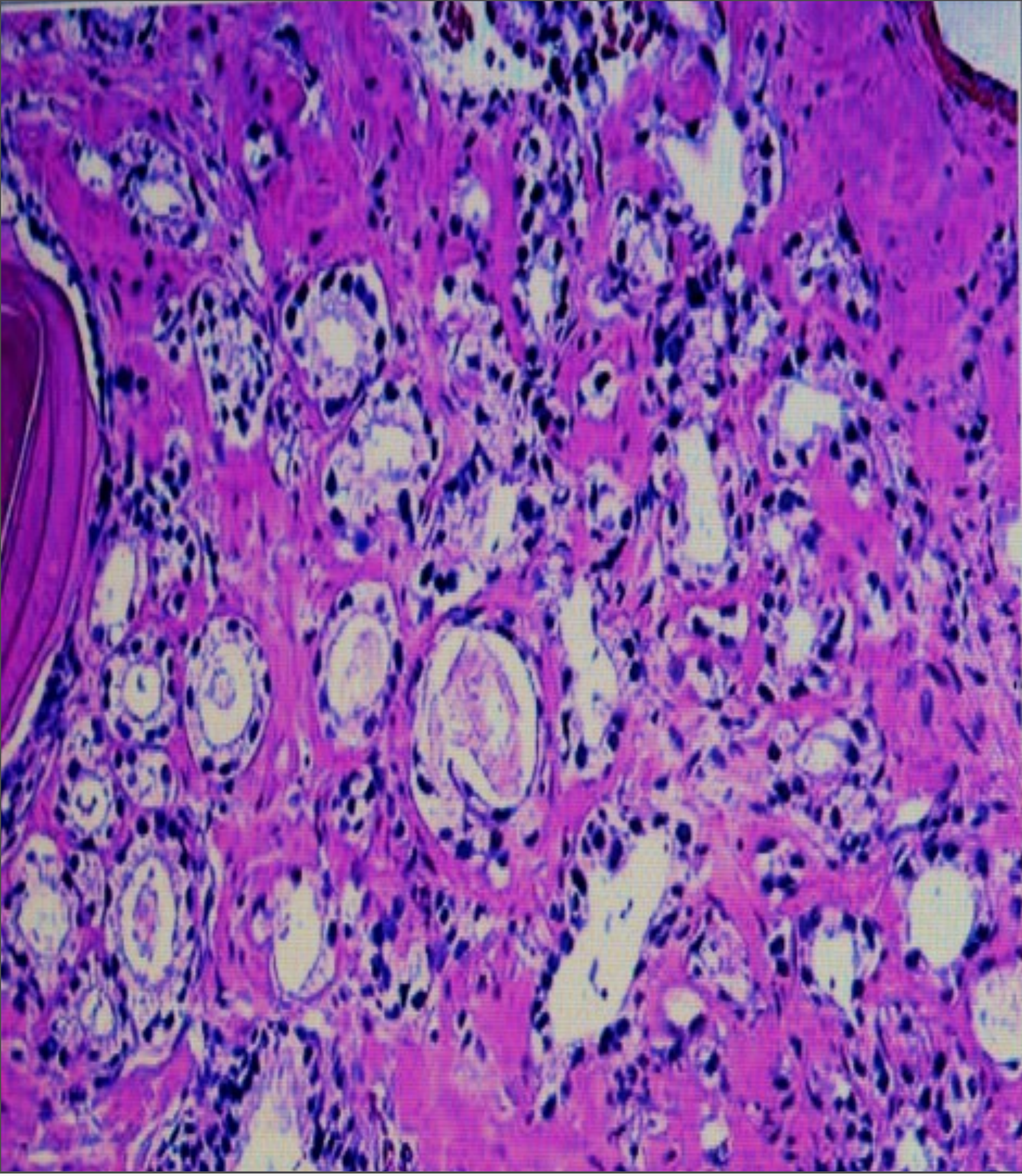
METASTATIC PATHWAYS

MARROW PERMEATION



BONE(LIGAND) ACTIVATION





Metastatic prostate carcinoma

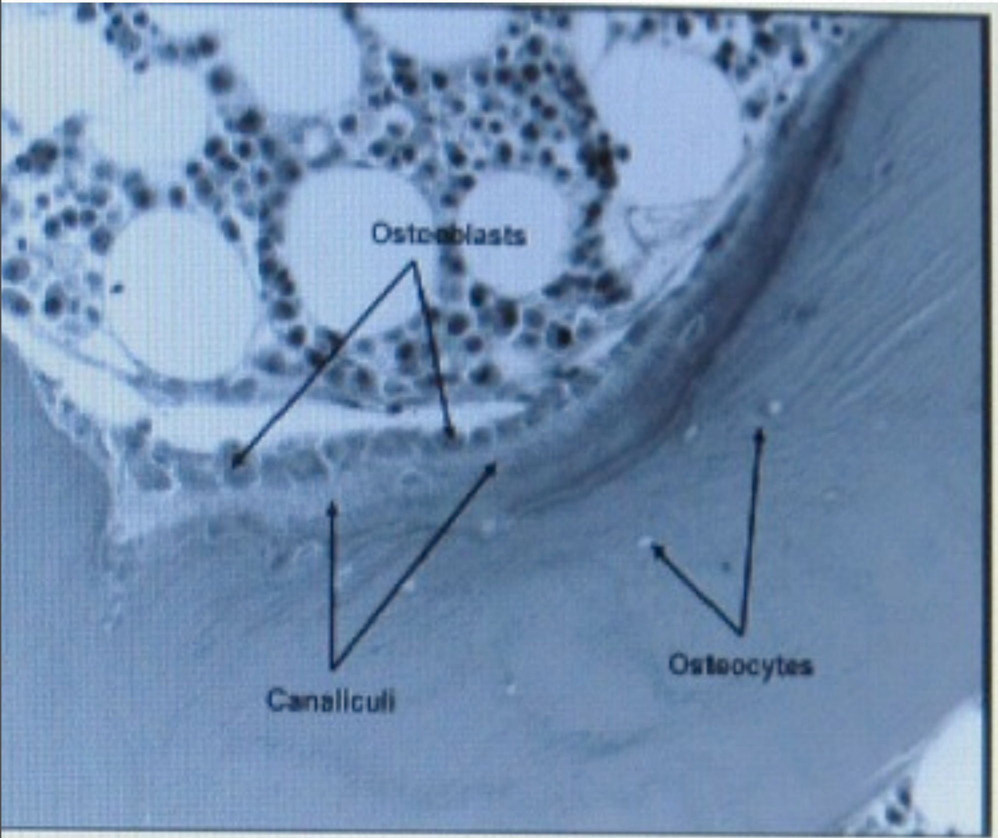
This is bone marrow replaced by tumor. A tiny fragment of bone is visible on th left of the image. There is no normal marrow present. The pink / red tissue i collagen (fibrosis). The remainder of th image consists of well differentiated glands. The tumor cells have clear cytoplasm.

Immunohistochemistry for Prostatic Specific Antigen (PSA) was strongly positive and PSA was also elevated in the patient's serum.

PSA immunohistochemistry is a reliable method for identifying the origin of metastatic prostatic carcinoma.

CELLULAR ANATOMY

OSTEOBLASTS



igure 3. Osteoblasts synthesize proteinaceous matrix, com-
osed mostly of type I collagen, to fill in resorption pits. The
roteinaceous matrix is gradually mineralized to form new
one.

OSTEOBLASTS------OSTOCYTES

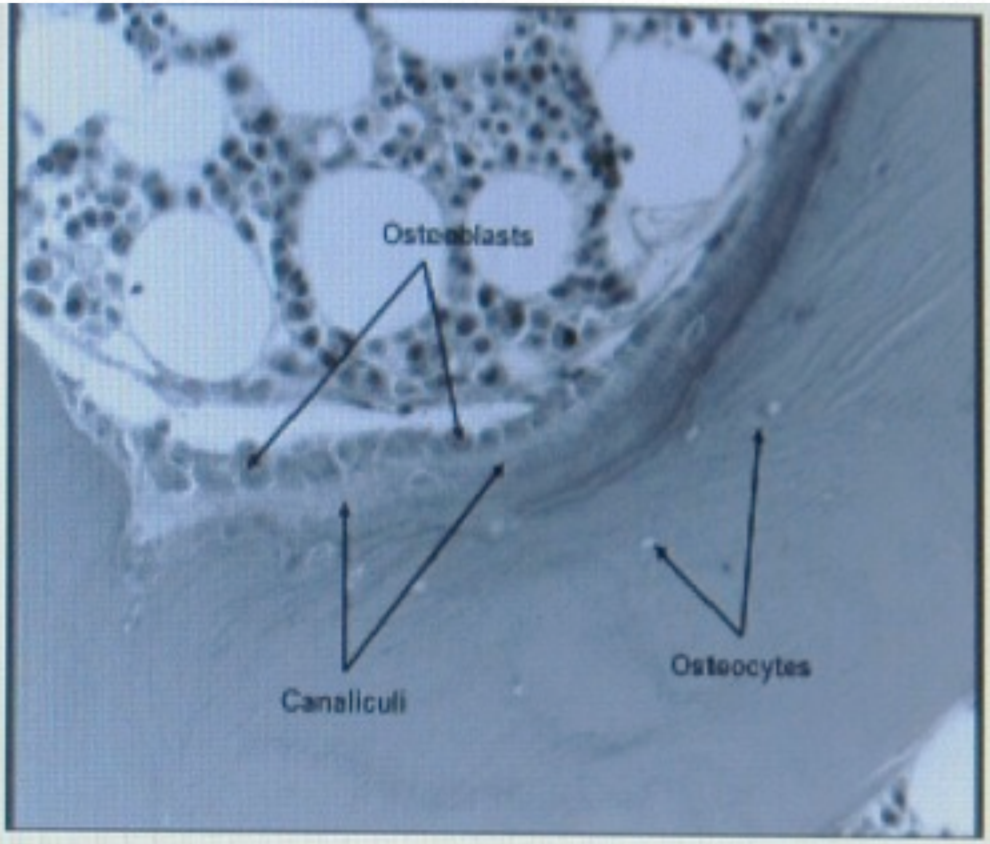


Figure 3. Osteoblasts synthesize proteinaceous matrix, composed mostly of type I collagen, to fill in resorption pits. The proteinaceous matrix is gradually mineralized to form new bone.

OSTEOCLASTS

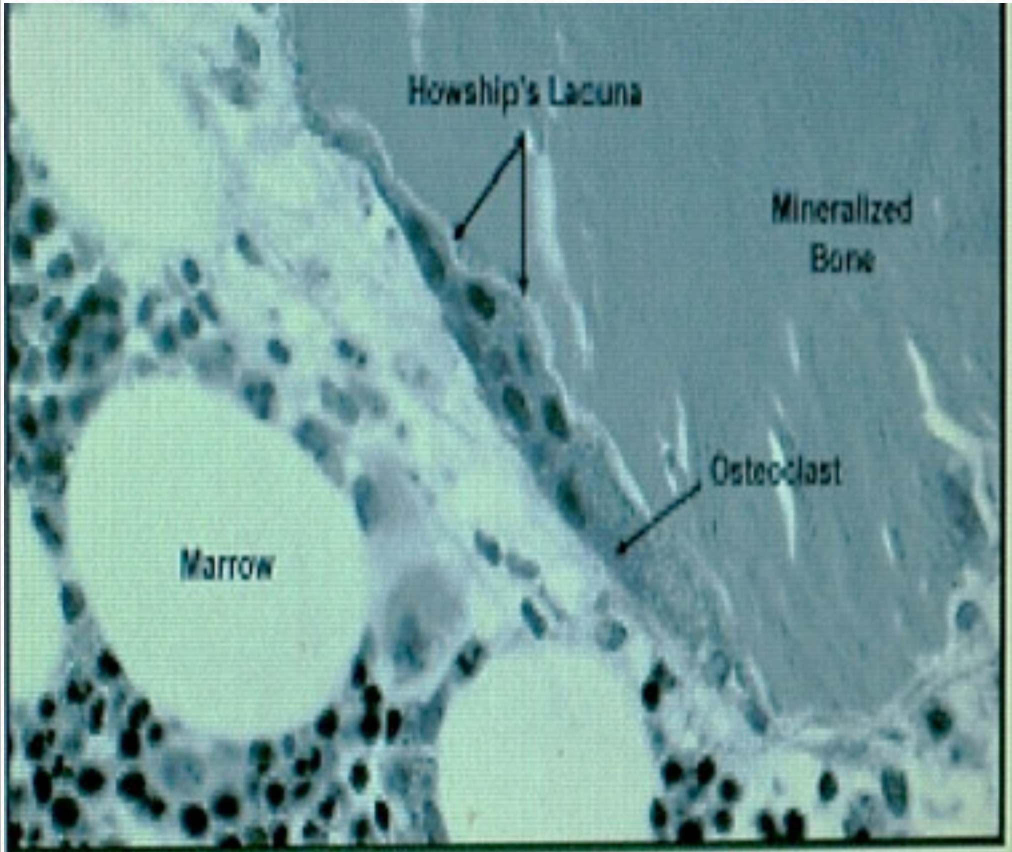
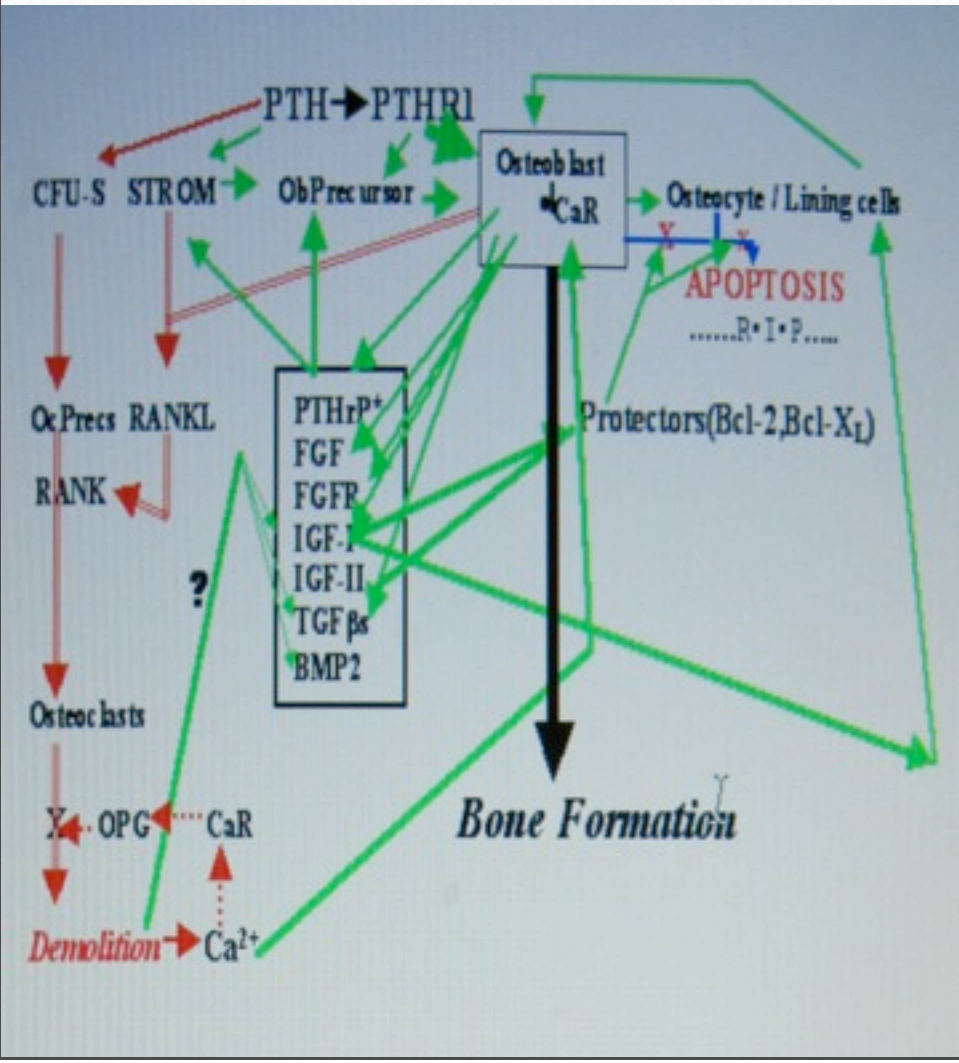


Figure 2. Multinucleated osteoclasts resorb bone to form resorption pits known as Howship's lacunae.

NORMAL BONE OSTEOGENISIS



Regulation of Osteoclastogenesis by RANKL and OPG

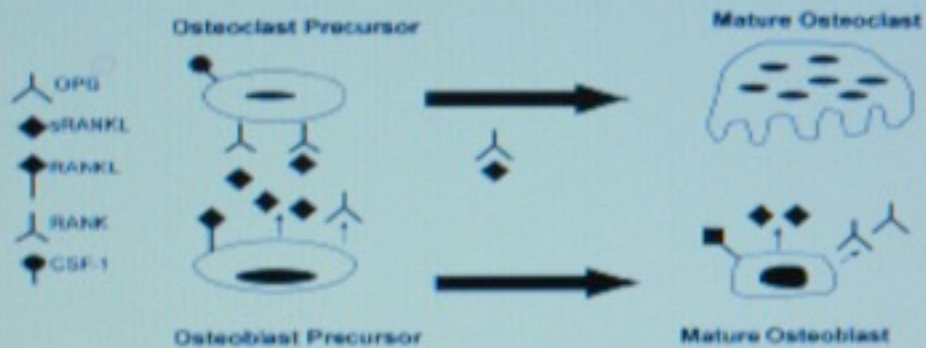


Figure 1. Regulation of osteoclastogenesis by receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG): Colony-stimulating factor 1 (CSF-1) normally stimulates osteoclast recruitment. Two forms of RANKL are produced by osteoblasts and osteoblast precursors to stimulate osteoclast recruitment and activation. The membrane-bound form directly interacts with membrane-bound RANK molecules on adjacent osteoclast precursors. The soluble form is released from osteoblasts or osteoblast precursors to diffuse through the intercellular space and interact with membrane-bound RANK molecules on nearby osteoclast precursors. OPG acts as a decoy receptor to prevent RANKL or sRANKL from interacting with RANK. The ratio between RANKL and OPG produced by osteoblasts and osteoblast precursors controls RANKL-stimulated osteoclastogenesis.

Osteoprotegerin-Prod.by Osteo-Blasts Neutralizes Osteo- Clasts

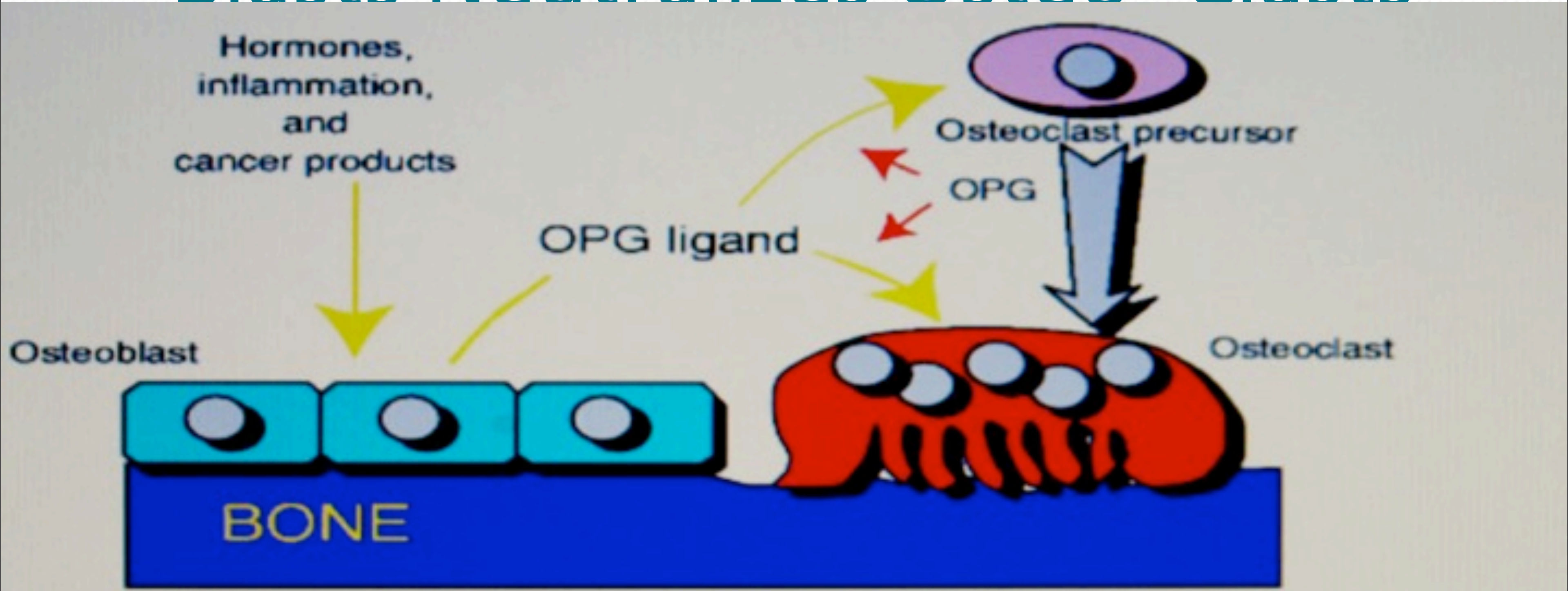


Figure 3.

Role of OPG in the control of bone resorption and osteoclast production and activity. *OPG acts to oppose the stimulation of osteoclast differentiation and activation by OPG ligand.*

OSTEOGENIC

- BREAST AND MULT. MYELOMA-OSTEOLYTIC(+marrow)
- PROSTATE-BOTH LYTIC. AND BLASTIC(marrow + bone)
  - INC. BLASTIC +CLASTIC=BRITTLE BONE
- PREFERENTIAL PROSTATE BONE METS (tumor by products)
  - TGF-TRANSFORMING GROWTH FACTOR+EPIDERMAL(EGF)
    - PROMOTES TUMOR ADHESION TO BONE/GROWTH OF METS.
    - INC. ANDROGEN-INDEPENDENT CELLULAR GROWTH
    - INC.CANCER CELLS=EGF PROMOTES BONE METS
    - OSTEOCLAST MATURATION=LYTIC METS.
  - BONE MORPHOGENIC PROTEINS
    - OSTEOGENIC FACTOR(prostate cancer)-BLASTIC METS.
- OSTEOGENIC PHYSIOLOGY OF NORMAL BONE(ligands , PTH)
  - RANKL-INC.CLASTS--OSTEOPROTEGERIN-HALTS RANKL
  - PTH INHIBITS OPG (RANKL VS OPG=+/-BONE FORMATION)

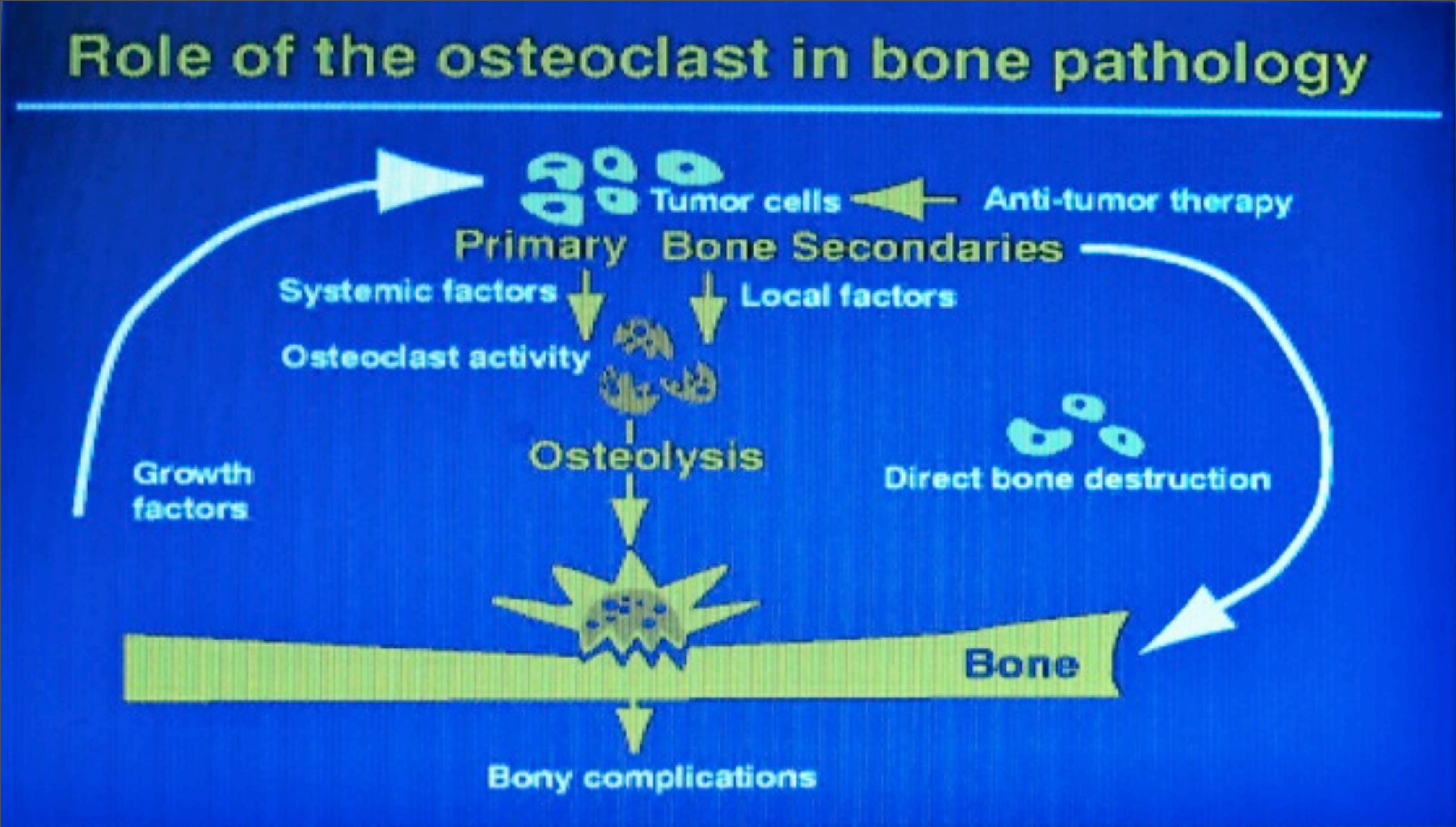
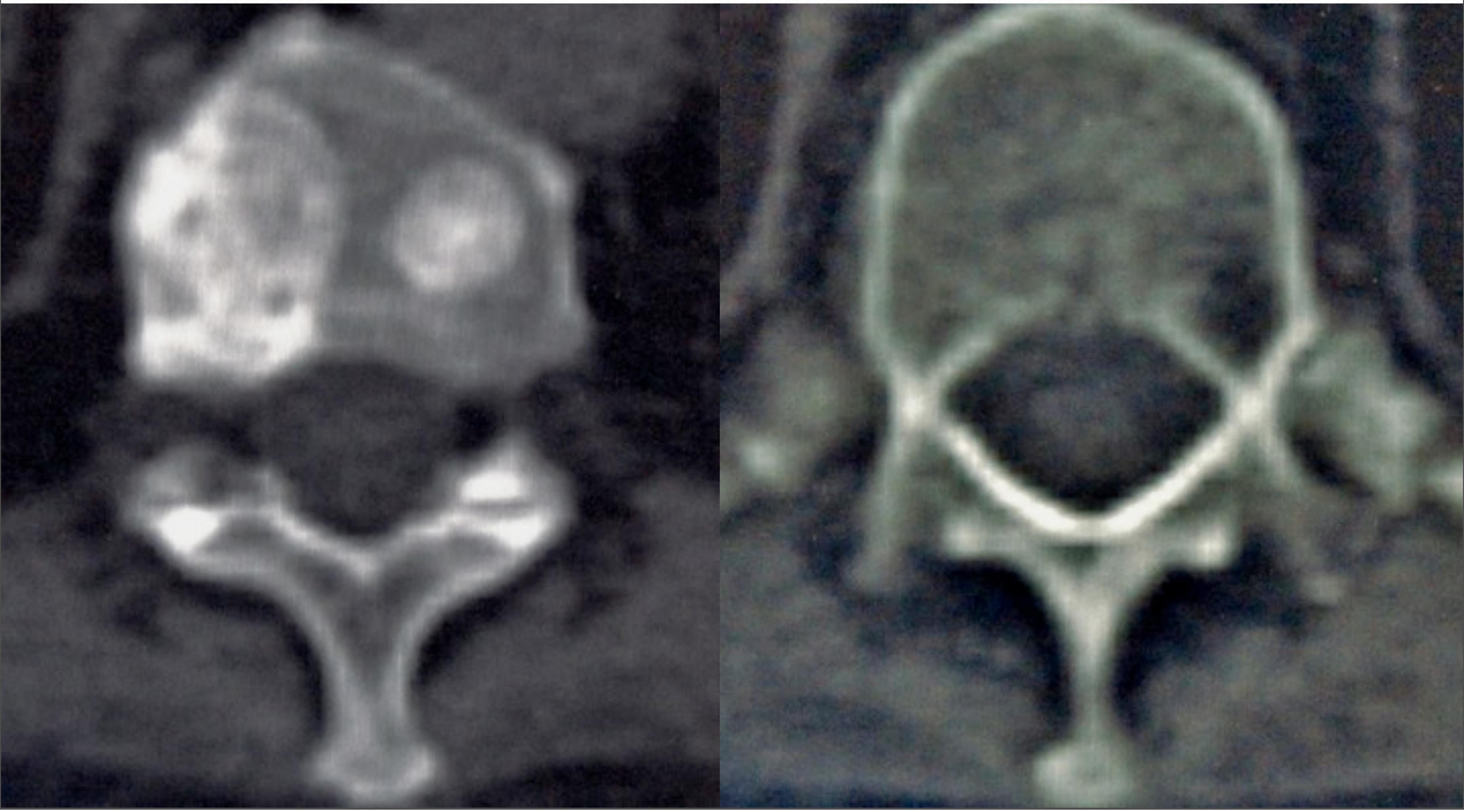


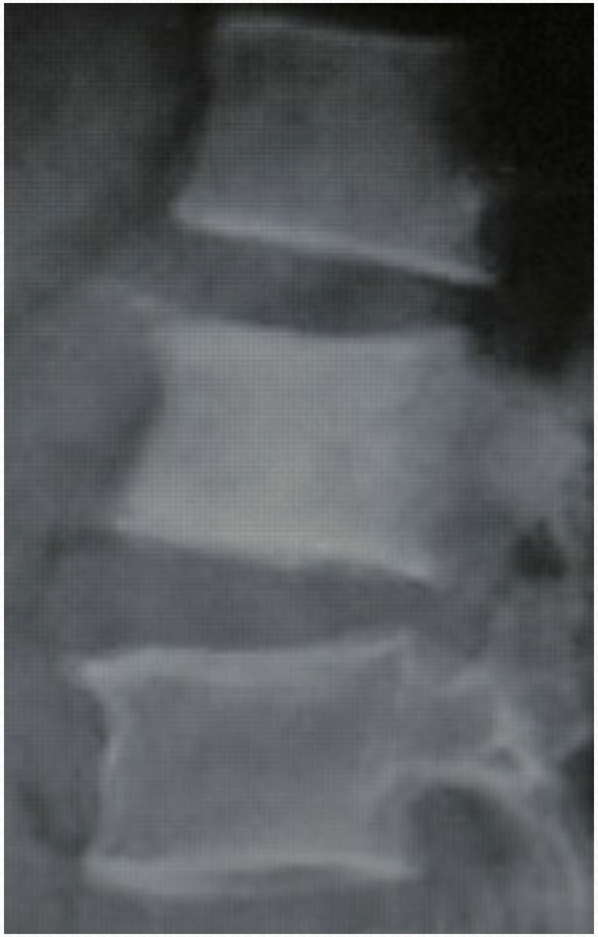
Figure 1.

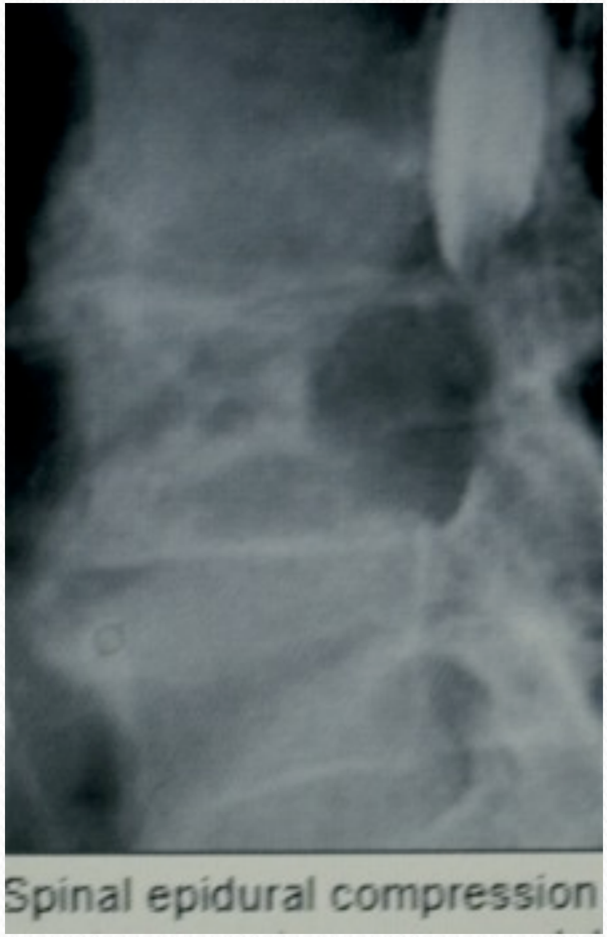
Interaction of tumor and bone cells within the bone microenvironment. *Osteoclastic bone resorption is the principle mechanism. Direct bone resorption is thought to be of minor importance. Release of bone-derived cytokines and growth factors may stimulate tumor cell proliferation.*

METASTASIS-BLASTIC/CLASTIC

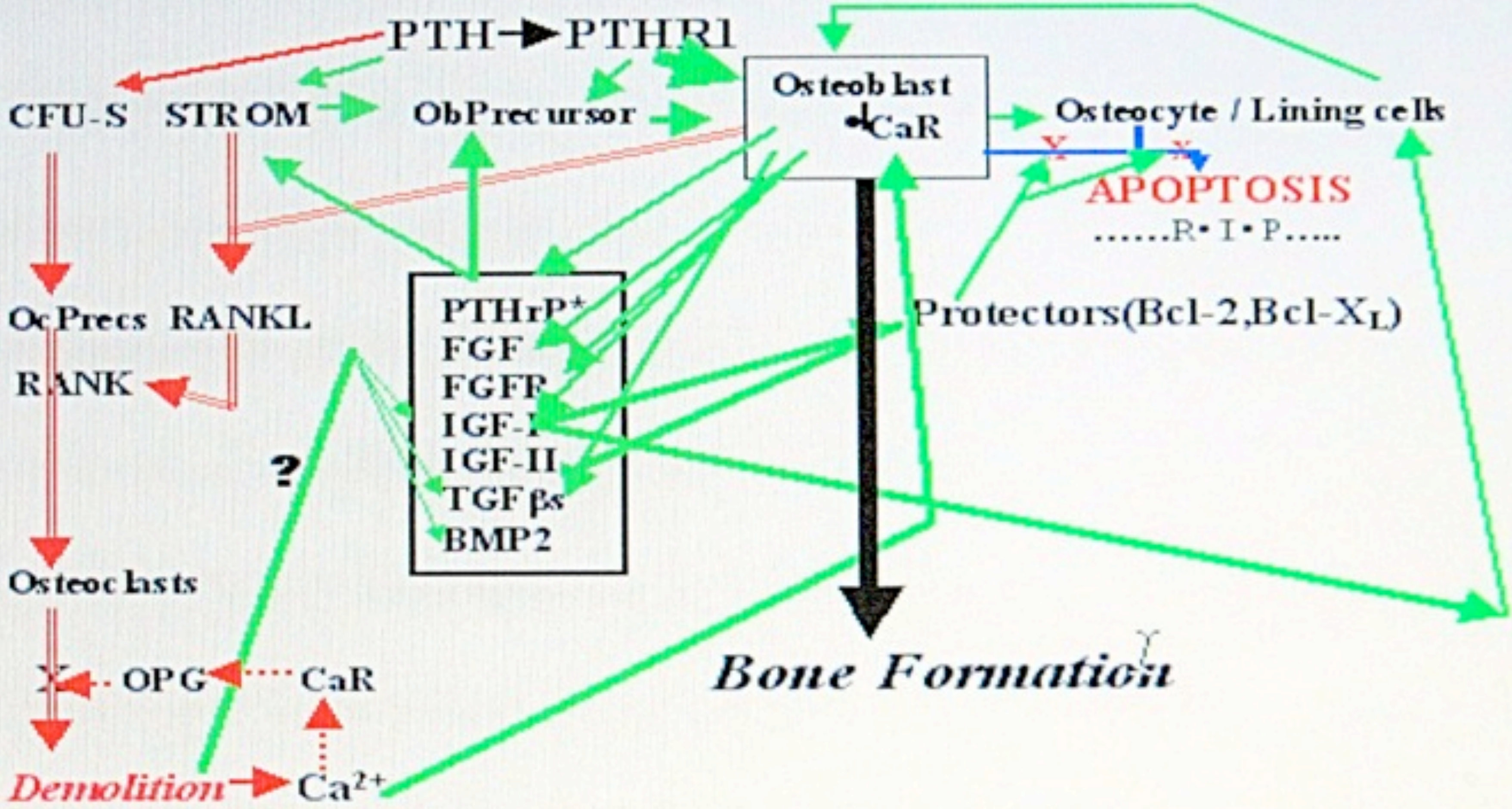


COMBINATION(BLASTIC/CLASTIC)

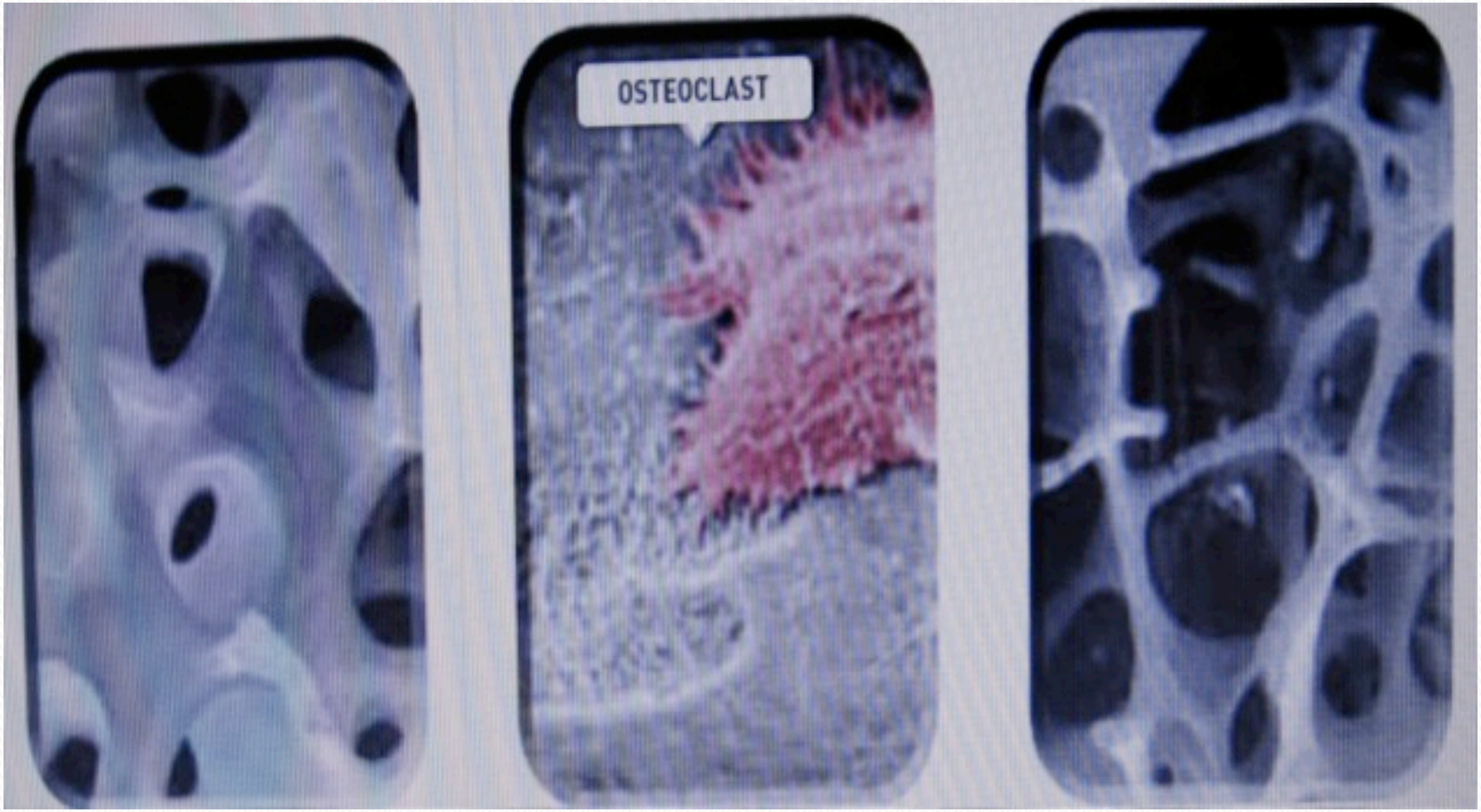




BONE IS NORMALY REPLACED



OESTEOCLASTIC RESORPTION



CANCER--% WITH BONE METS

The most prevalent cancers in the US are commonly associated with a high incidence of metastatic bone disease:

- 45-85% of breast cancer patients
- 33-85% of prostate cancer patients
- 33-50% of lung cancer patients
- 33-40% of renal cell carcinoma patients
- 28-60% of follicular thyroid cancer patients

BONE IMGING EQUIPMENT

Rectilinear Scanners (1960's to 1970's)

- ^{18}F Sodium Fluoride, Ga-69, Sr-85

Anger Gamma Camera - planar (1970's – present)

- Tc-99m MDP, Tc-99m HDP or Tc-99m pyrophosphate

SPECT (one, two or three head – (1980's- present)

- circular and non-circular acquisitions

PET (full ring, partial ring, coincidence – (1990's to present)

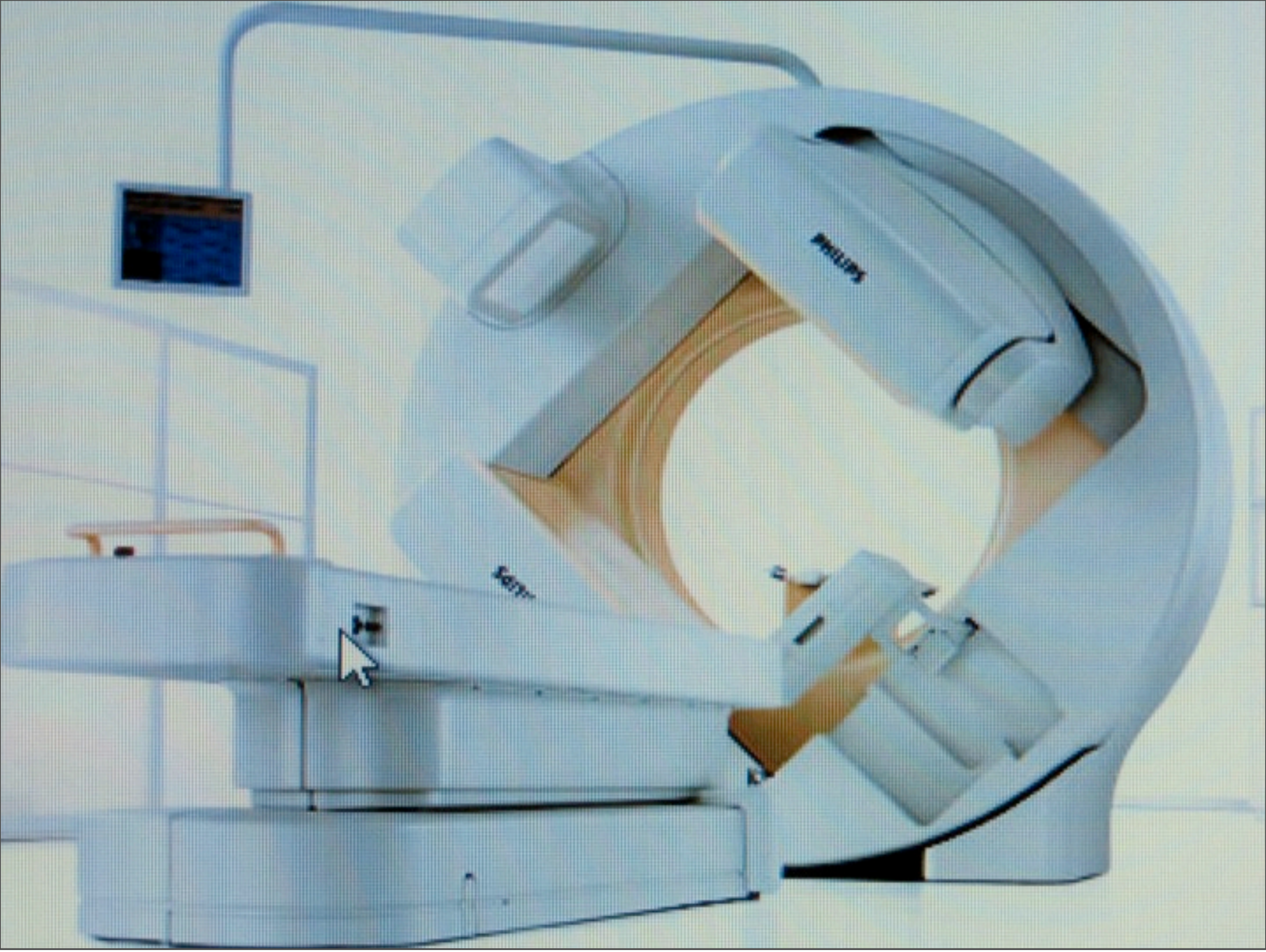
- ^{18}F Sodium Fluoride

Hybrid Imaging – PETCT & SPECT CT (2000's to present)

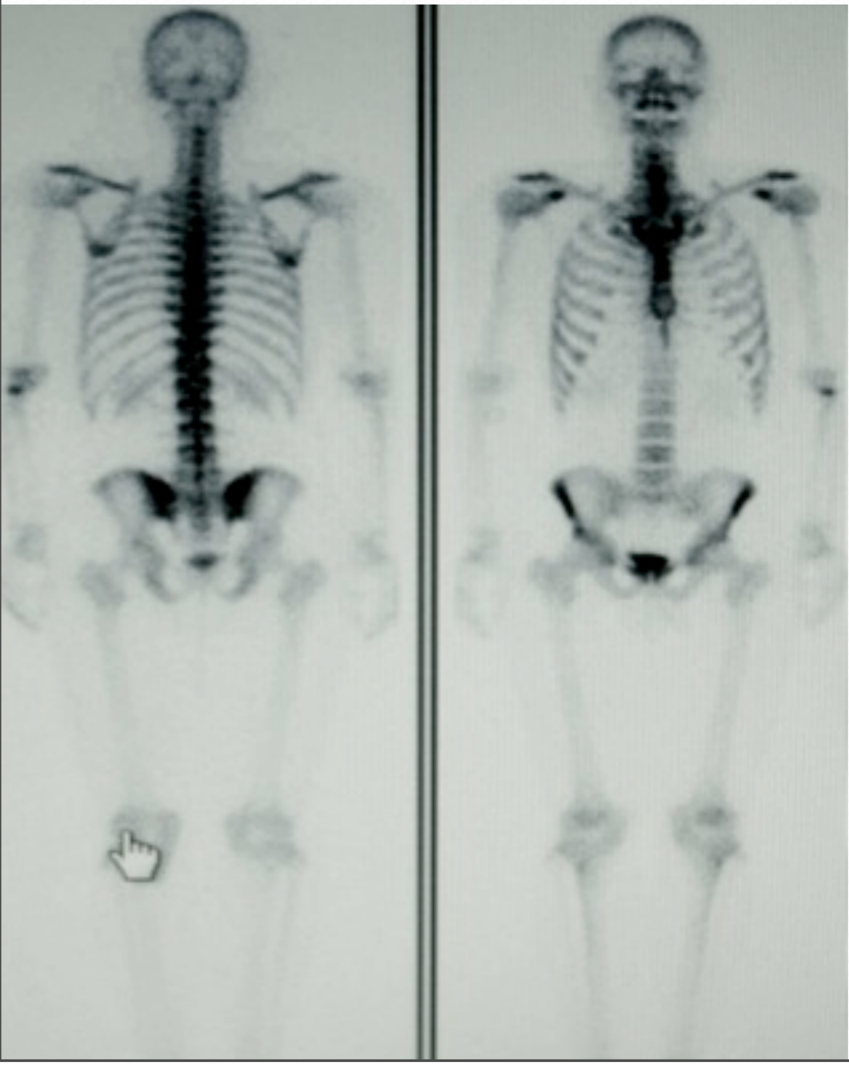
AGENTS TAG TO BONE (CHEMOADSORPTION)

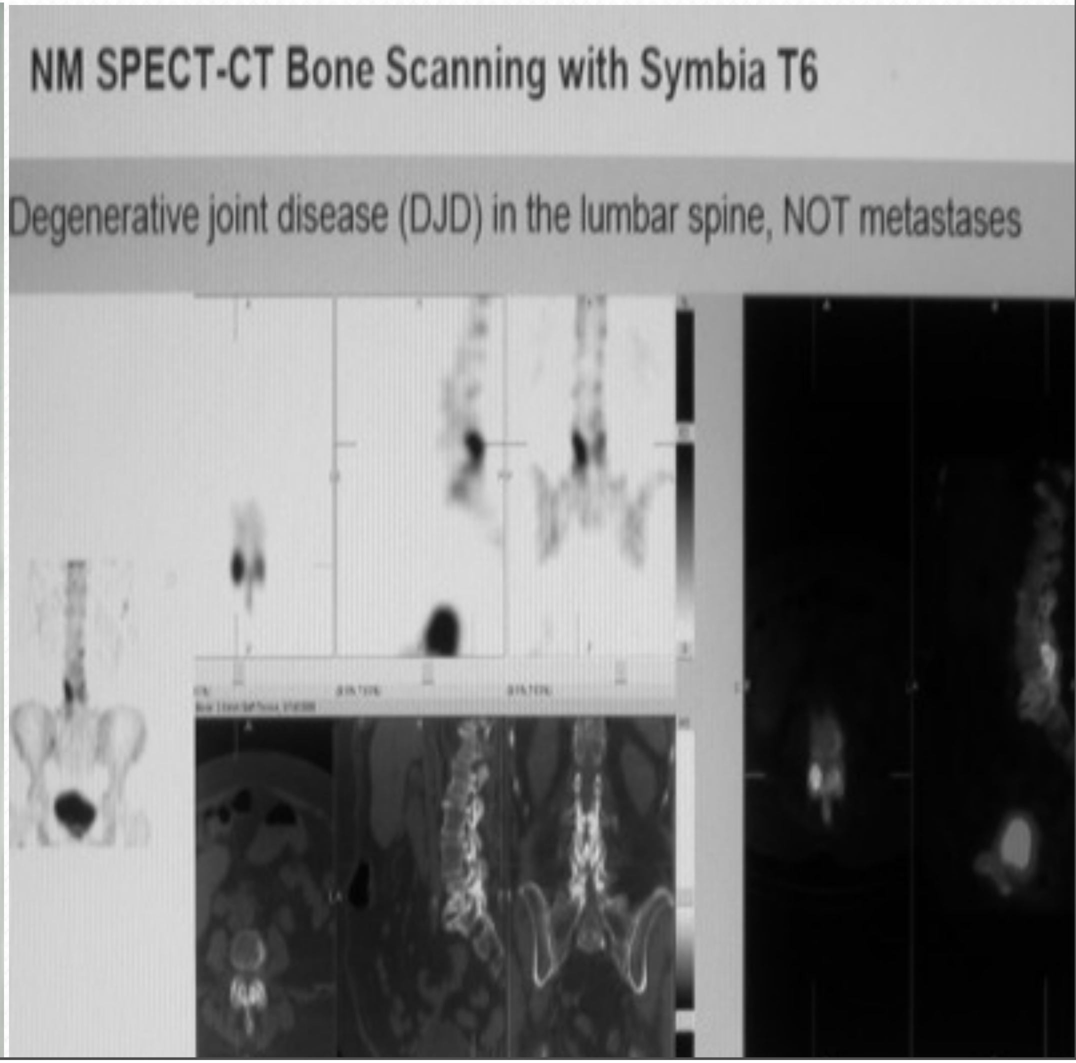
Bone Imaging Agents

	keV	$T_{1/2}$	Imaging Delay	Year
Sr-85	514	65 d	3-7 d	1961
Sr-87m	388	2.8 h	(1-3 h)	1969
F-18 sodium fluoride	(511)	1.8 h	0.5 – 1 h	1962
Tc-99m phosphates	140	6 h	4-6 h	1971


PHILIPS

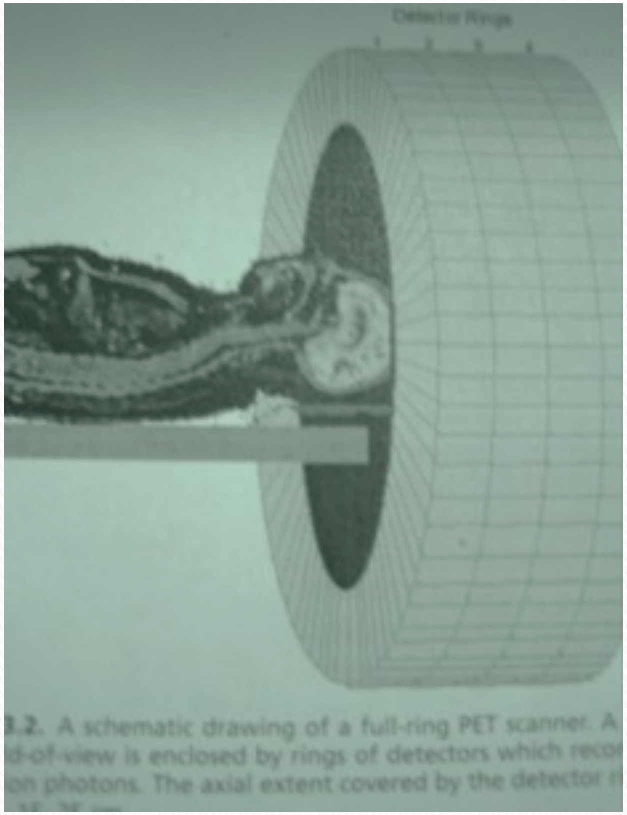
PLANAR IMAGING + SPECTCT



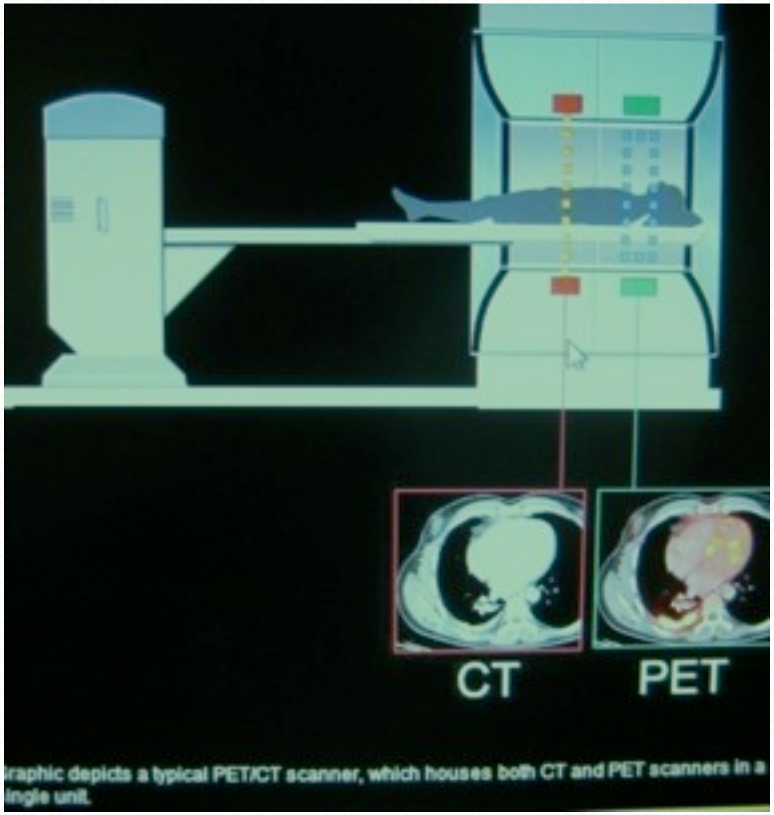


PET/CT-ANATOMY +”FUSION”

PET ONLY—1990,S



PET/CT----2004-to present

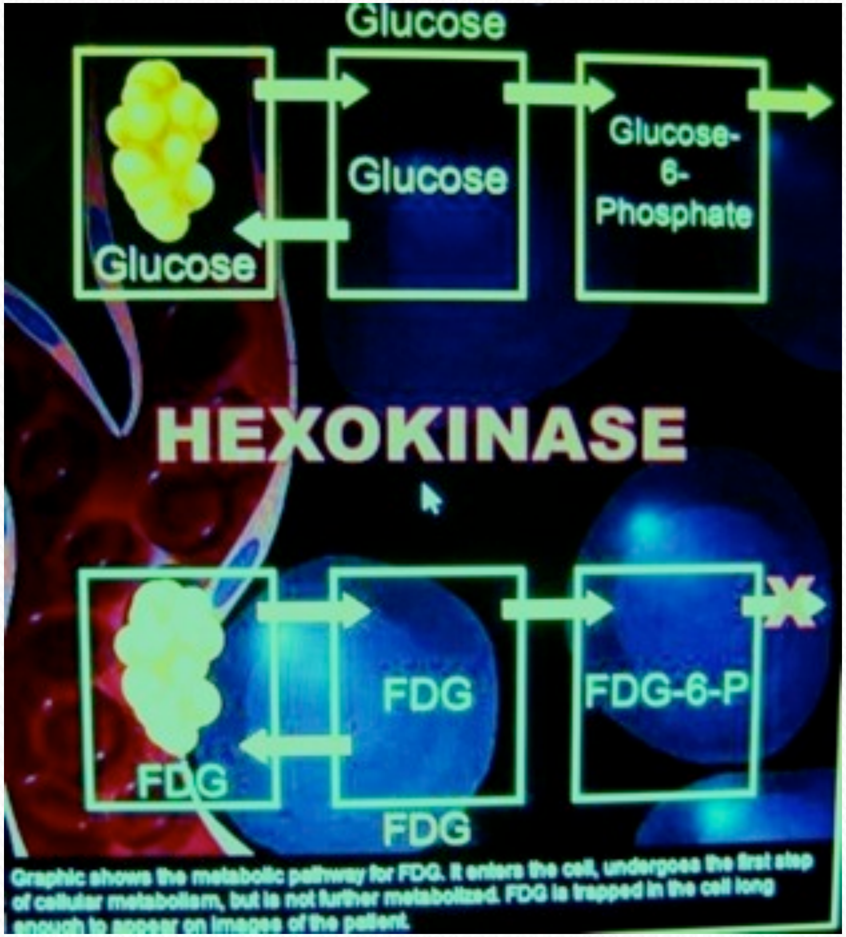


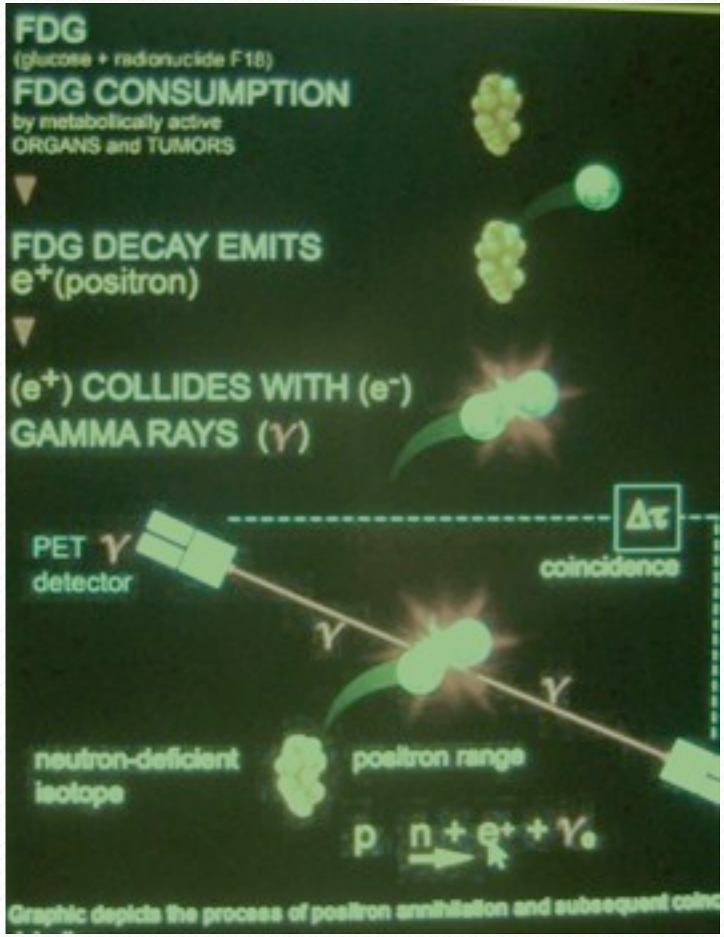
PET/CT PHYSIOLOGIC IMAGING

- TUMOR GLYCOLYSIS(F18 GLUCOSE=FDG)
  - GLUT -1-TRANS MEMBRANE TRANSPORTER
  - IF OVER EXPRESSED=FDG DEPOSITION
  - HEXOKINASE-F18-6-PHOSPHATE=TRAPPED
  - NOT ALL TUMORS ARE FDG AVID

- PET/CT -CURRENT AND FUTURE ISOTOPES
  - OSTEOGENIC UPTAKE-F18 (OSTEOGENIC ACTVATION)
  - COMBINED (COMBO) STUDIES-FDG+F18
  - NEW ISOTOPES-CHOLINE,ACETATE,AMYLOID,ETC.

F18 GLUCOSE(FDG) IMAGING

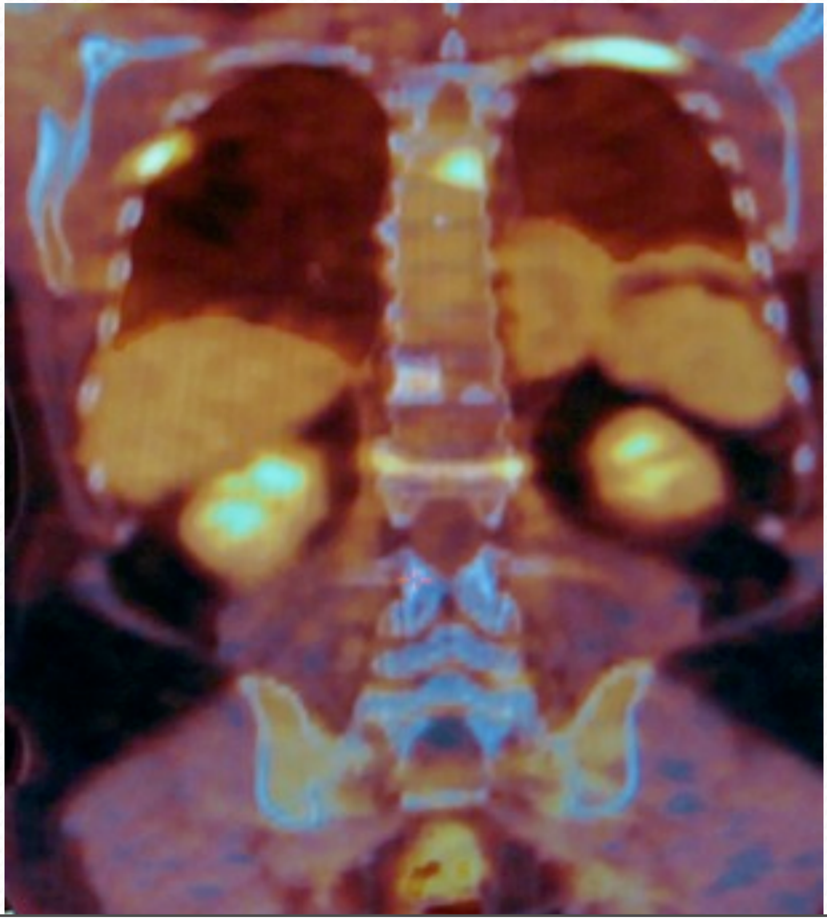




FDG MARROW IMAGING

MARROW/HEMOPOESIS

FDG++ MARROW METS

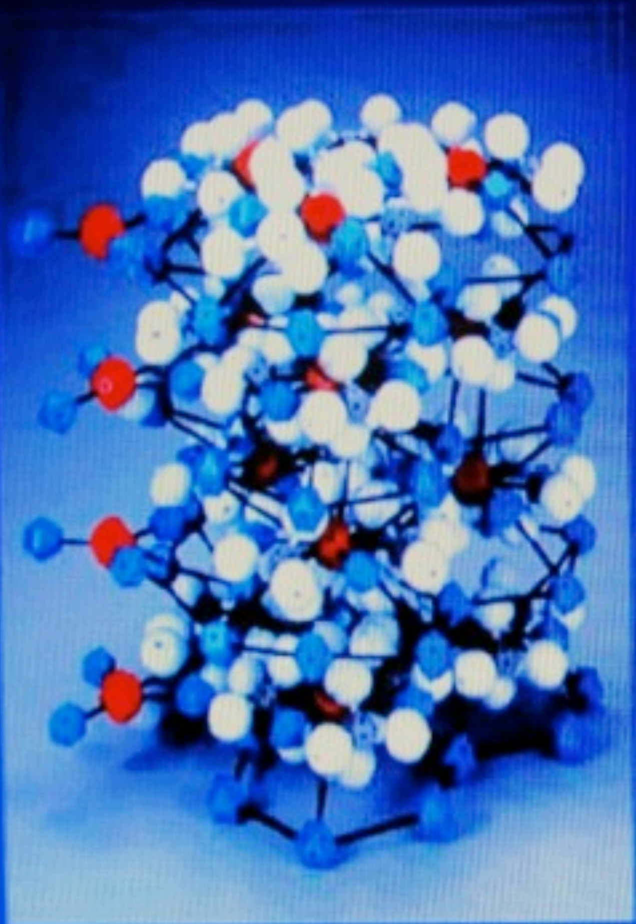


F18 PET/CT-BONE IMAGING

Na F-18 fluoride is FDA approved

"Sodium fluoride F18 injection is indicated for PET as a bone imaging agent to define areas of osteogenic activity"

Chemiadsorption



Hydroxyapatite Ca10(PO4)6(OH)2

⇌ F—Na

Hydroxyfluorapatite Ca10(PO4)6(OH)F

⇌ F—Na

Fluorapatite Ca10(PO4)6F2

THE SNM PRACTICE GUIDELINE FOR **Sodium 18F-Fluoride PET/CT Bone Scans**

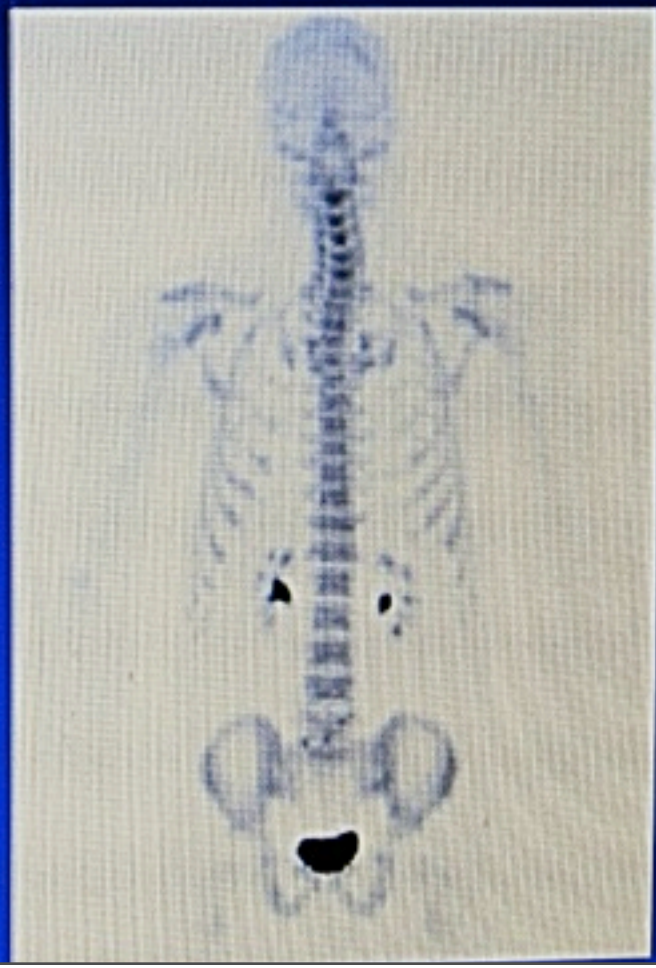
Version 1.0 June 4, 2010

- Hydration
- Dose

  Adult: 5 - 10 mCi

  Ped: 1 - 5 mCi

  (.07 mCi/kg)

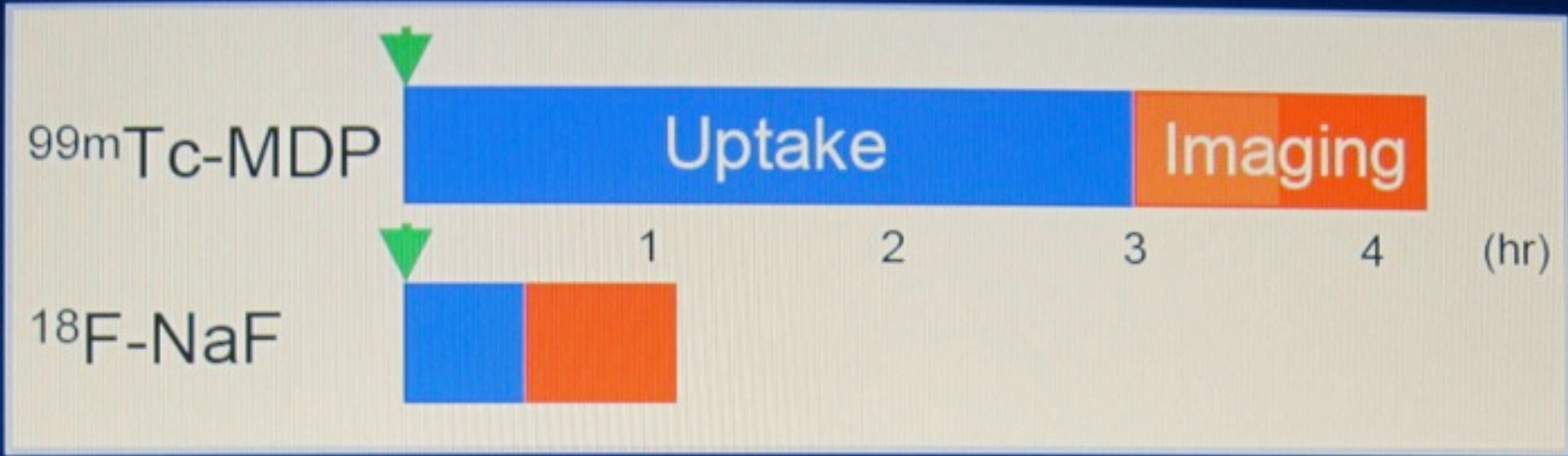


Tc99m MDP vs F-18 Fluoride

	MDP	NaF
RBC uptake	negligible	30 - 40%
Protein binding	25 – 70%	negligible
First pass extract.	40 – 60%	70 – 100%
Renal excretion	GFR	GFR – tub reabsp

Sodium Fluoride-18 PET/CT

- Like MDP, distribution dependent upon:
  - Regional blood flow
  - Bone turnover
- Uptake may be 2x higher than MDP
- Negligible plasma protein binding
- Rapid first pass clearance from capillaries to bone ECF
- Chemisorbtion onto hydroxyapatite at remodeling sites



- Imaging Workflow with ^{18}F-NaF
  - faster turnaround than ^{99m}Tc-MDP
  - facilitates same day follow-up
  - requires PET scanner availability
- Image Acquisition with ^{18}F-NaF
  - less patient motion with faster PET scan
  - no motion correction with PET

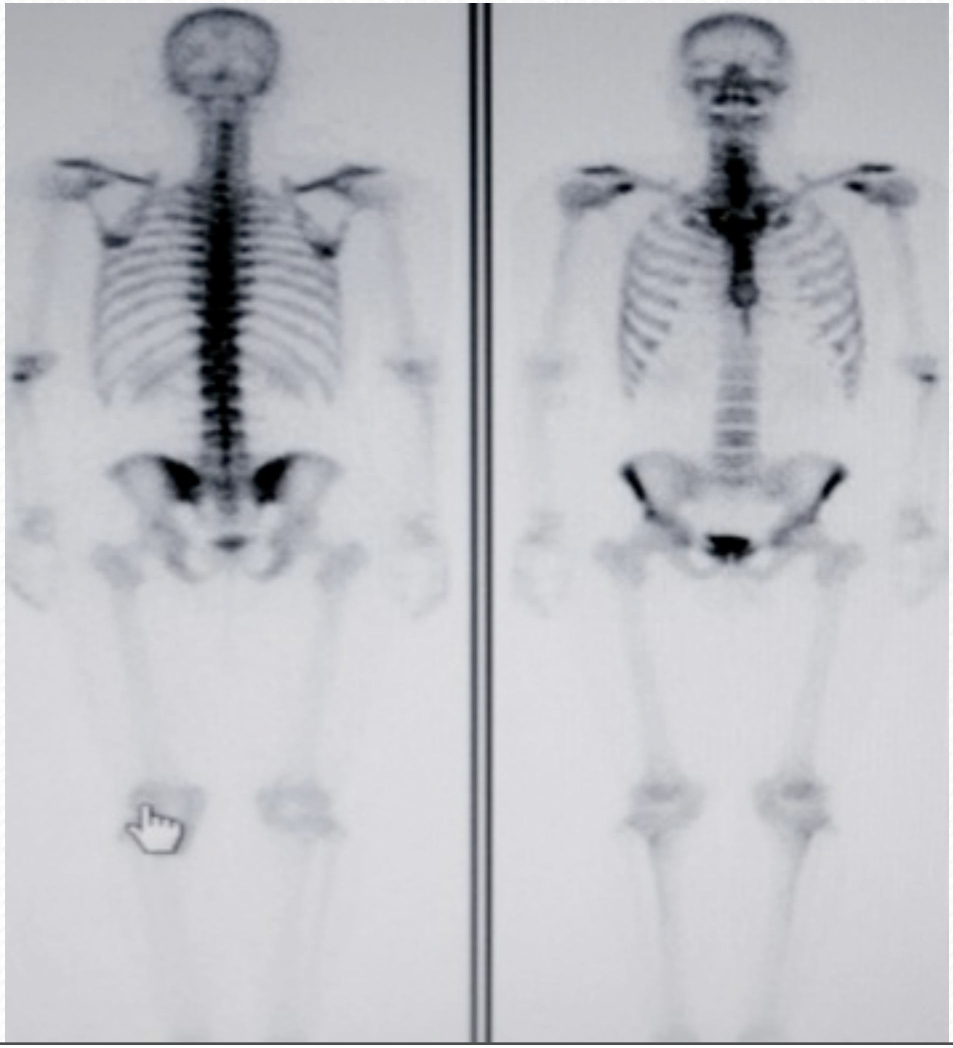
^{18}F-NaF Skeletal PET: Dosimetry compared to ^{99m}Tc-MDP

70 kg Adult	^{99m}Tc-MDP	^{18}F-NaF
Administered Dose (mCi) (MBq)	14 518	4 148
Effective Dose (mSv)	3.0	4.0
Bladder Wall (mGy)	24.9	32.6
Bone surfaces (mGy)	32.6	5.9
Red Marrow (mGy)	4.8	5.9

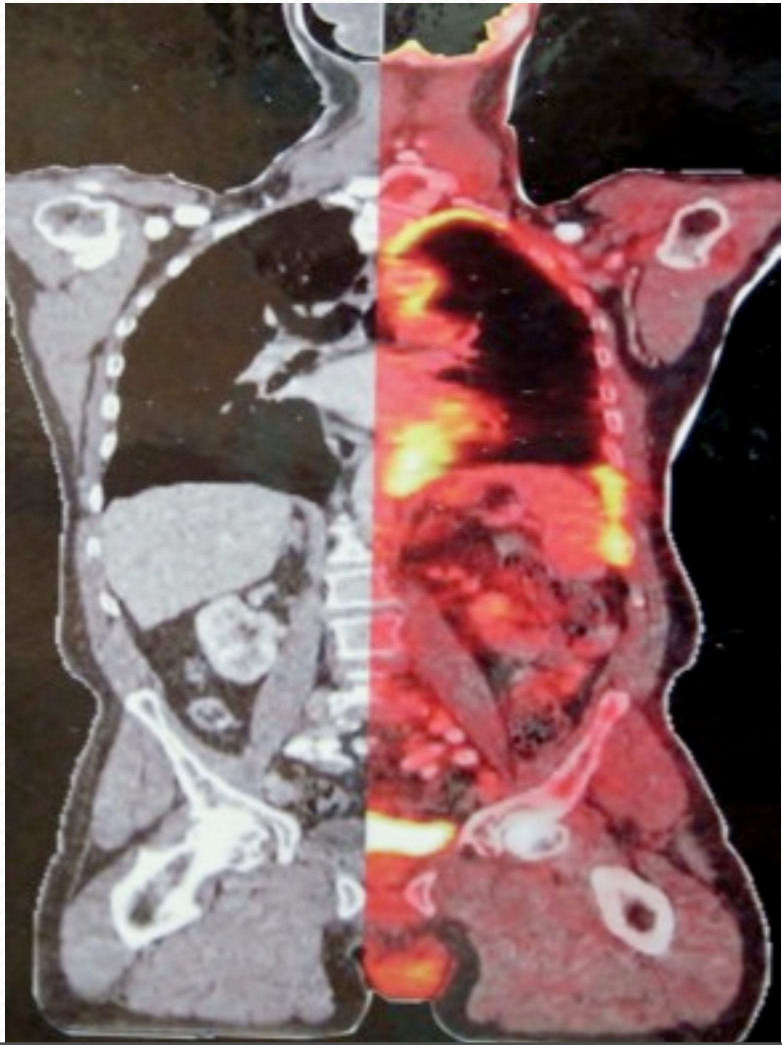
PROSTATE CANCER-STAGING

Variant 8: Prostate nodule on physical examination proven to be a poorly differentiated carcinoma or PSA ≥20 mg/mL. Patient asymptomatic.

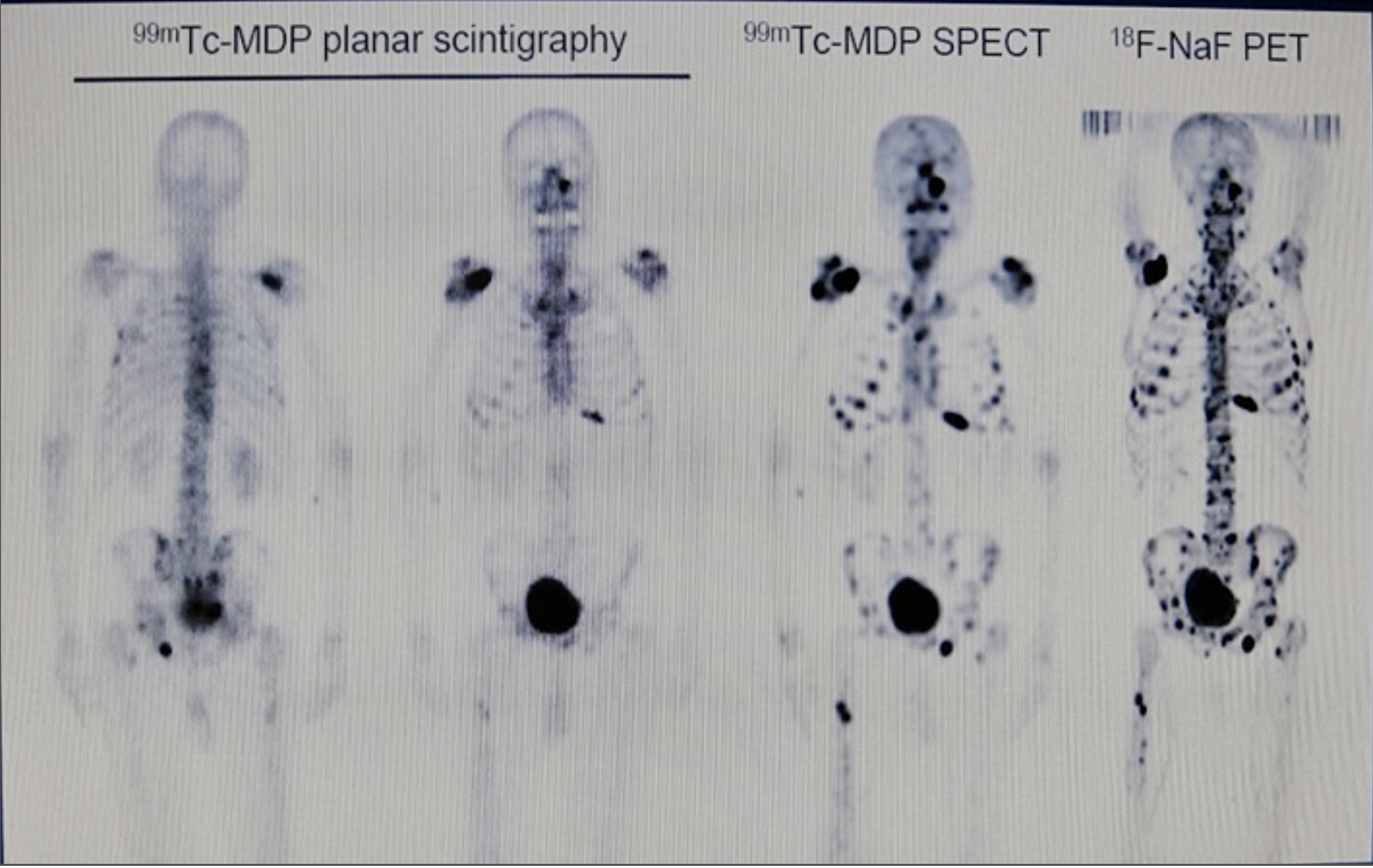
Radiologic Procedure	Rating	Comments	RRL*
Tc-99m bone scan whole body	9		Med
CT area of interest without contrast	1		NS
X-ray radiographic survey whole body	1		Med
MRI area of interest without contrast	1		None
FDG-PET whole body	1		High
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level



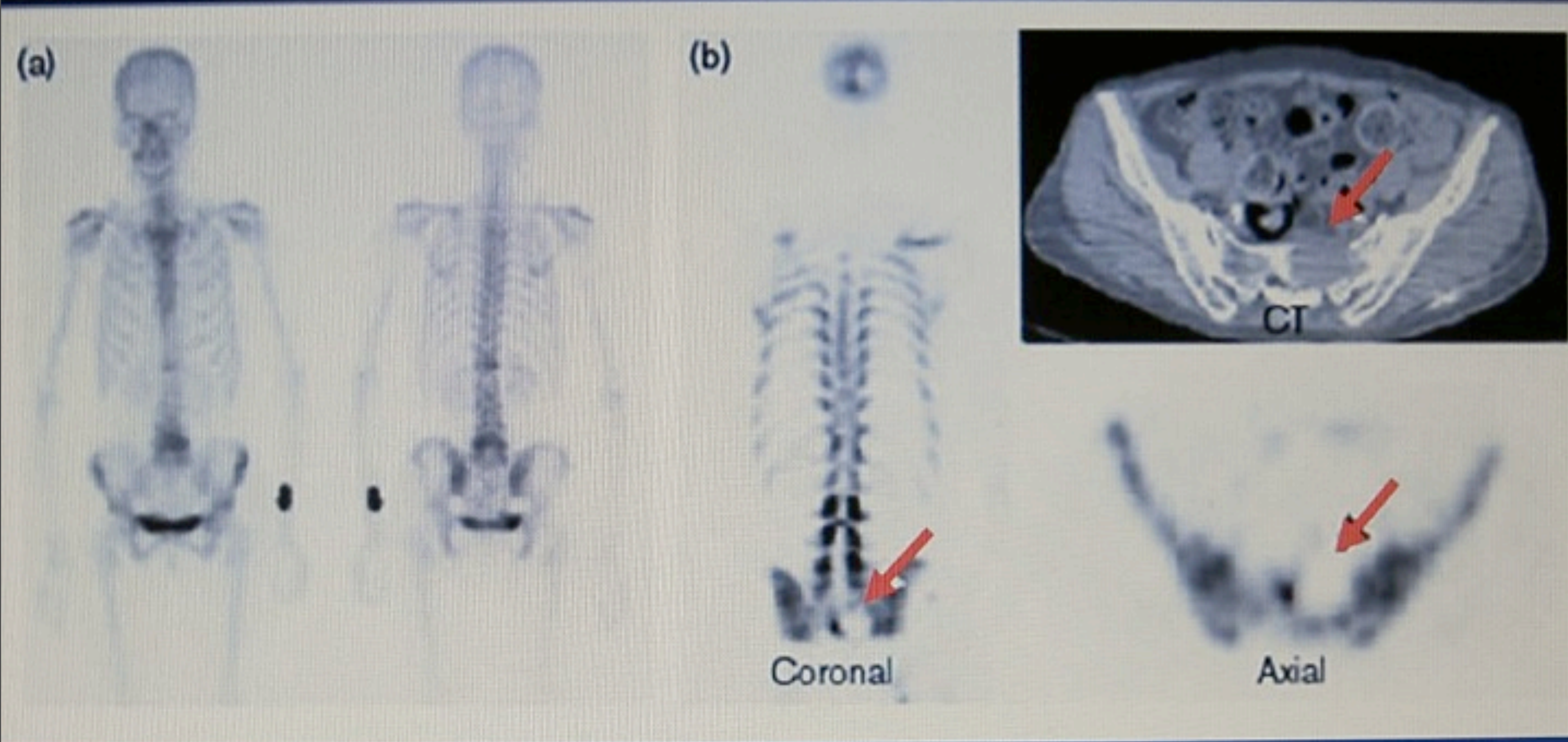
PET/CT---NEW *DIMENSIONS*



Imaging skeletal metastases

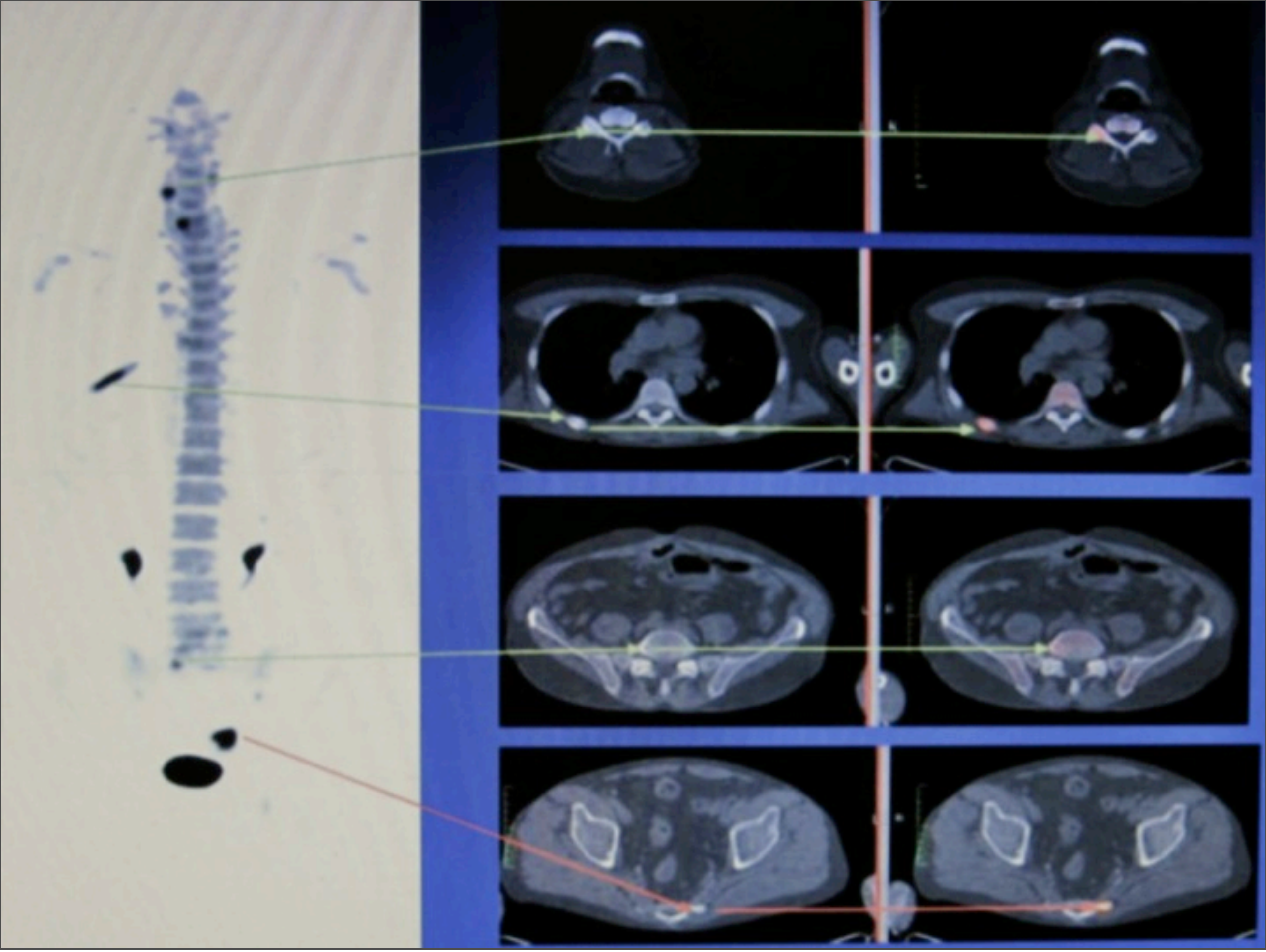


Yen et al. Nucl Med Commun 2010;31:637-645



47 yr old woman with thigh pain

False - MDP planar bone scan, True + NaF PET/CT



Thursday, May 31, 12

Metastatic Disease

Schirrmeister. J Nucl Med 2001;42:1800-04

- 52 patients with lung cancer
- 13 (23%) had bone mets

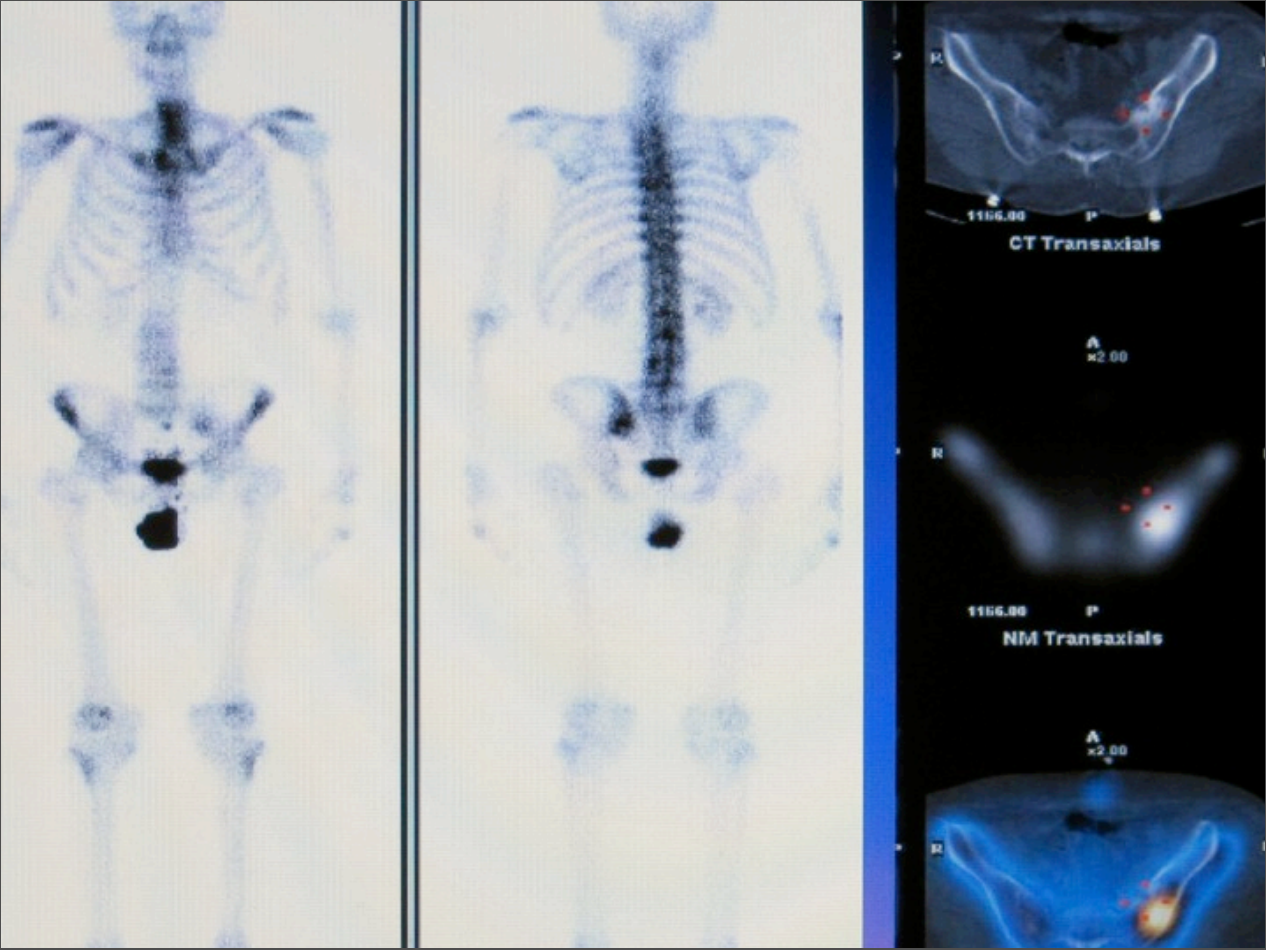
	sens	spec
Planar bone scan	54%	88%
Planar + SPECT	92%	100%
F18 fluoride PET	100%	100%

Metastatic Disease

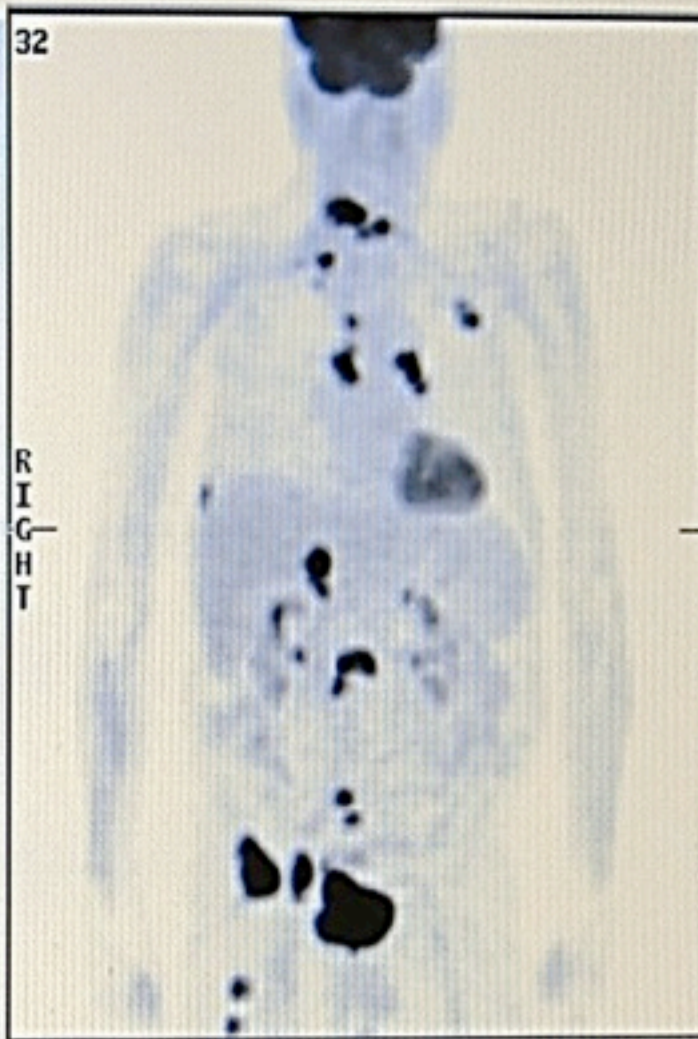
Even-Sapir. J Nucl Med 2006;47:287-97

- 44 patients with high risk prostate cancer
- 23 (52%) had bone mets

	sens	spec
Planar bone scan	70%	57%
Multi FOV SPECT	92%	82%
F18 PET/CT	100%	100%


R
1166.00
P
CT Transaxials
A
x2.00
R
1166.00
P
NM Transaxials
A
x2.00
R

Case study – Lung Cancer, ? bony mets

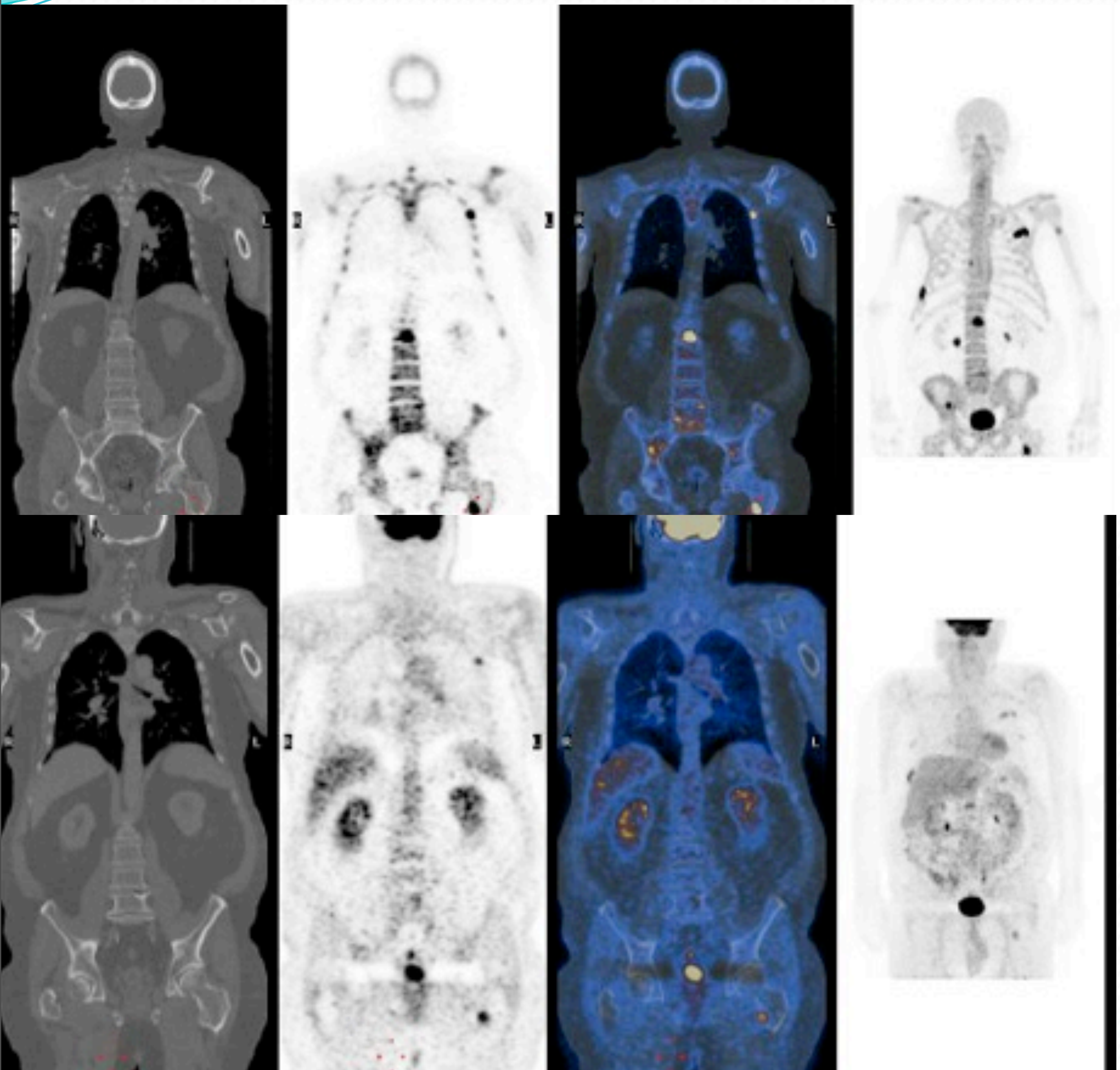


Tc MDP Bone Scan – blastic mets

abnormal uptake sternum, isolated rib lesion

^{18}FFDG – lytic mets

multiple foci of marrow based mets

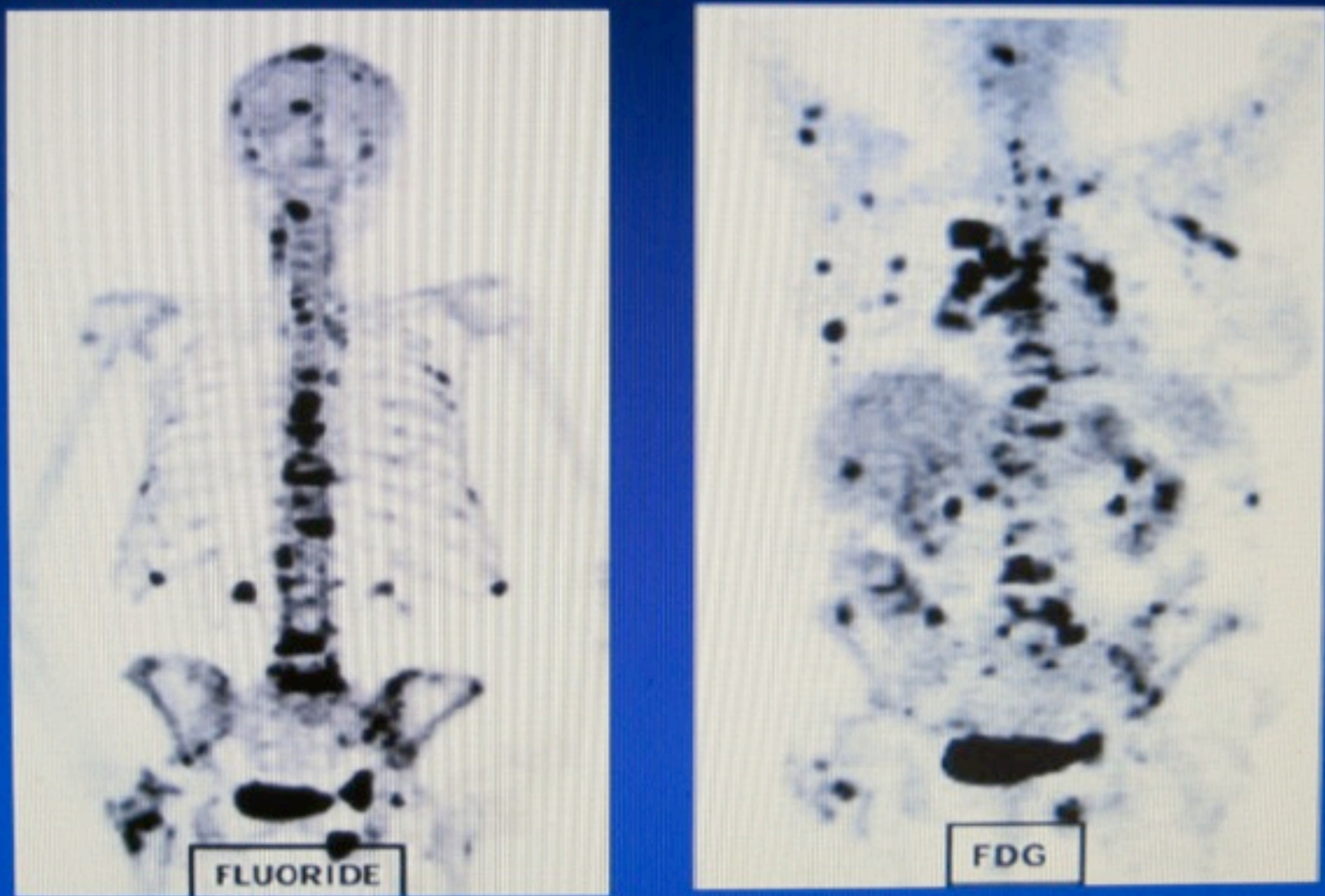


Fluoride PET Bone Scan

FDG PET Whole Body Scan

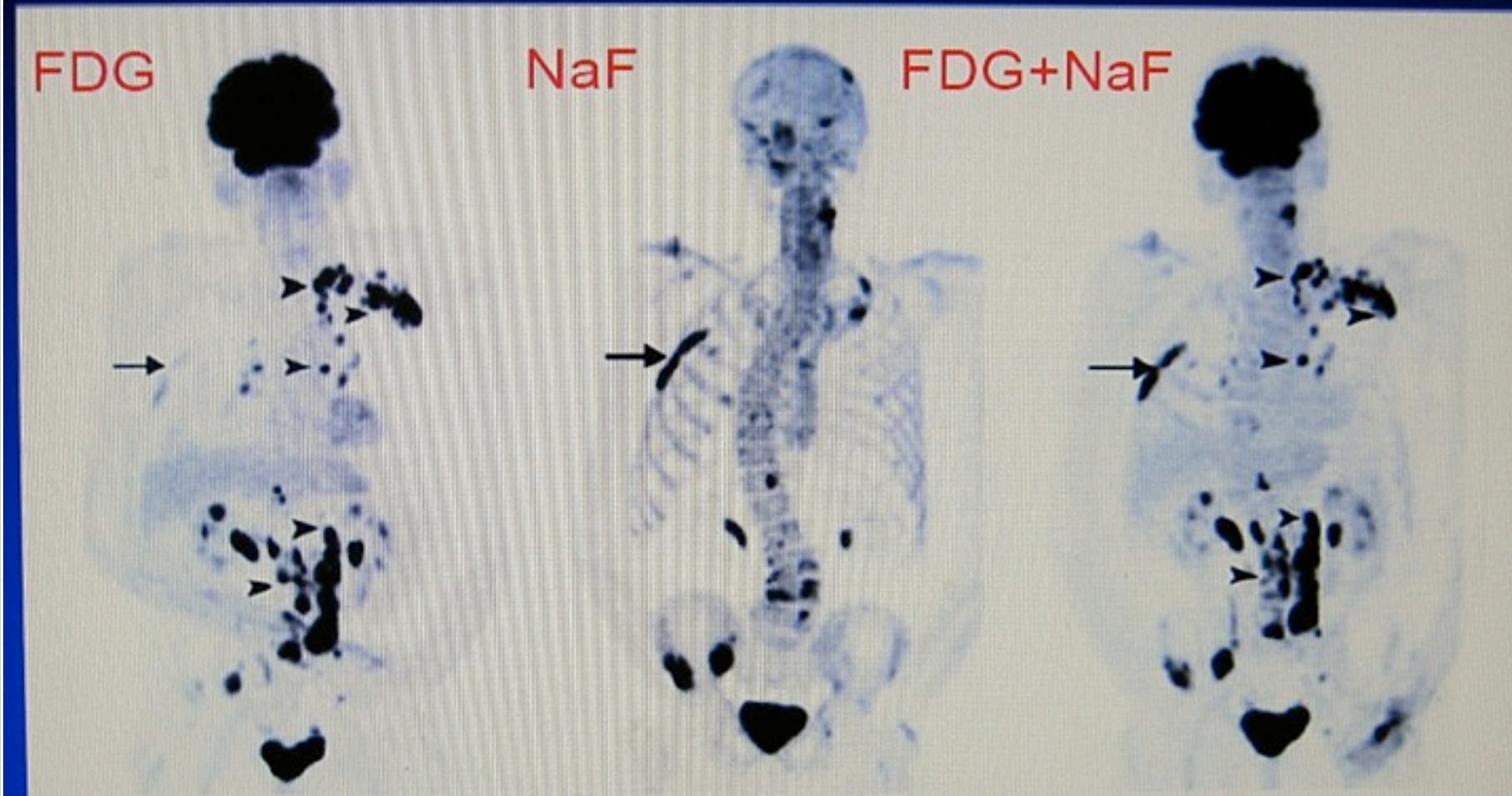
F-18 Fluoride vs FDG

Langsteger. Semin Nucl Med 2006;36:73-89



F-18 Fluoride + FDG

Iagaru. J Nucl Med 2009;50:501-505



75 yr old man with prostate cancer

F-18 Fluoride vs FDG

Langsteger. Semin Nucl Med 2006;36:73-89

20 patients with different cancers

150 Metastatic Lesions

- 72 FDG and F18 +
- 44 FDG + but F18 -
- 34 FDG - but F18 +

FDG "COMBO" STUDIES

- FDG DETECTS TUMOR GLYCOLYSIS- HOWEVER SOME TUMORS ARE NOT FDG AVID!
- F18 DETECTS METABOLIC BONE ACTIVATION OF METASTATIC TUMOR-OSTEOCALSTIC/BLASTIC
- " COMBO" FDG/F18 STUDIES ARE DEFINITIVE IN DETECTING TOTAL TUMOR BURDEN

PET/CT BONE IMAGING

- BONE IMAGING CAN ACCURATELY DETECT EARLY TUMOR INVOVELMENT
  - TUMOR STAGING-SENS/SPEC NEAR 100%!
  - TUMOR RESPONSE-QUANTITATIVE/QUALITATIVE
    - SPECIFIC UNIT VALUE(SUV)
    - MEASURED HOUNDSFIELD (HUV) RESPONSE
    - REPETATIVE MEARSURMENTS ARE ACCURATE!
    - CORRELATE WITH PSA,ALK.PHOS.,ETC.
- BONE IMAGING CAN ACCESS TREATMENT PROTOCOLS
  - RADIOACTIVE,BISPHOSPHONATES,ETC.

BASELINE T SPINE METS

3 MONTH QUANTITATIVE

Why F-18 Fluoride?

- Faster
- Higher Resolution
- Anatomic Correlation

Indications for ^{18}F-Fluoride Skeletal PET

- Oncology
  - Skeletal metastatic disease
    - Identification
    - Assessing response to therapy
  - Bone pain in cancer patients
  - Primary bone tumors
- Benign Bone Disease
  - Sports Medicine (back, extremities)
  - Fractures

^{18}F-NaF Bone PET: Other Indications

- Femoral head osteonecrosis
- Bone graft viability
- Quantitative bone turnover studies

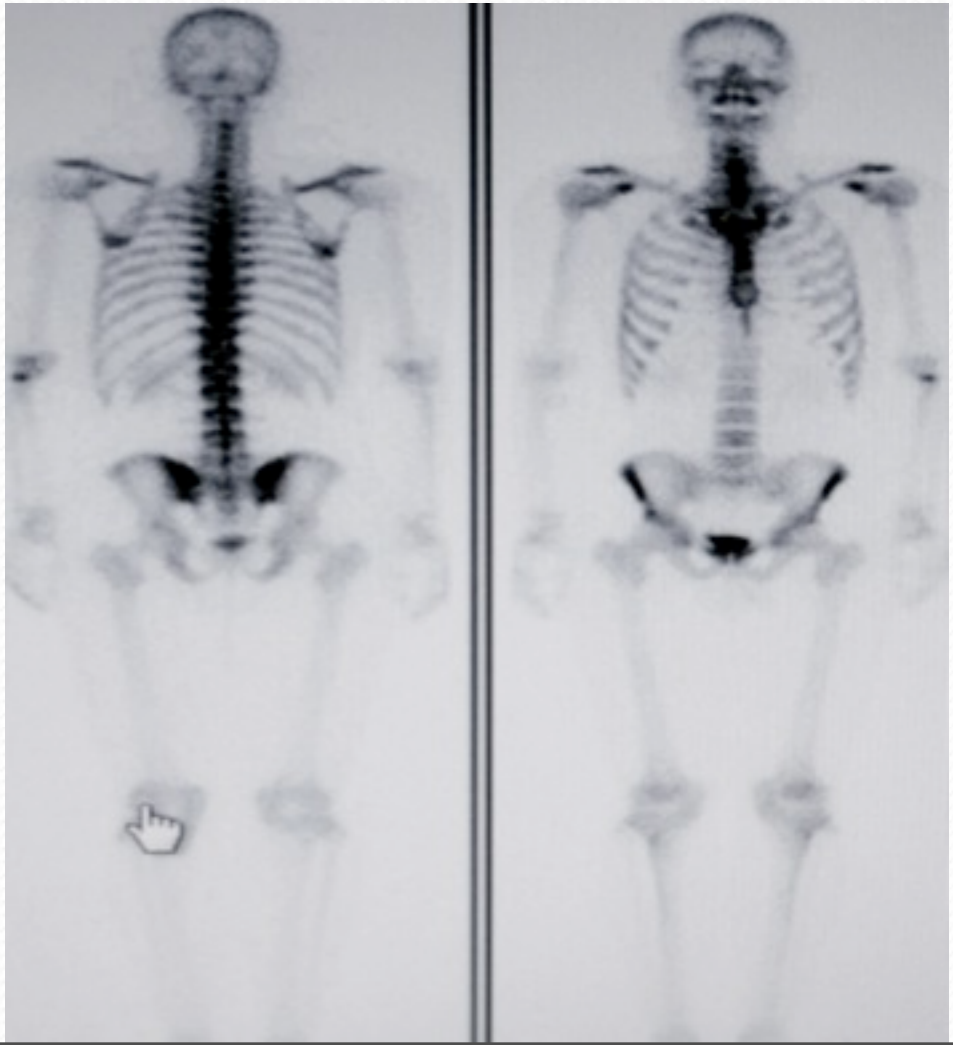
- Three-phase bone scan??

Bone Imaging with ^{18}F-NaF Skeletal PET

- Higher quality images than ^{99m}Tc-MDP SPECT, with similar radiation dose
- Potential for improved workflow
- More accurate than ^{99m}Tc-MDP SPECT in detecting both benign and metastatic skeletal disease
- Unresolved Questions:
  - How will ^{99m}Tc-MDP SPECT/CT compare?

Imaging Skeletal Metastases: ^{18}F-NaF and ^{18}F-FDG PET

- ^{18}F-NaF and ^{18}F-FDG both have higher sensitivity than ^{99m}Tc-MDP
- ^{18}F-FDG more likely to detect:
  - non-osseous disease
  - bone marrow metastases
  - small lytic lesions
- ^{18}F-NaF is specific for cortical bone involvement
- ^{18}F-NaF more likely to detect:
  - tumors with low FDG avidity



WHAT ARE THE BEST DECISION APPROPRIATNES CRITERIA?

Kosuda S, Yoshimura I, Aizawa T, et al. Can initial prostate specific antigen determinations eliminate the need for bone scans in patients with newly diagnosed prostate carcinoma? A multicenter retrospective study in Japan. *Cancer* 2002; 94(4):964-972.

Bone scans are not necessary for staging prostate cancer if PSA $\leq$20 ng/mL, stage <T4, and Gleason score <8 unless major Gleason pattern is 4.

Leibovici D, Spiess PE, Agarwal PK, et al. Prostate cancer progression in the presence of undetectable or low serum prostate-specific antigen level. *Cancer* 2007; 109(2):198-204.

Progression of prostate cancer may occur despite undetectable or low PSA levels. Complete physical evaluation and imaging studies may be indicated in the surveillance of patients with high-grade, locally advanced tumors.

Sodium Fluoride-18 PET/CT

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Planar BS	39 (23)	83 (98)	56 (87)	70 (69)
Planar and SPECT	61 (21)	87 (97)	73 (80)	80 (81)
^{18}F-Fluoride PET	100 (33)	79 (96)	73 (86)	100 (100)
^{18}F-Fluoride PET/CT	100 (81)	100 (100)	100 (100)	100 (90)

Evan-Sapri et al, J Nucl Med 2006; 47:287–297.

- F-18 PET markedly improves sensitivity
- CT improves specificity
- F-18 PET/CT optimizes skeletal evaluation

DISCUSSION POINTS

- CURRENT NATIONAL PET REGISTRY PROJECT
- IS CURRENT RVU/BILLABLE DATA JUSTIFIABLE?
  - CPT/RVU CODES ARE NOT RELEVANT!
  - COST SAVINGS THRU TUMOR UPSTAGING ARE NOT REIMBURSABLE-UPSTAGE DISEASE=LESS TREATMENT
  - CURRENT APPROPRIATNESS CRITERIA MUST CHANGE

Has The Future Arrived?

Langester, Heinisch, Fogelman. Semin Nucl Med 2006;73-92

"…we can expect that F18-fluoride will replace bone scintigraphy completely within several years."

THE LESSON ENDS!!

"Sage nodding got me where I am today."