Sodium Fluoride PET/CT: An Advanced Imaging Technique to Identify and Predict The Behavior of Painful Osseous Metastases For Early Intervention

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Objectives

1. Review the clinical significance of bone metastases.
2. Review pathophysiology of osseous metastases.
3. Review PET/CT technology.
4. Review mechanism of action of Fluoride Ion radiotracers.
5. Demonstrate how fluoride ion PET/CT can predictor which osseous metastases are painful or could become painful.

Clinical Significance

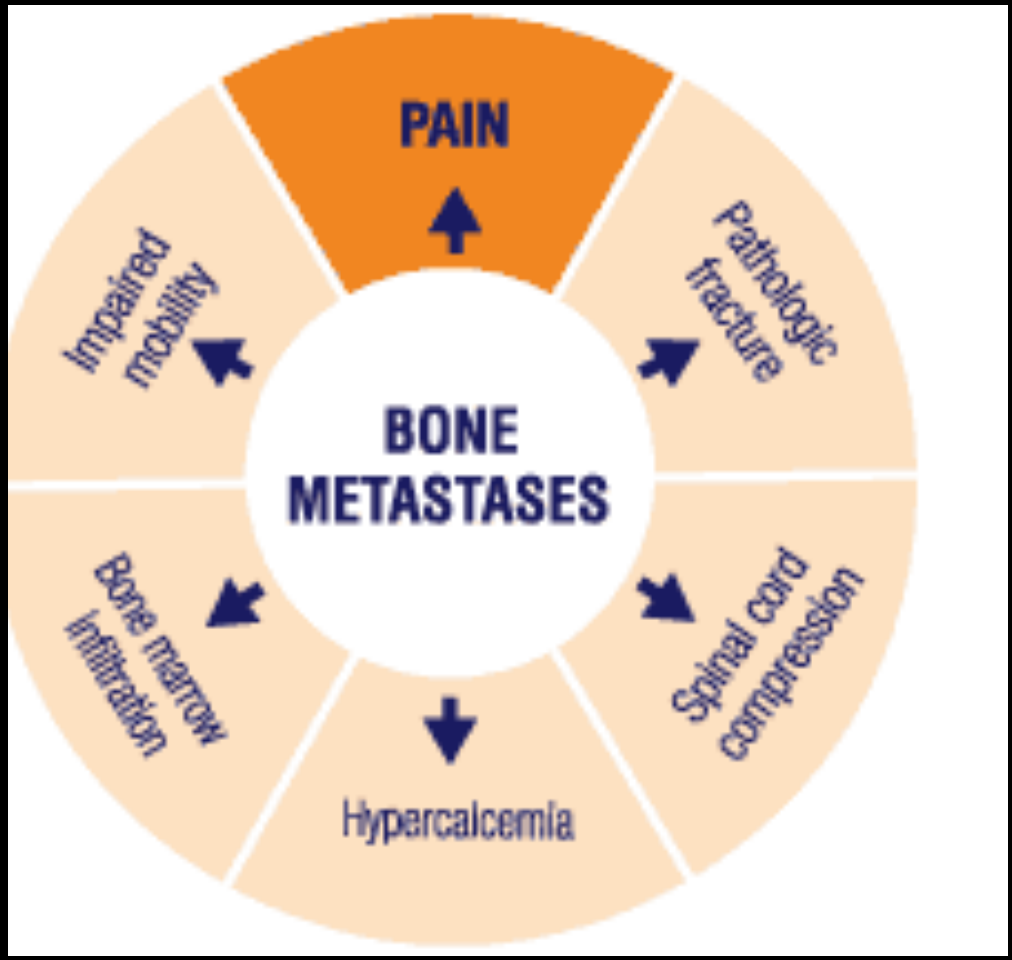
Clinical Importance and Prognosis of Bone Metastases

	US Prevalence (in thousands)	Bone Mets Incidence* (%)	Median Survival (mo)
Prostate	1,448	65-75	36
Bladder	582	40	6-9
Renal	198	20-25	12
Breast	1993	65-75	24
Myeloma	75-100	70-95	24
Lung	386	30-40	7
Melanoma	467	14-45	6
Thyroid	207	60	48

*In advanced disease cases.

National Cancer Institute. 1999.
International Myeloma Foundation. 2001.

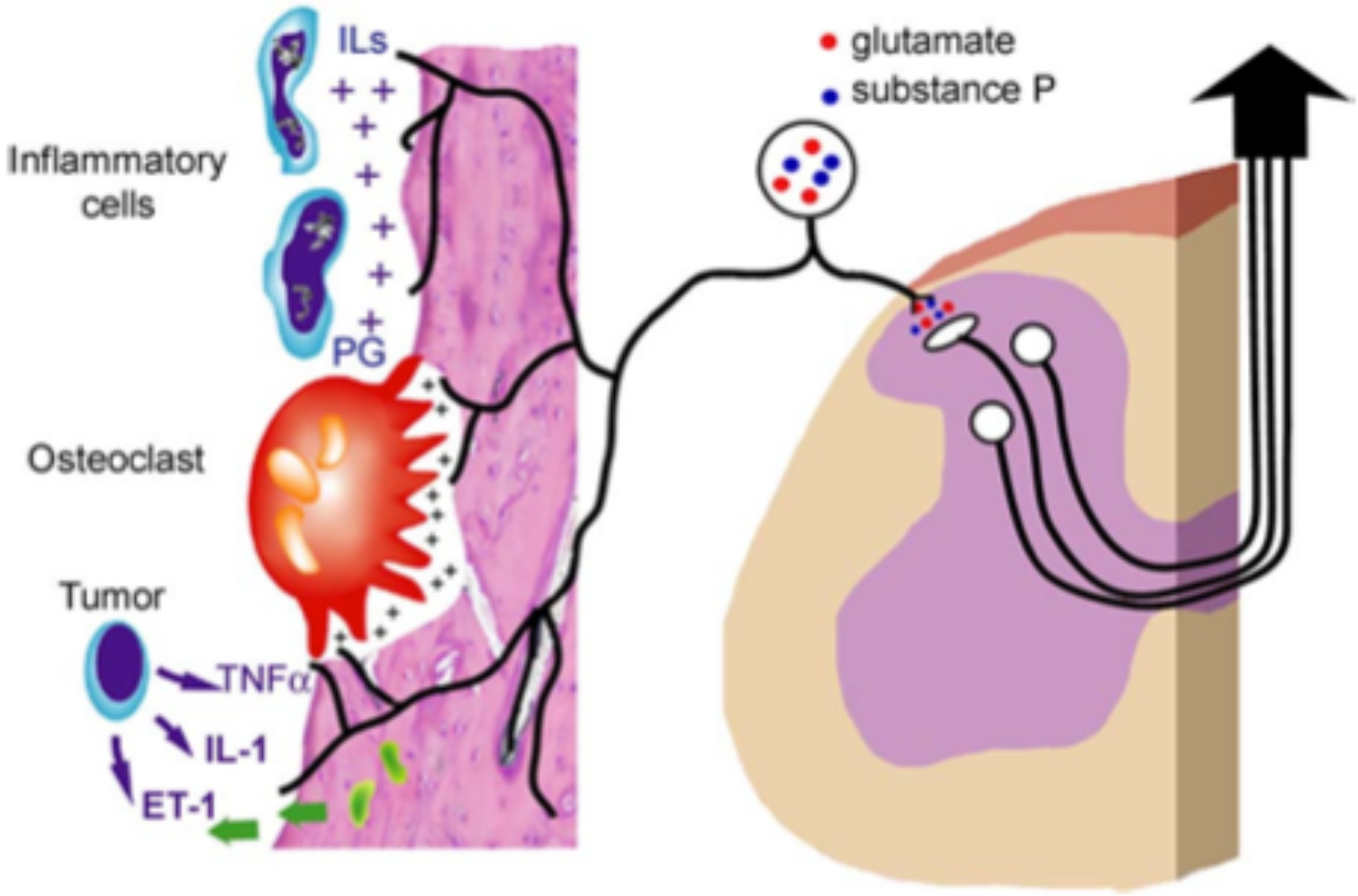
Clinical Significance



Bone Pain

- Reported as the most disruptive symptom in life of a cancer patient .
- Complex molecular and physiology mechanism of pain recently elucidated by Luger et al.
- Involves bone destruction and inflammation of the periosteal nerves
- Also later stage involves remodeling of spinal cord/CNS

Mechanism of Bone Pain

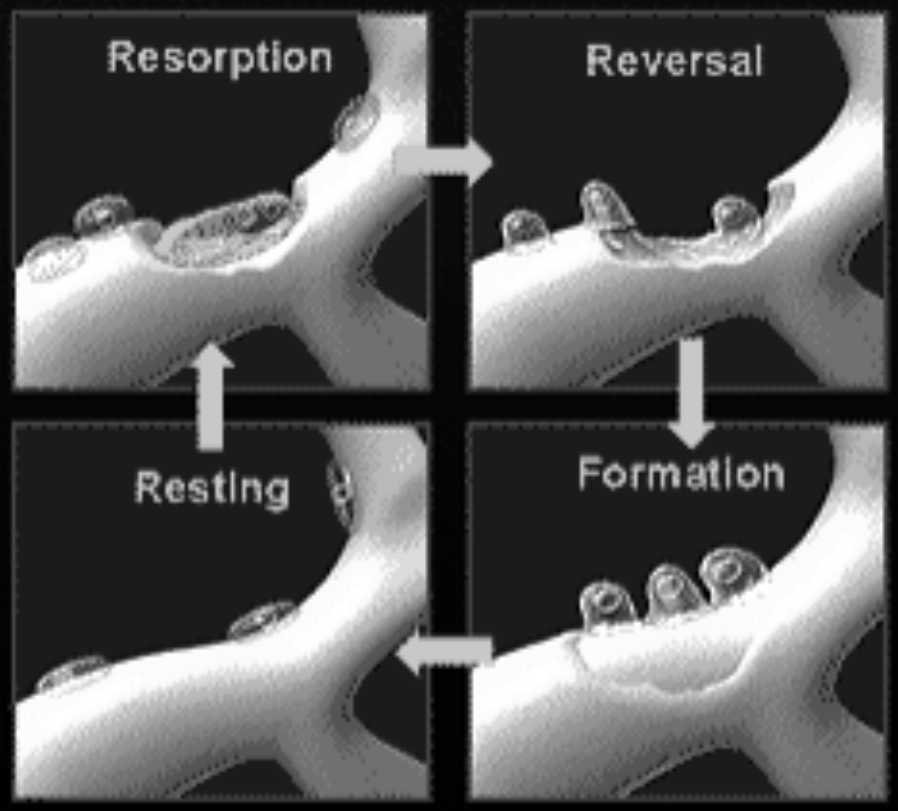


Mirel's Criteria

Mirel's criteria score > 8 suggests prophylactic fixation			
Score	**1**	**2**	**3**
Site	upper limb	lower limb	peritrochanteric
Pain	mild	moderate	functional
Lesion	blastic	mixed	lytic
Size	< 1/3	1/3 to 2/3	> 2/3

Classification of Bone Metastases

Normal Bone Remodeling



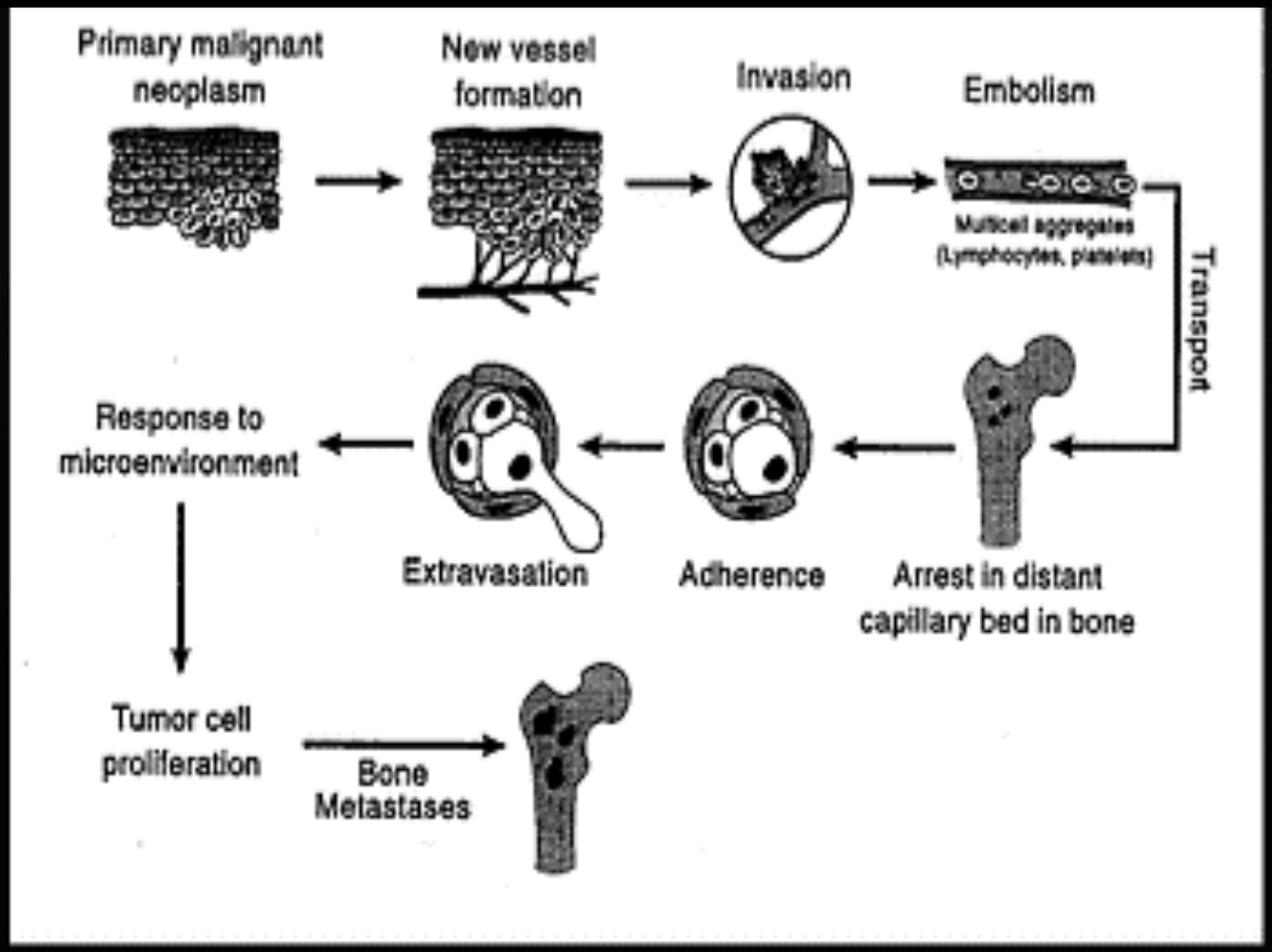
Resorption
Osteoclasts remove bone mineral and matrix, creating an erosion cavity (3-4 weeks)

Reversal
Mononuclear cells prepare bone surface for new osteoblasts to begin building bone

Formation
Osteoblasts synthesize a matrix to replace resorbed bone with new bone (3-4 months)

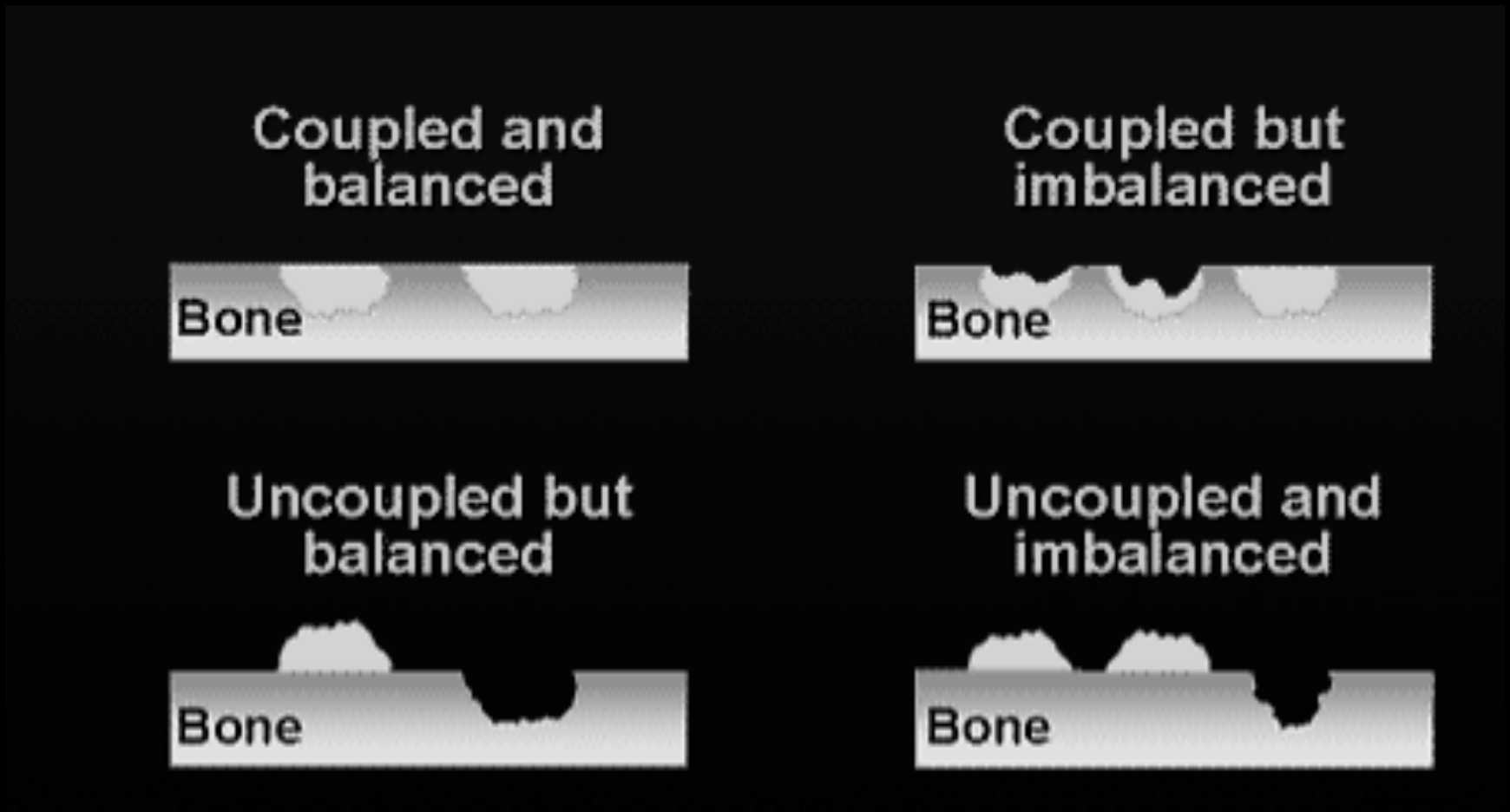
Resting
A prolonged resting period follows until a new remodeling cycle begins

Spread to Bone

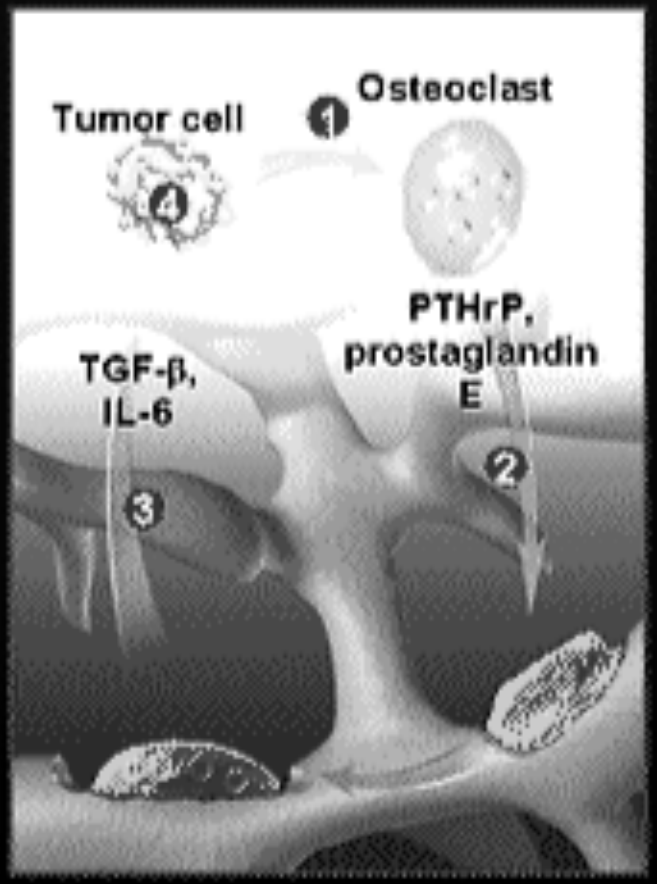


Guise TA, Mundy GR. *Endocr Rev*. 1998;19:18-54.

Bone Remodeling in Cancer

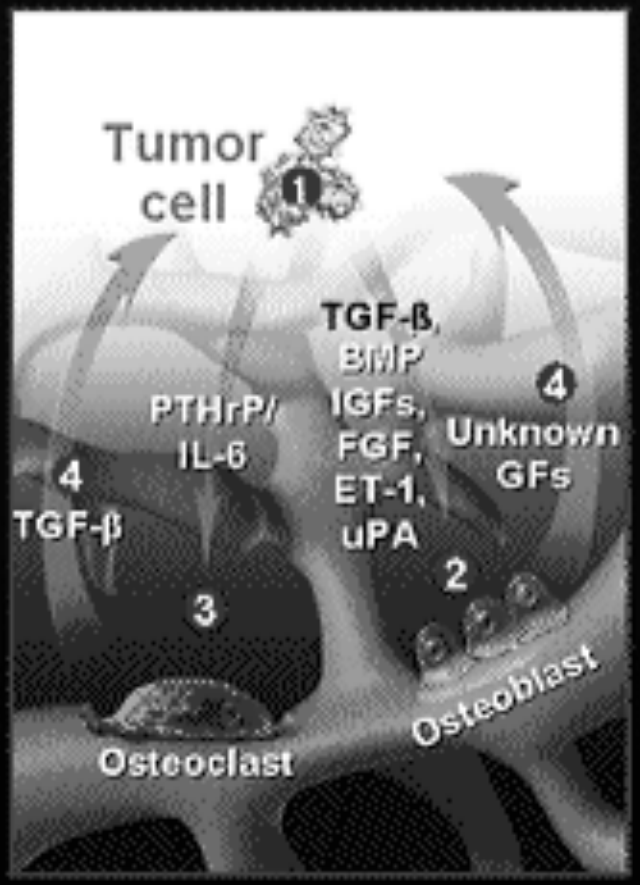


Osteolytic Metastases



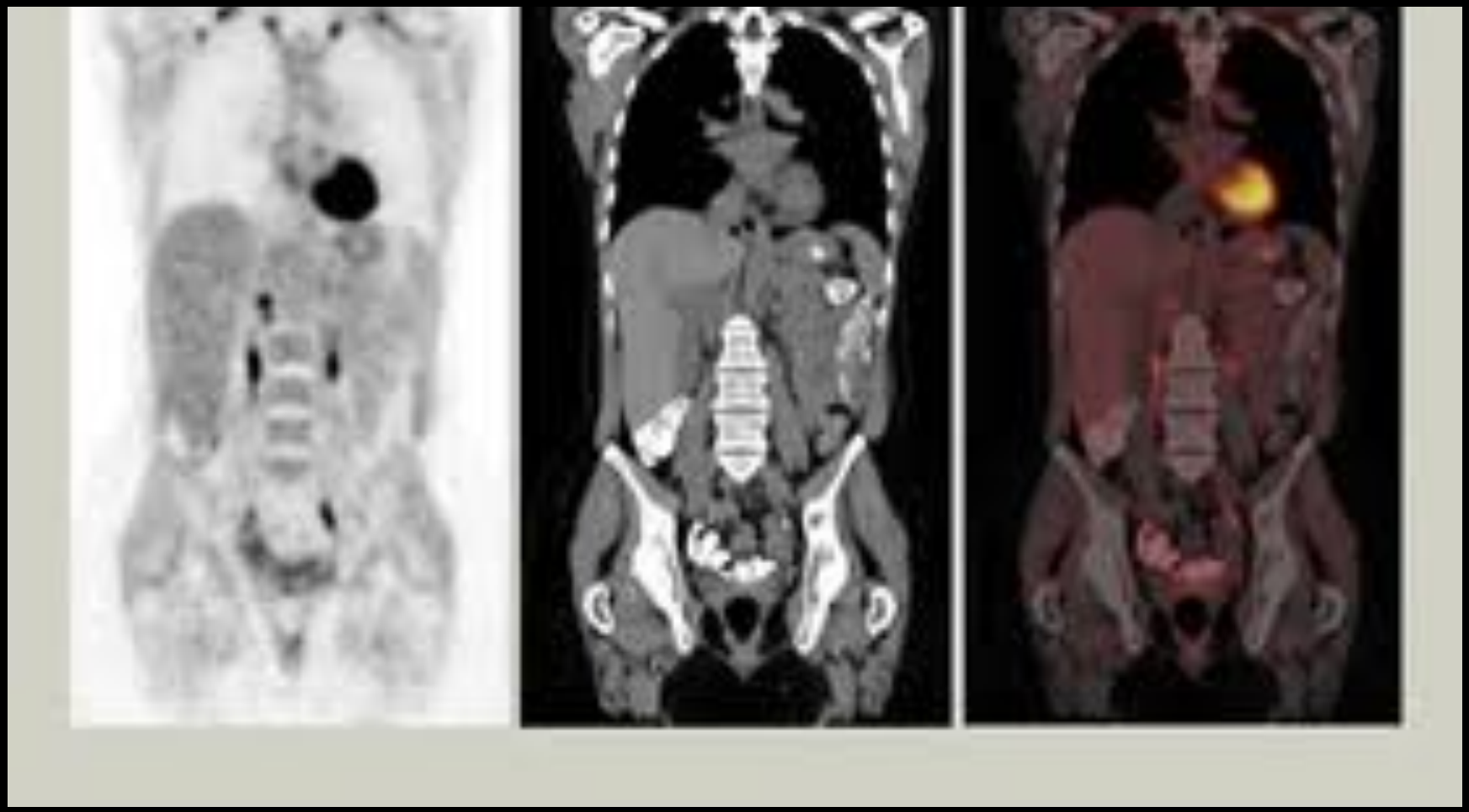
1. Tumors produce substances that attract and stimulate the osteoclasts indirectly through osteoblasts
2. Osteoclasts begin to break down (resorb) the bone
3. When the bone breaks down, it releases factors that help the tumor cells grow
4. As the tumor grows, it increasingly produces the substances that stimulate osteoclasts (intensified cycle of osteolysis)

Osteoblastic Metastases

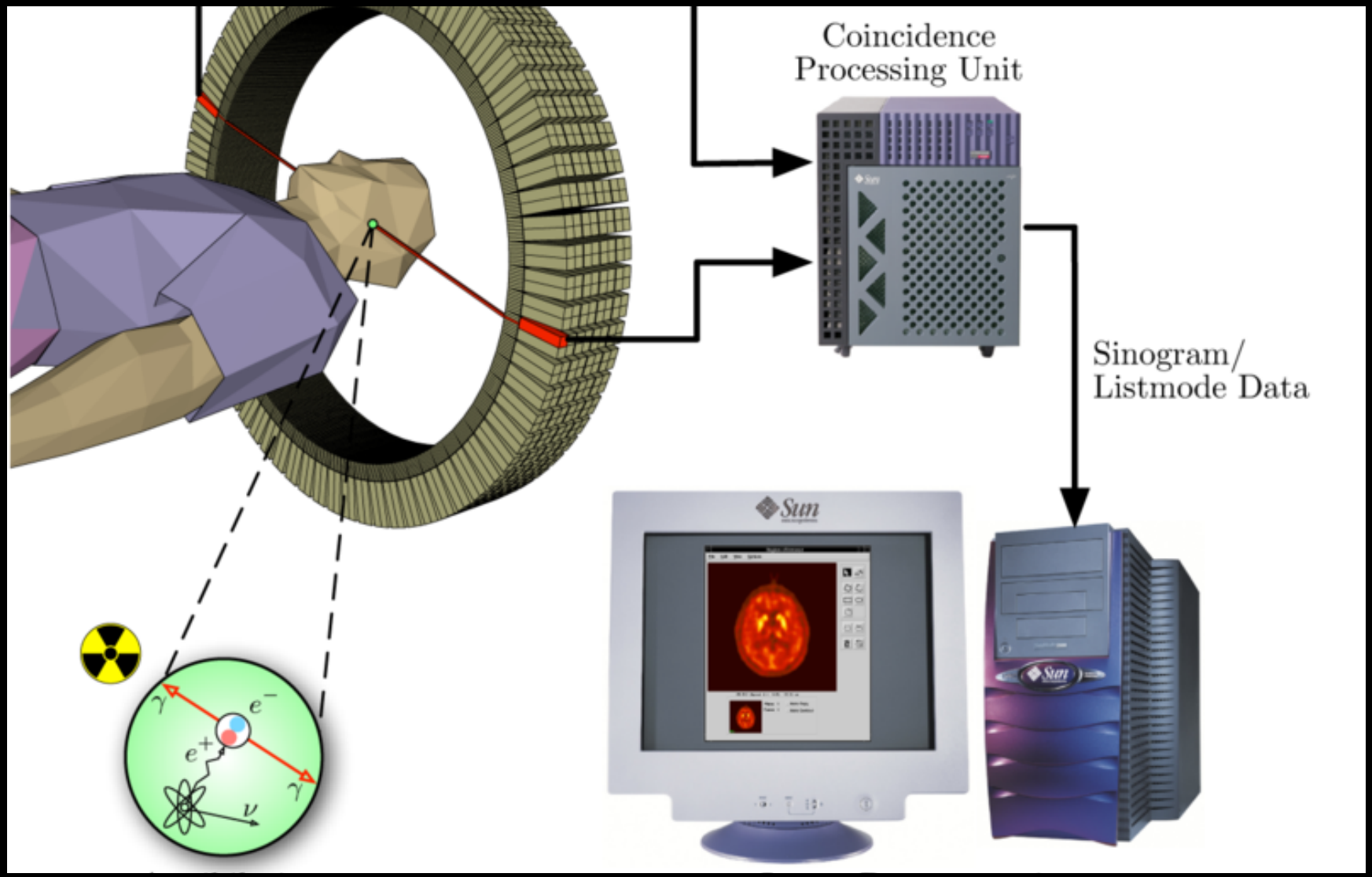


- Factors are released by 1 tumor cells that stimulate both 2 osteoblast and 3 osteoclast activity
- Excessive abnormal bone formation around tumor cell deposits, results in low bone strength
- Osteoclastic and osteoblastic activity releases growth factors that stimulate tumor cell growth, 4 perpetuating the cycle

PET/CT Technology



PET/CT Technology



Components to PET/CT Exam

1. Radiotracer
2. PET Camera
3. CT exam

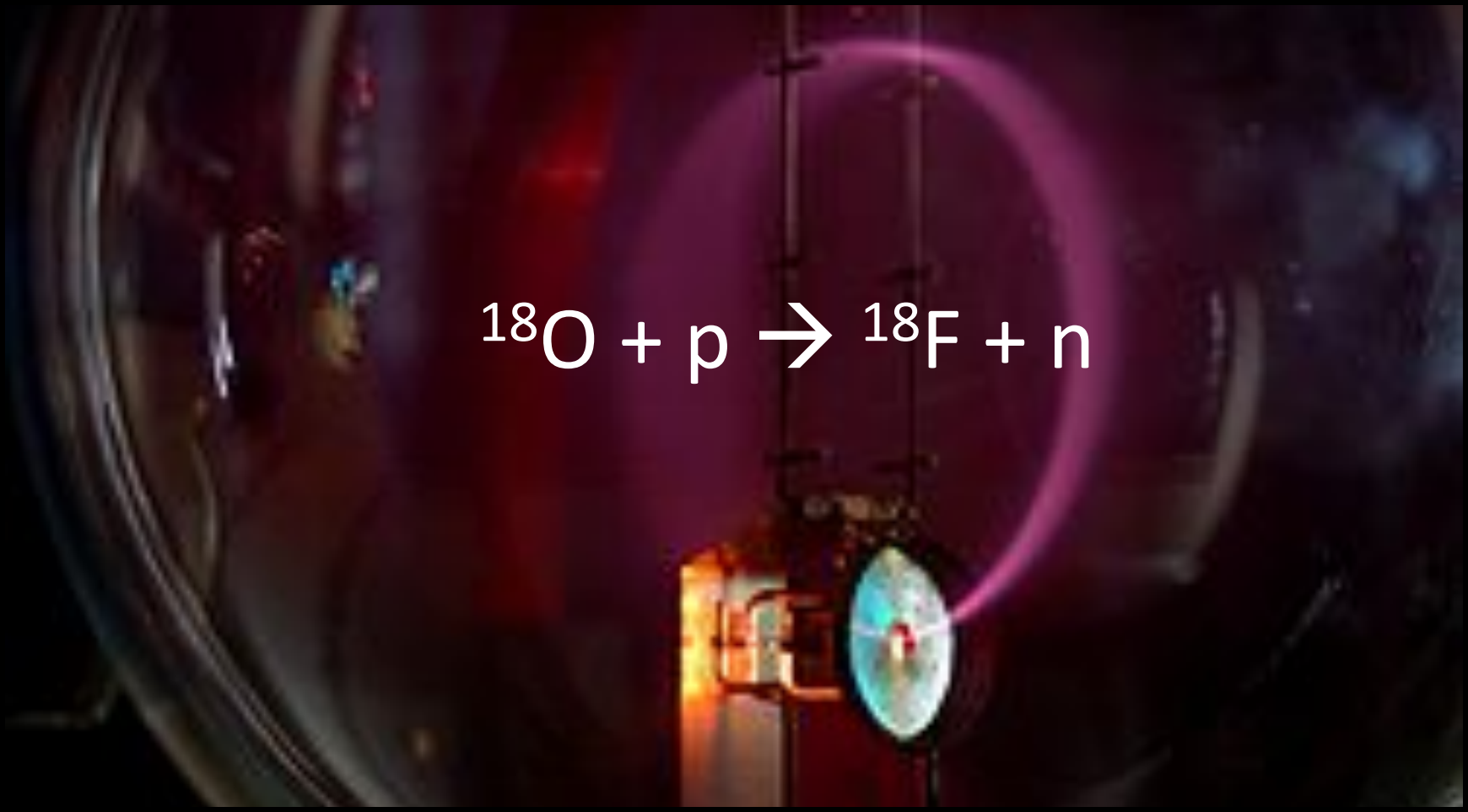
PET Data Quantification

- Standardized Uptake Value (SUV) is often used in PET imaging for a simple semi-quantitative analysis.
- SUV (t) = $\frac{\text{radioactivity concentration (t)}}{\text{injected activity / body weight}}$

Sodium Fluoride

- Introduced in early 1960s as superior radiopharmaceutical for skeletal imaging.
- In pre-PET imaging era, 511-keV annihilation photons produced by the decay of 18F required thick NaI(Tl) crystals detectors.
- In pre-PET imaging era, detectors were optimized for 140-keV photons of 99Tc
- Widespread availability of the 99Mo/99mTc generators led to a sudden decline in the use of 18F agents and generated an interest in the development of 99mTc bone agents…ie. 99mTc MDP Bone scan.

NaF production

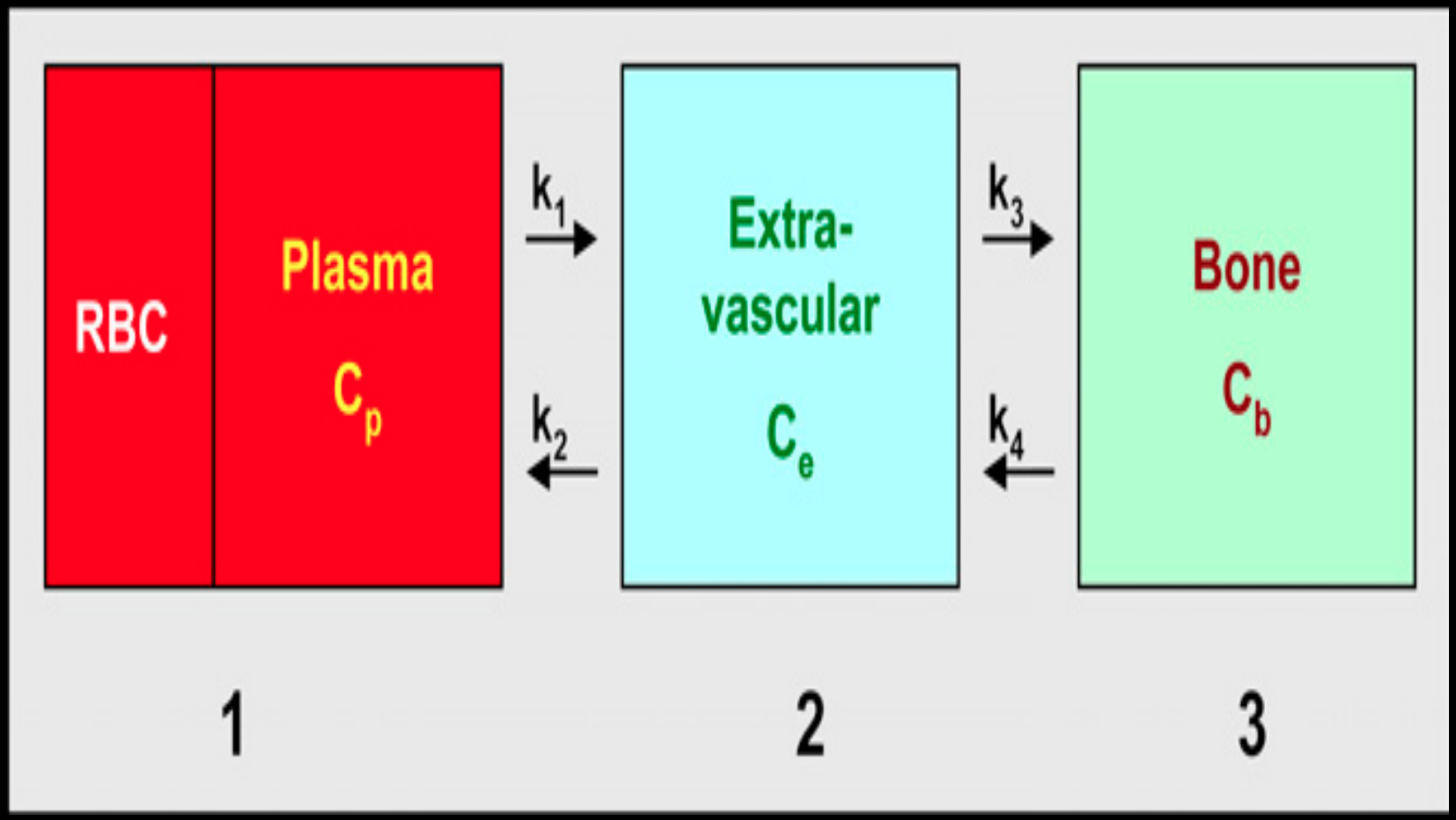


$$^{18}O + p \rightarrow {}^{18}F + n$$

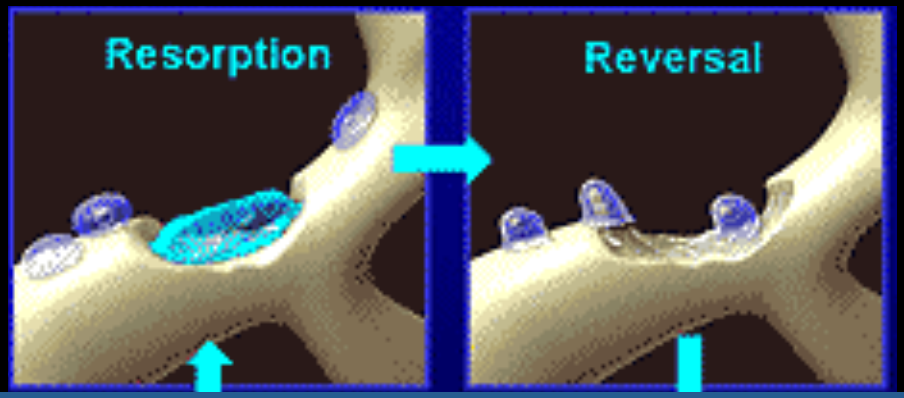
Tc99m MDP vs F-18 Fluoride

	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

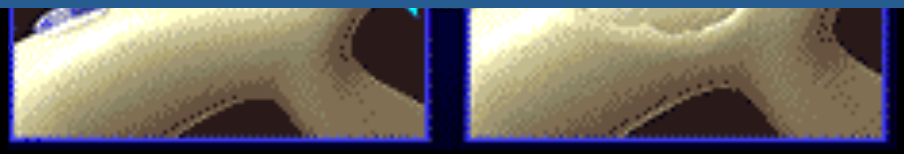
Fluoride ion deposition into bone



NaF Incorporation into Bone



$$(Ca_{10}(PO_4)_6OH_2) + {}^{18}F \rightarrow (Ca_{10}(PO_4)_6F_2)$$



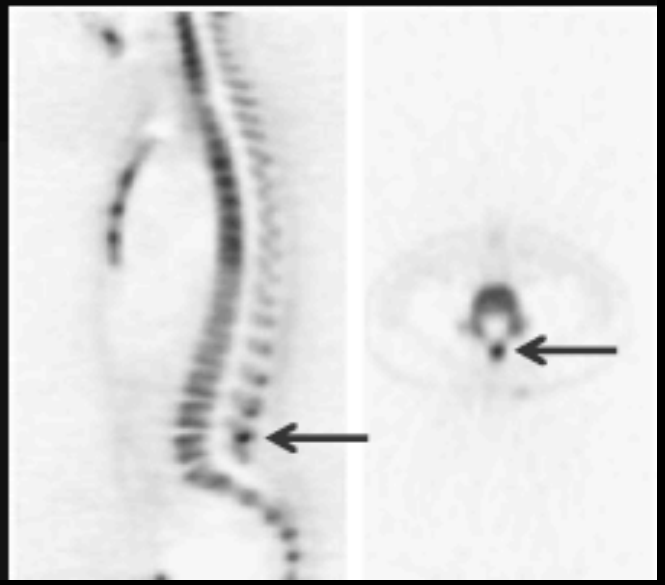
NaF PET/CT vs. MDP Bone Scan

Assessment of Back Pain

Lim. J Pediatr Orthop 2007;27:277-282

- 94 patients (4-26 yrs) with back pain
- PET/CT diagnostic in 52/94 (54%) patients

pars/pedicle stress	34%
spinous process injury	16%
vertebral body ring	14%
transitional L5/S1	7%
SI joint stress/inflam	3%



Hypothesis

- Can NaF PET/CT predict what lesions are painful or likely to become painful?
- Can NaF PET/CT provide insight on to what lesions will fracture and why?
- Can NaF PET/CT create a new classification system to pre-emptively treat metastatic bone lesions given the prevalence of the problem.

Retrospective Study: Methodology

- N = 15 patients
- 4 women and 11 men from ages 19-81
- Asked to fill out a questionairre that asked them about back pain
- Whole body [^{18}F] fluoride ion PET-CT
- Whole body [^{18}F]FDG PET/CT study

Retrospective Study: Methodology

Divided into 3 categories:

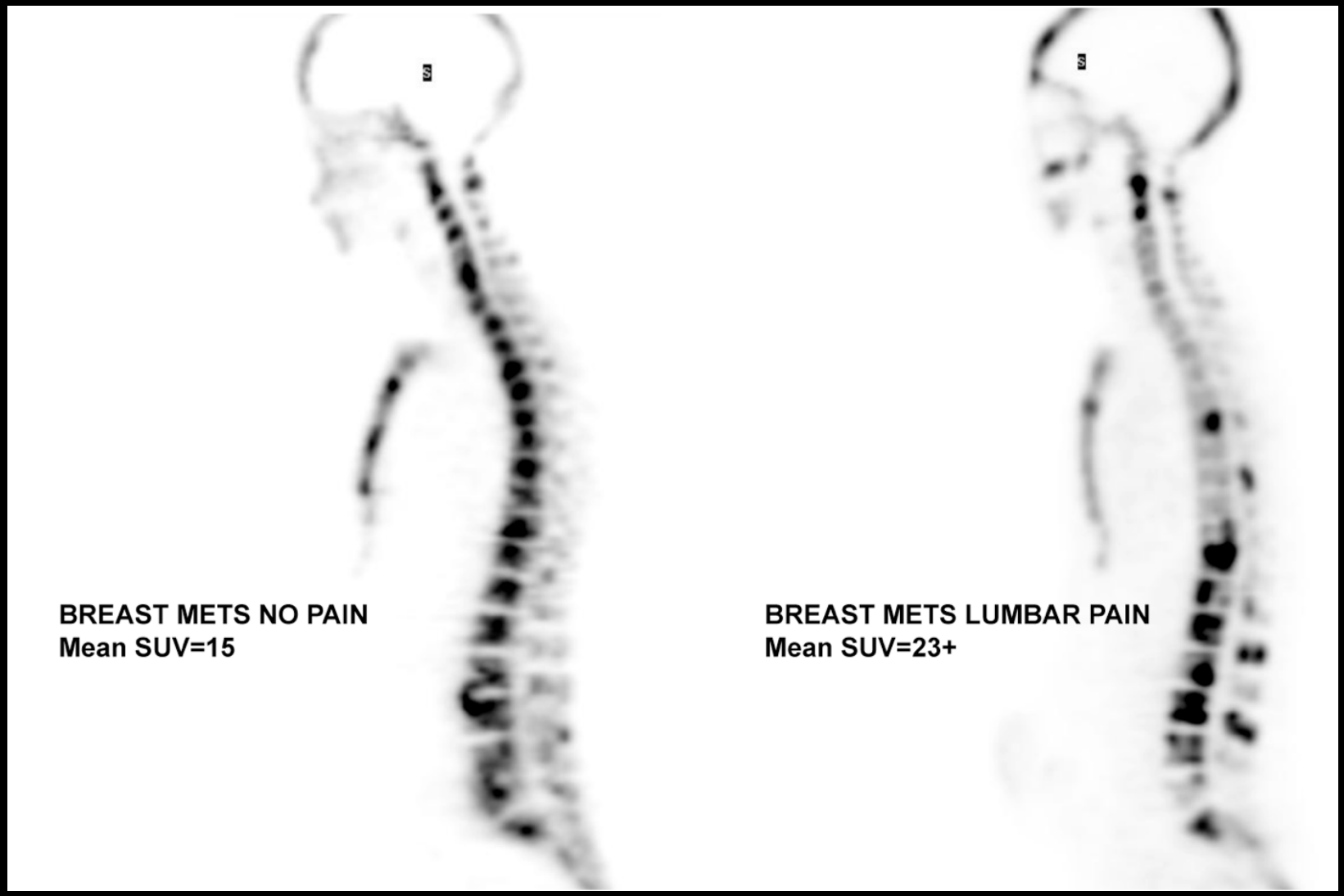
I. Category 1: Subjects with metastatic lesions to the thoracolumbar spine who described 'back pain' on the entrance questionnaire (n=3).
II. Category 2: Subjects with metastatic disease to the spine and described 'no pain' (n=6
III. Category 3: Subjects (control) who described 'no pain' on their entrance questionnaire and had no metastatic lesions to the spine (n=6).

Data Analysis

- CT images used to define bone margins.
- Rounded region of interest (ROI) placed from T1 to S1 vertebral body levels in both FDG and NaF PET/CT exams.
- Patients with spine metastases (Category I and II) mean SUV recorded for each level affected by disease in both FDG and NaF PET/CT exams.
- Highest SUV labeled maximum mean SUV
- Compared patients with spine metastases and back pain vs maximum mean SUV of patients with spine metastases and no back pain.

Table 2-Maximum Mean SUV for Patients in Category 1 and 2 and Aggregate Mean SUV for Patients in Category 3		
Category Type	**Maximum Mean SUV [^{18}F] Fluoride Ion Study**	**Maximum Mean SUV- [^{18}F] FDG PET CT study**
Category 1		
Patient 1	23.3	5.4
Patient 2	18.8	2.6
Patient 3	41.1	15.7
Category 2		
Patient 1	15.9	2.1
Patient 2	11.7	2.6
Patient 3	11.8	5.9
Patient 4	14.4	1.3
Patient 5	7.2	3
Patient 6	7.8	2.7
Category 3	**Aggregate Mean SUV - [^{18}F] Fluoride Ion Study**	**Aggregate Mean SUV – [^{18}F] FDG PET CT study**
Patient 1	7.5	8.6
Patient 2	8	4.9
Patient 3	7.5	1.6
Patient 4	7.1	1.6
Patient 5	8.6	2.4
Patient 6	9	4.1

Figure 1-Single sagittal view of [^{18}F] Fluoride ion PET-CT in a patient with no back pain and breast cancer metastases vs patient with back pain and breast cancer metastases



Additional Data Analysis

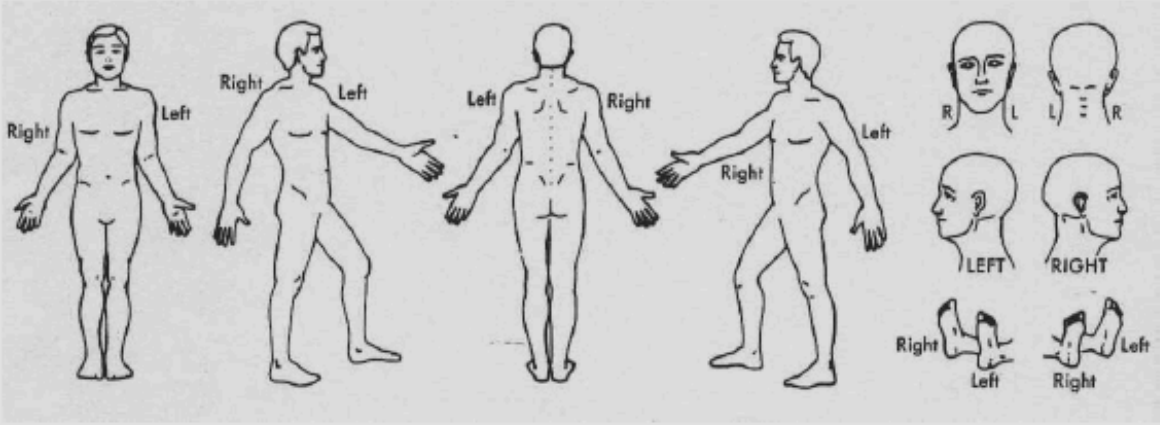
- All 3 patients with painful spinal metastases treated with radiotherapy.
- Approximately 2-4 weeks after treatment all presented with pain at a secondary site of know metastases seen on NaF PET/CT.
- NaF PET/CT SUV values at secondary site, where the second highest SUV after the treated primary lesion.

Prospective Study Design

- 35 patients
- Standardized pain questionairre
- Receive NaF PET/CT exam after completing questionaire
- Randomize to treatment by standard of care
- Treatments include: surgery, local anesthetic injection, MR guided HIFU, radiofrequency ablation, and radiotherapy.

Location: (Resident or nurse mark drawing) Mark on the areas where you feel pain. If you feel more than one sensation in the same area, mark over that area with all the symbols that apply. Make sure you show all affected areas.

O Aching
/ Burning
Cramping
= Crushing
• Dull
* Numbness
+ Pins/needles
● Sharp
↓Stabbing
↑Throbbing



History of Pain

Onset of Pain: ❑ New (within the last 7 days) ❑ Recent (within the last 3 mos.) ❑ More distant (> 3 mos.)

Type/Frequency of Pain: ❑ Constant ❑ Intermittent ❑ Other, describe: _____

Change in Pattern of Pain: Has the discomfort changed in description or intensity the last 7 days? ❑ Yes ❑ No

If yes, describe the change: _____

What Relieves the Pain: ❑ Cold ❑ Eating ❑ Exercise ❑ Heat ❑ Medication ❑ Massage ❑ Relaxation ❑ Rest ❑ Repositioning ❑ Other, describe: _____

Manner of expressing pain: (per resident or by observation) ❑ Facial expressions ❑ Guarding ❑ Moaning ❑ Readily describes pain ❑ Restlessness ❑ Rubbing area ❑ Other, describe: _____

Effects of Pain: (Note decreased function) Using the following scale, rate how the pain has had an effect in each area in the past 24 hours: 0 (no effect) 2 (mild effect) 5 (moderate effect) 10 (severe effect)

Accompanying Symptoms (e.g., nausea) _____ Sleep Disturbance _____ Appetite Change _____

Physical Activity Change _____ Mood/Behavior _____ Concentration _____

Relationship with Others _____ Other (describe): _____

Plan for Addressing Pain: ❑ Initiate pain management flow sheet ❑ Call physician/NP/PA-C ❑ Refer to pain team ❑ Rehab referral (PT, OT, ST) ❑ Non-med intervention ❑ Medications prescribed ❑ Spiritual counseling ❑ Staff education/communication

Project Aims

- CT Data: Evaluate for periosteal reaction or break.
- NaF PET Data: Evaluate number of lesions and comparative SUVmaximum.
- Determine if 3D visualization of tumor location is can better determine the source of pain.
- Determine if combination or each data set alone can quantify/predict risk of fracture or amount of tumor present.

Conclusions

1. NaF PET/CT is more sensitive and specific for bone pathology than MDP Bone Scan.
2. Preliminary results suggest that NaF PET/CT may be a diagnostic tool in predicting bone lesions that are painful or will become painful.

Future Directions

1. New classification system could be derived that could predict risk of fracture.
2. Ability to predict source/type of pain based on 3D localization of pathology to guide intervention.
3. Availability of PET/MRI may be even more sensitive and specific.

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