

Prostate Cancer

Prostate Cancer

- **CT:**

- Limited in staging/restaging, especially low sensitivity for LN metastases
- CT-guided brachytherapy

- **MRI/MRS:**

- Variable performance- similar to CT for LN metastases, but superior to CT for bone metastases
- MRI-SPIO- may be superior to all imaging modalities for detection of LN metastases

Clinical Results for Diagnosis and Local Staging With PET.

Studies investigating the role of PET with FDG in primary prostate cancer produced disappointing results.

In contrast to other malignancies, most primary prostate carcinomas show relatively low FDG uptake. Small size, slow doubling time (2-4 years in most cases) and specifics of prostate metabolism (see above) might be contributing factors.

Prostate Cancer

- Comparison of FDG-PET and ¹¹C-acetate-PET : initial staging

	C-11 Acetate		FDG	
	+/Total	%	+/Total	%
Primary Tumors	22/22	100	15/18	83
Nodal Metastases	5/5	100	2/5	40
Bone Metastases	6/7	86	4/7	57

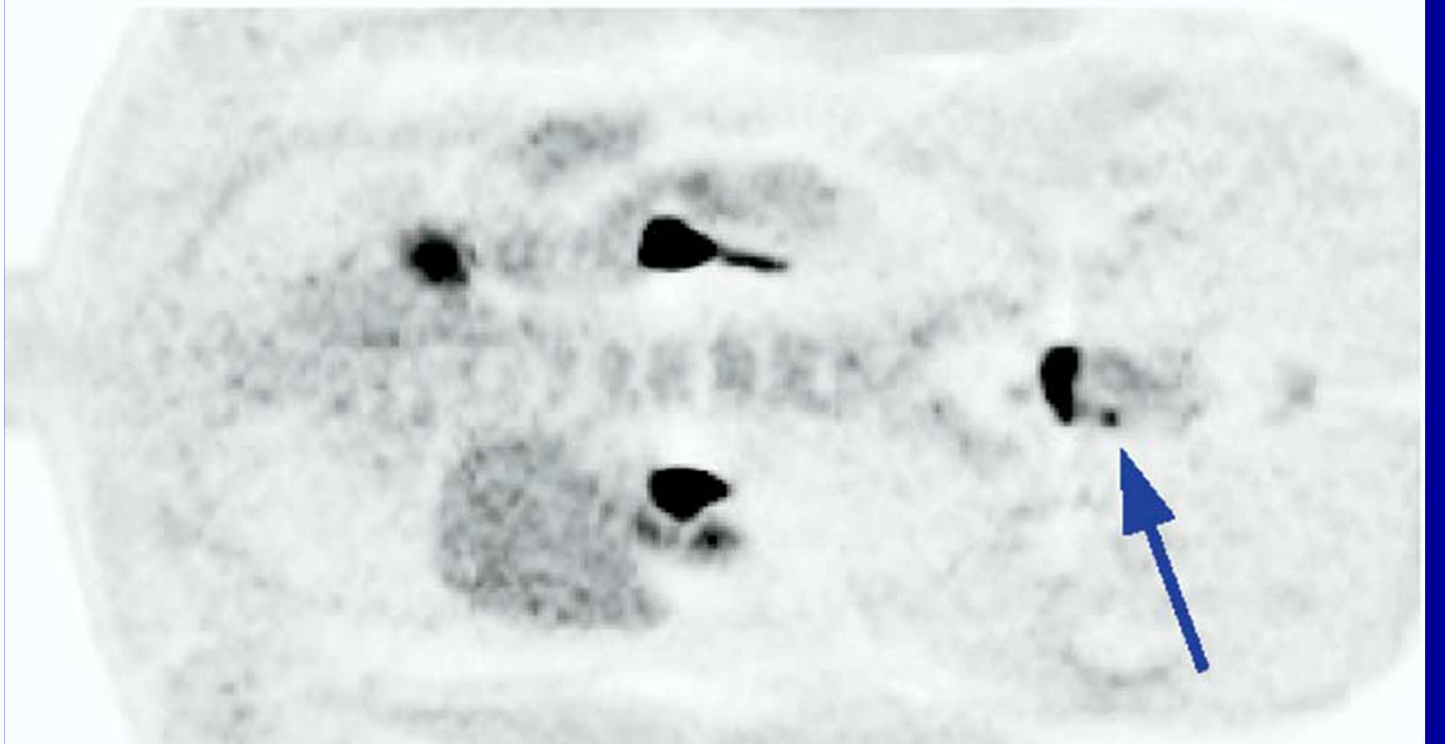
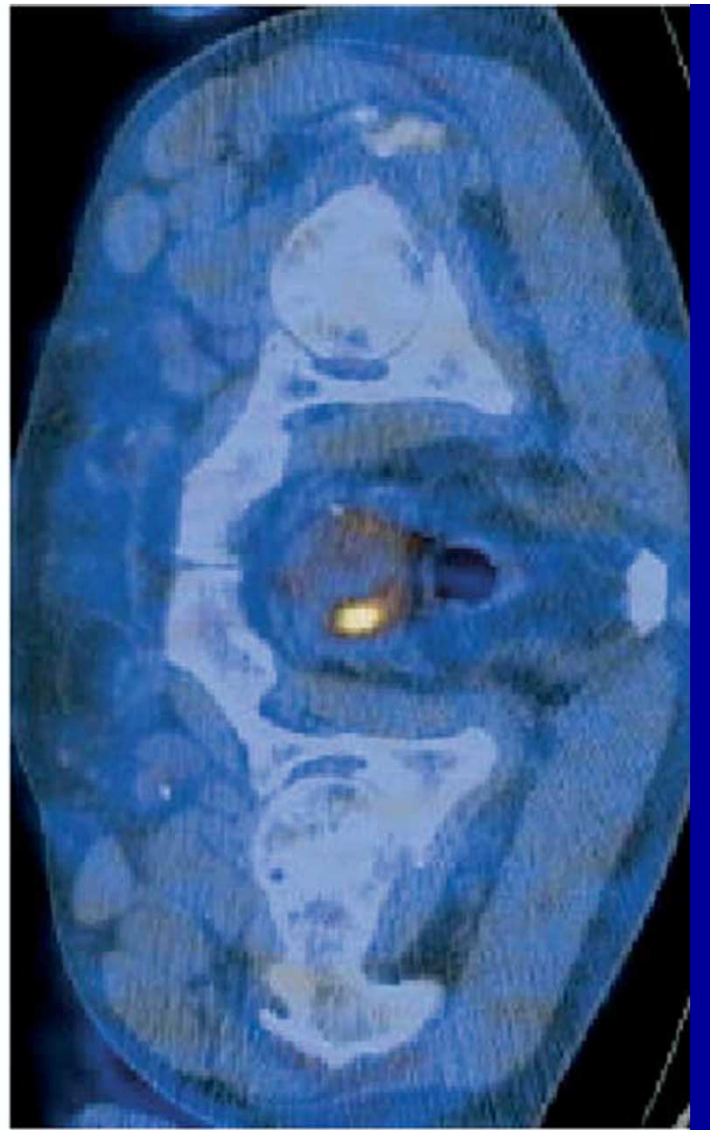
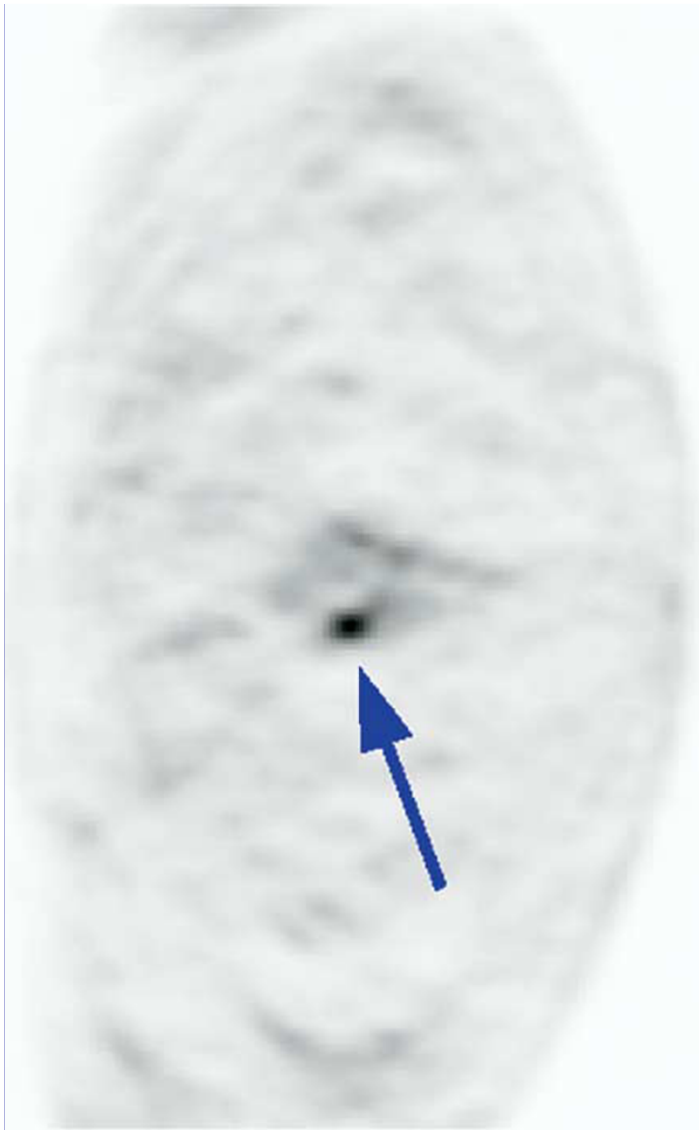
Oyama et al. J Nucl Med 2002; 43:181-6

Incidentalomas.

Occasionally, focal intense tracer uptake can be noted in the prostate gland. This can be noted for FDG and has also been described for ^{11}C -choline.

Such findings always require further investigation.

Recommended at least a digital rectal examination and PSA measurement.



Metastatic Disease

The prevalence of pelvic lymph node metastases correlates directly with T stage, serum PSA levels, and histologic grade.

Consequently, a high suspicion of lymph node metastases is based on the finding of

- 1) prebiopsy serum PSA level greater than 20 ng/mL,
- 2) poorly differentiated tumor on needle biopsy of the prostate (Gleason score 8-10), or
- 3) palpable locally advanced tumor.

In these patients, the probability for nodal metastases is 30% or greater. Detection and localization of metastases is an important clinical issue in this group of patients, which may affect patient management.

Treatment with curative intent may not be justified once the cancer has spread to lymph nodes and distant sites.

It is generally accepted that FDG-PET has low a sensitivity to be useful for the diagnosis of lymph node metastases during primary staging of prostate cancer

FDG also has a limited sensitivity for the detection of osseous metastases

¹¹C-acetate PET detected lymph node and bone metastases with 100% and 86% sensitivity, respectively

The utility of ¹¹C-choline PET for nodal staging of prostate cancer before prostatectomy was assessed by de Jong and coworkers. In 67 patients, lymph node metastases were detected with a sensitivity of 80% and specificity of 96%.

PSA recurrence

In most cases, recurrent disease presents initially as biochemical recurrence (BCR), with an increase in serum levels of PSA.

Approximately one-third of patients undergoing radical prostatectomy and a similar number of patients with radiation therapy will develop BCR.

In the majority of cases, this early rise in PSA occurs in isolation without any symptoms or other objective findings. The clinical behavior of the patient group is extremely heterogeneous and it is not unusual for patients to survive for 5 to 10 years with an elevated PSA as the only evidence of recurrent disease.

Imaging studies are frequently negative.

Role of conventional imaging for PSA relapse

Trus : Not good for local recurrence evaluation

CT : Not good for local recurrence evaluation

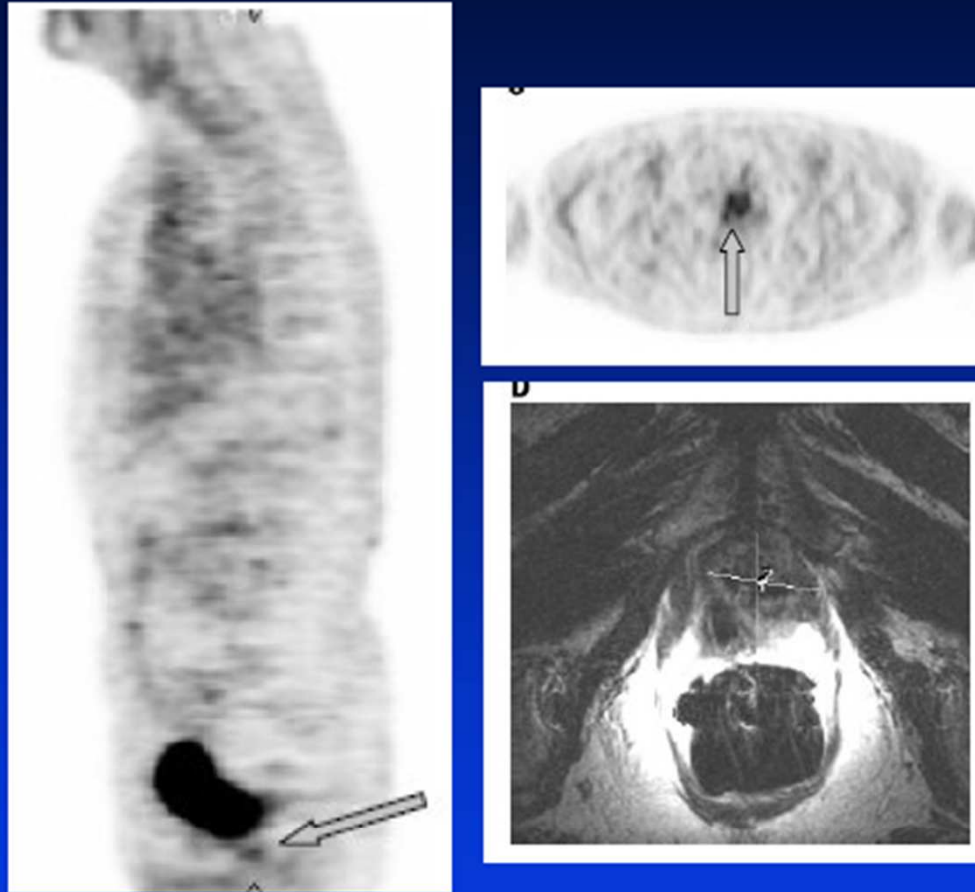
MRI : Good for local recurrence

**For distant metastases especially bone metastases most
Urologists favor Bone scan compared to MRI**

**The bone scan is the most commonly used test in
patients with BCR; a survey among urologists revealed
that 70% order a bone scan as part of the workup in
patients with rising PSA after radical prostatectomy or
radiation therapy**

Prostate Cancer

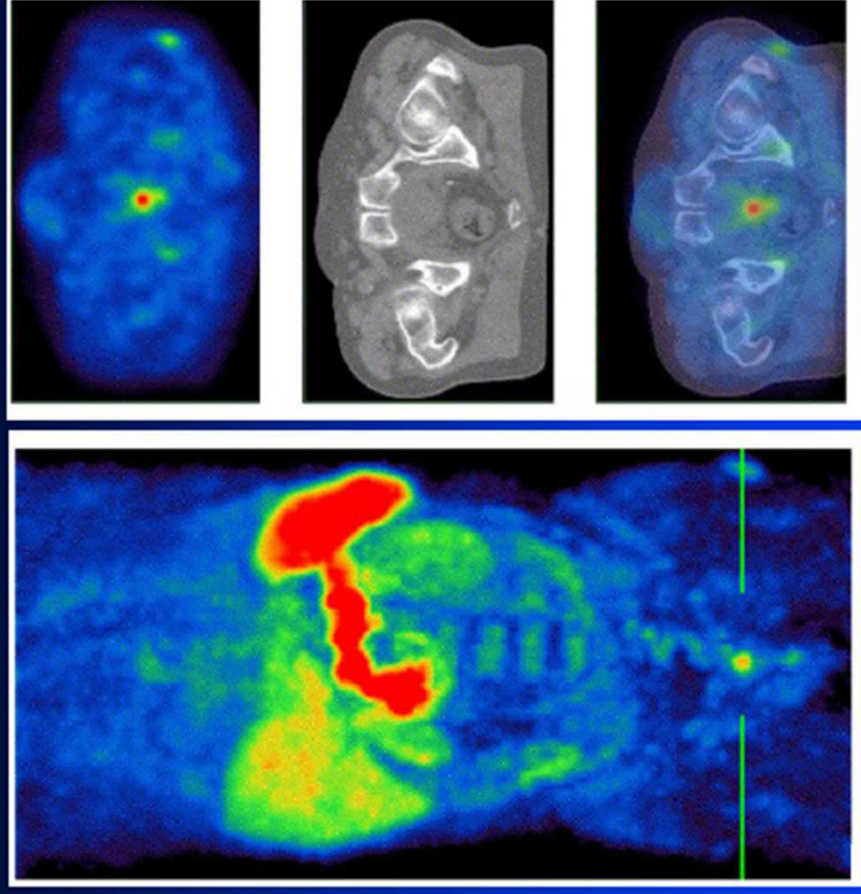
Contributions
by PET for PSA
relapse



Local recurrence
Gleason score 4+4, PSA 6.2

Prostate Cancer

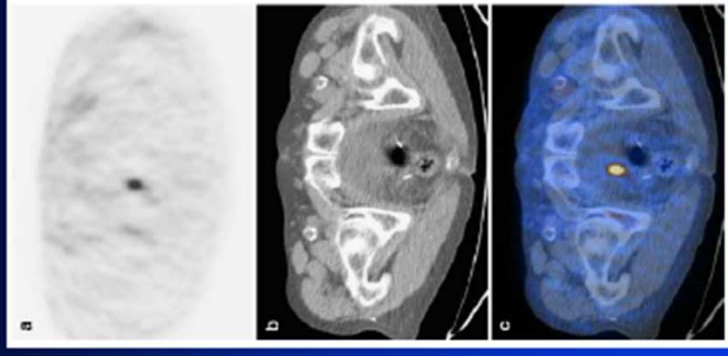
Recurrent disease
PSA 2.5



^{11}C -Acetate-PET

Sandblom et al. Urology 2006; 67:996-1000

Prostate Cancer



Local recurrence
S/P prostatectomy
PSA = 1.98

Recurrence

Early imaging
(during 8 min after
injection)

Delayed imaging
(~15 min after injection)

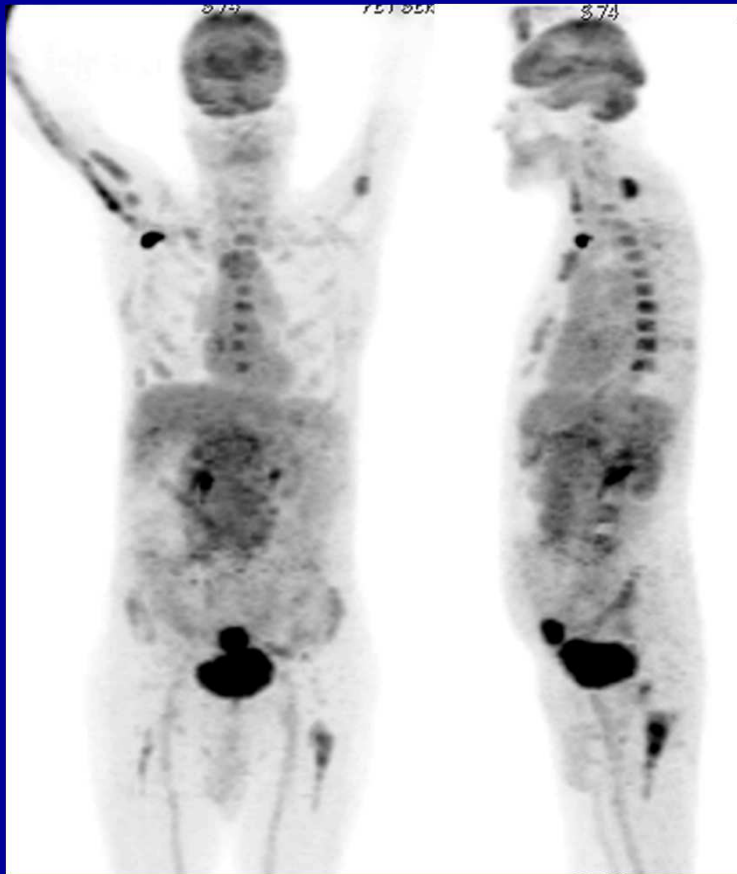
Bladder

^{18}F -choline eliminated by urinary system (dual imaging)

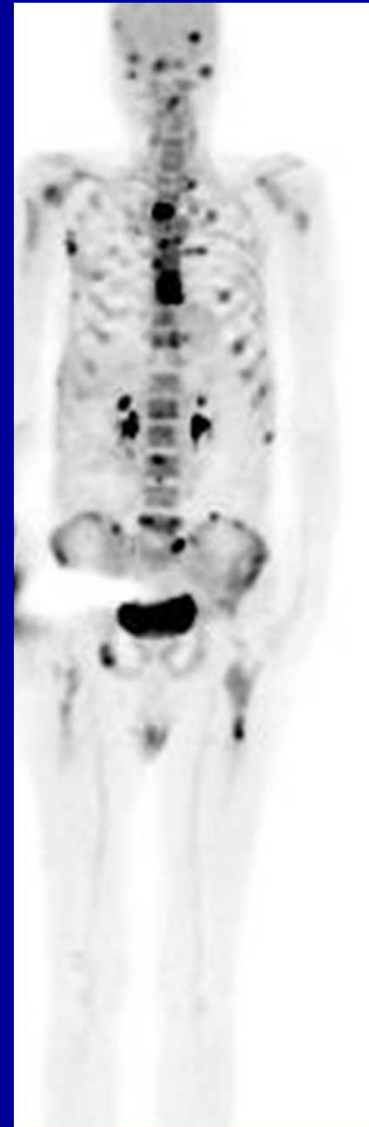
Prostate Cancer

- FDG-PET detection of metastatic/recurrent cancer – ? correlation with PSA level
- Osseous metastases:
 - FDG-PET had 65% sensitivity and 98% PPV (n = 34, 202 osseous lesions) (Shreve et al. Radiology 1996; 199:751-6)
 - FDG-PET detected 18% of lesions (n = 13, 131 osseous lesions) (Yeh et al. Nucl Med Biol 1996; 23:693-7)
- Local recurrence and metastatic disease:
 - FDG-PET was TP in 31% (n = 91) patients with local recurrence or metastatic disease (Schöder et al. Clin Cancer Res 2005; 11:4761-9)

FDG PET



F18 PET bone scan



Prostate Cancer: PSA Recurrence

- ¹¹C-acetate-PET in 20 patients with two consecutive rising PSA measurements following radical prostatectomy
 - ¹¹C-acetate-PET was true-positive in 11 (75%) and false-positive in 3 (15%); lung ca, esophagitis and lymphadenitis)
 - » All patients with a PSA level of ≥ 2.0 ng/mL and 4/9 with a PSA level < 2 ng/mL had positive PET for local/systemic disease

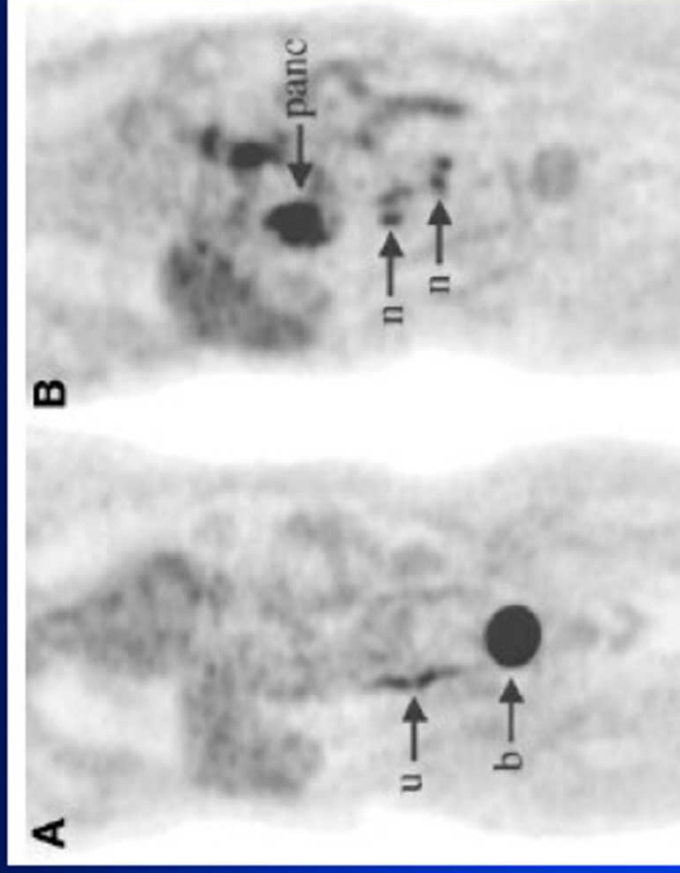
Prostate Cancer: Local Recurrence and Metastases

FDG-PET

¹¹C-Acetate-PET

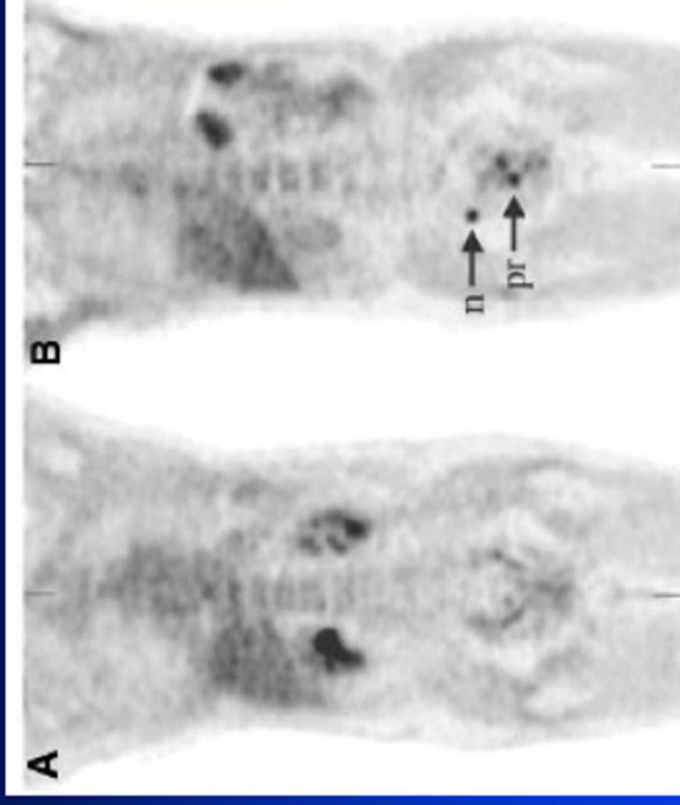
FDG-PET

¹¹C-Acetate-PET



Recurrent disease

Gleason score 8, PSA 10.5

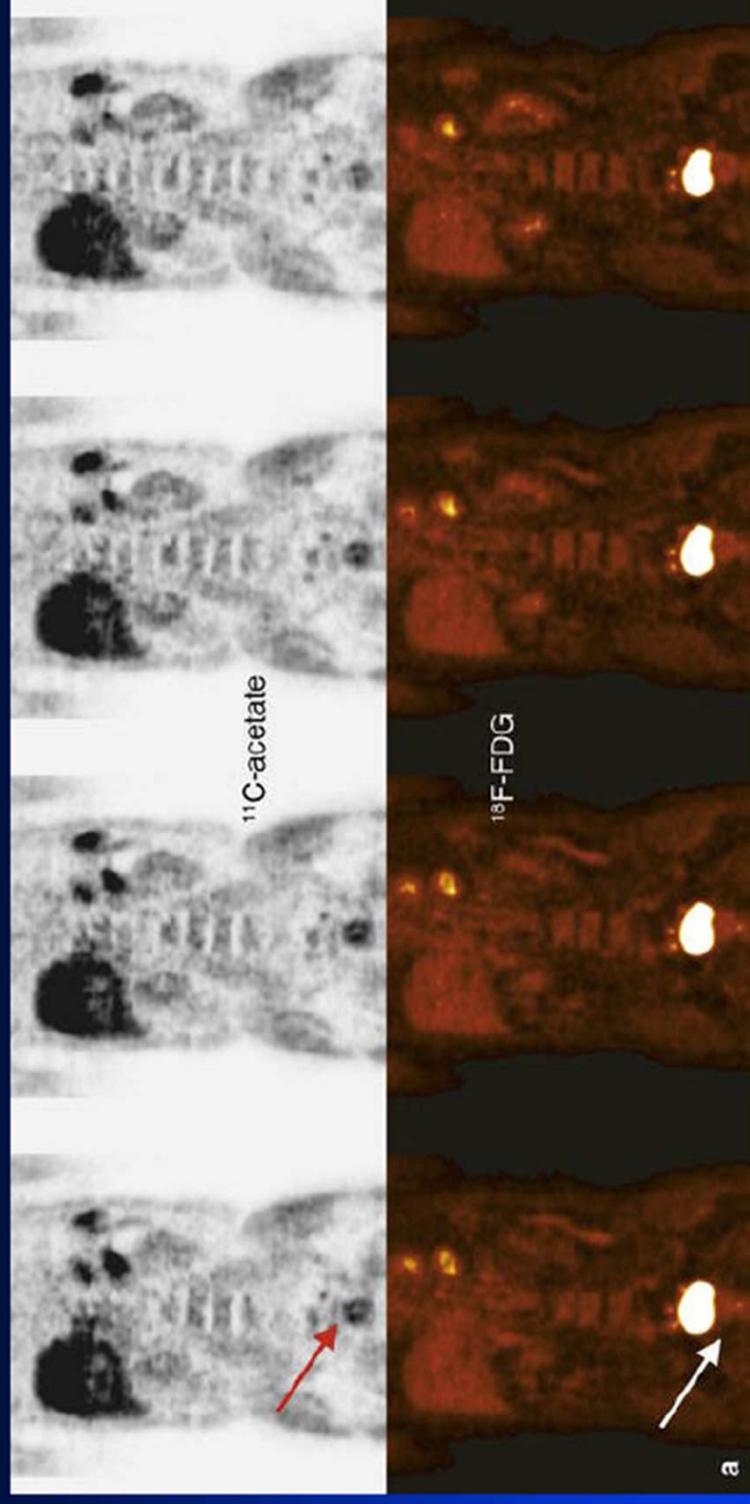


Local recurrence

Gleason score 10, PSA 3.7

Oyama et al. J Nucl Med 2003; 44:549-55

Prostate Cancer



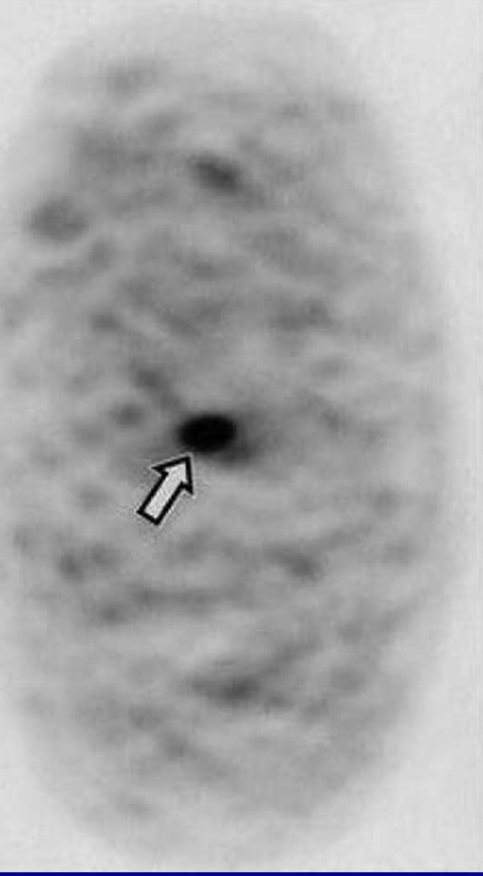
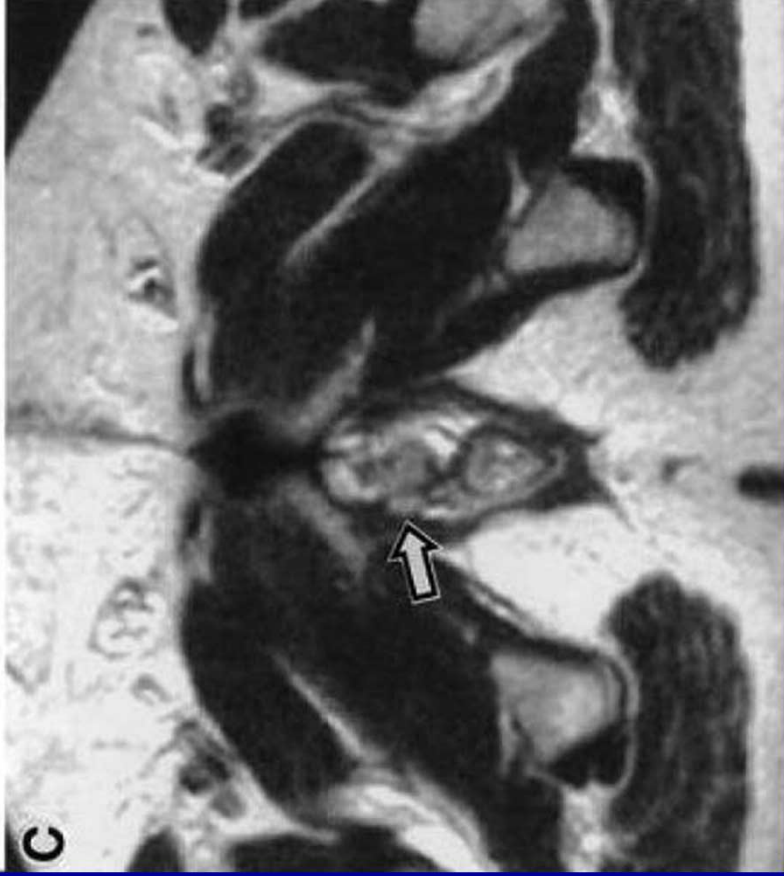
Local Recurrence

Ericke et al. Eur J Nucl Med Mol Imag 2003; 30:607-11

^{11}C -Acetate-PET

Potential Advantages of ^{11}C -Acetate over FDG

- Alternate metabolic pathway (lipid synthesis vs. glucose metabolism) may predominate in certain tumor types
- No renal excretion of ^{11}C -acetate
 - Absence of ureteral and bladder activity may allow improved visualization of tumor in the prostate bed and pelvic LNs
- ^{11}C -acetate typically localizes in low-grade malignant lesions

A**Choline****B****FDG****C****D**

Summary: Prostate Cancer

- ^{11}C -acetate-PET:
 - Useful for staging and restaging - detection of local recurrence
 - Positive correlation with PSA level (low detection rate with $\text{PSA} \leq 3 \text{ ng/mL}$)
 - No data in monitoring response to therapy or predicting prognosis
 - *Short half-life (20 min)*, role of ^{18}F -fluoroacetate?

^{11}C -Choline-PET & ^{18}F -Choline-PET

Metabolic Pathway of Choline

- Choline incorporated into cells via phosphorylcholine synthesis and is integrated into membrane phospholipids
 - P-31 MRS has shown elevated phosphatidylcholine levels in various tumors, including prostate cancer
- Upregulation of choline kinase in tumor cells



Response to therapy and prognostic value

Treatment Monitoring

Most prostate cancers are dependent on androgen for growth and metastasis.

Androgen ablation is one of the main treatment modalities in patients who do not qualify for radical treatment with curative intent and also for many patients with recurrent or metastatic disease.

In selected cases, chemotherapy is also used.

The current means of assessing the response to hormonal and chemotherapy are imprecise and inadequate because changes in tumor size are often slow to occur and alterations in PSA levels do not always correlate with clinical outcome.

Androgen blockade causes a decline in PSA to undetectable levels, but this does not necessarily reflect an improved survival in these patients.

Bone lesions are notoriously difficult to quantitate on conventional imaging studies, and bone scan may actually get worse, even when tumor has responded ie, (“flare” phenomenon). Should have baseline study or serial studies.

Treatment monitoring - PET contributions.

Changes in tumor metabolism precede changes in tumor volume and PSA.

The decline in tumor glucose uptake also was associated with a decrease in the proportion of tumor cells in the active cell cycle

Prostate Cancer

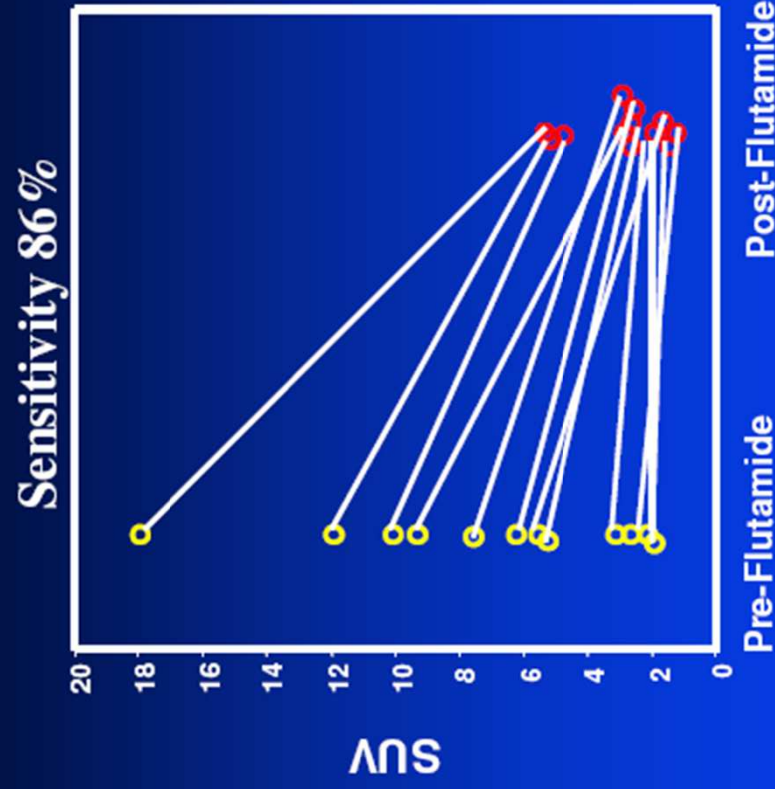
- Androgen deprivation therapy (chemical or castration surgery) is the only effective palliative therapy in patients with advanced disease
- Limited availability of *in vitro* assays for assessment of AR - hormonal therapy has been empirically based

Prostate Cancer

- $^{16}\beta$ -[^{18}F]fluoro- 5α -dihydrotestosterone (FDHT), androgen analogue
 - FDHT selectively binds to AR in prostate cancer
 - Rapid uptake and prolonged tumor retention
 - Binding of FDHT to AR is a receptor-mediated process
 - » FDHT uptake can be blocked by an androgen-receptor antagonist (flutamide; Eulexin®)

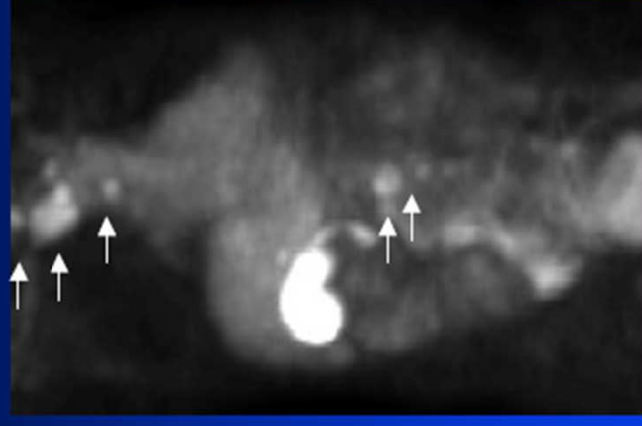
Dehdashti et al. Eur J Nucl Med Mol Imaging 2005; 32:344
Larson et al. J Nucl Med 2004; 45:366

Effect of Flutamide on FDHT Uptake in Primary and/or Metastatic Prostate Cancer



Pre-flutamide

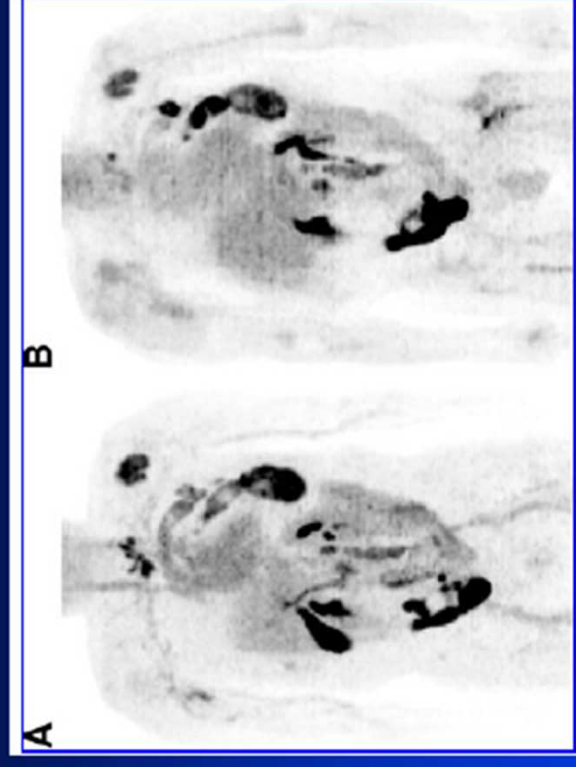
Post-flutamide



ANT

Prostate Cancer

- 7 patients with advanced prostate cancer
 - 46/59 lesions (sen 78%) detected by FDHT-PET
 - 57/89 lesions (sen 97%) detected by FDG-PET
 - Testosterone therapy resulted in diminished tumor uptake of FDHT



FDHT-PET

FDG-PET

Summary: Prostate Cancer

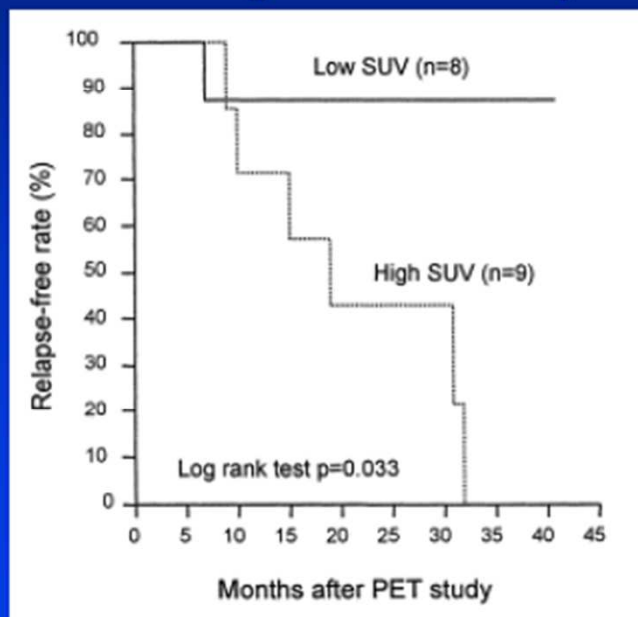
- **FDHT-PET:**
 - Specific to prostate cancer - imaging AR in prostate cancer is feasible
 - May be useful in selection of patients for hormonal therapy and monitoring response to such therapy

Prognosis

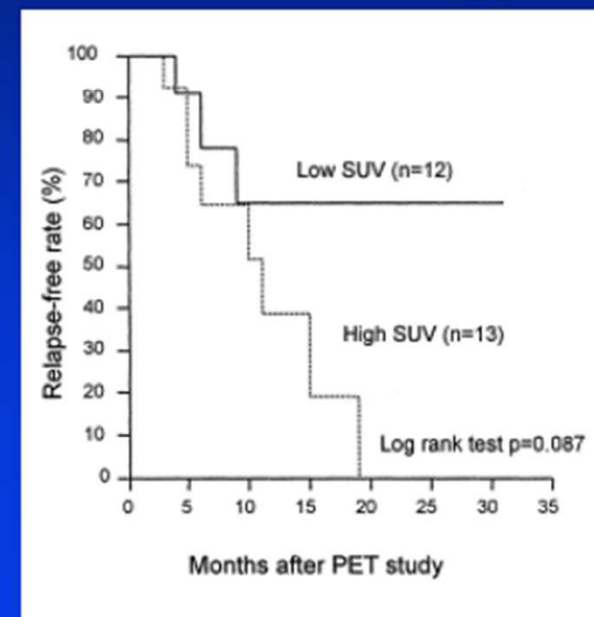
Prostate Cancer

- **FDG uptake - predictive of outcome to surgery or hormonal therapy**
 - Patients with high FDG uptake had a significantly poorer prognosis compared to those with low FDG uptake

Radical prostatectomy



Hormonal therapy



The prognostic value of FDG-PET in patients with bone metastases was addressed in a study by Morris and coworkers.

33 Of a total of 137 of the lesions (in 17 patients), 71% were noted on both PET and bone scan, whereas 23% were only seen on bone scan and 6% only on PET.

All but one of the lesions noted on bone scan alone remained stable, but all lesions detected only by FDG-PET showed further progression with positive bone scans developing at the site on follow-up.

This suggested that FDG-PET might reflect more accurately the tumor biology and aggressiveness of the disease.

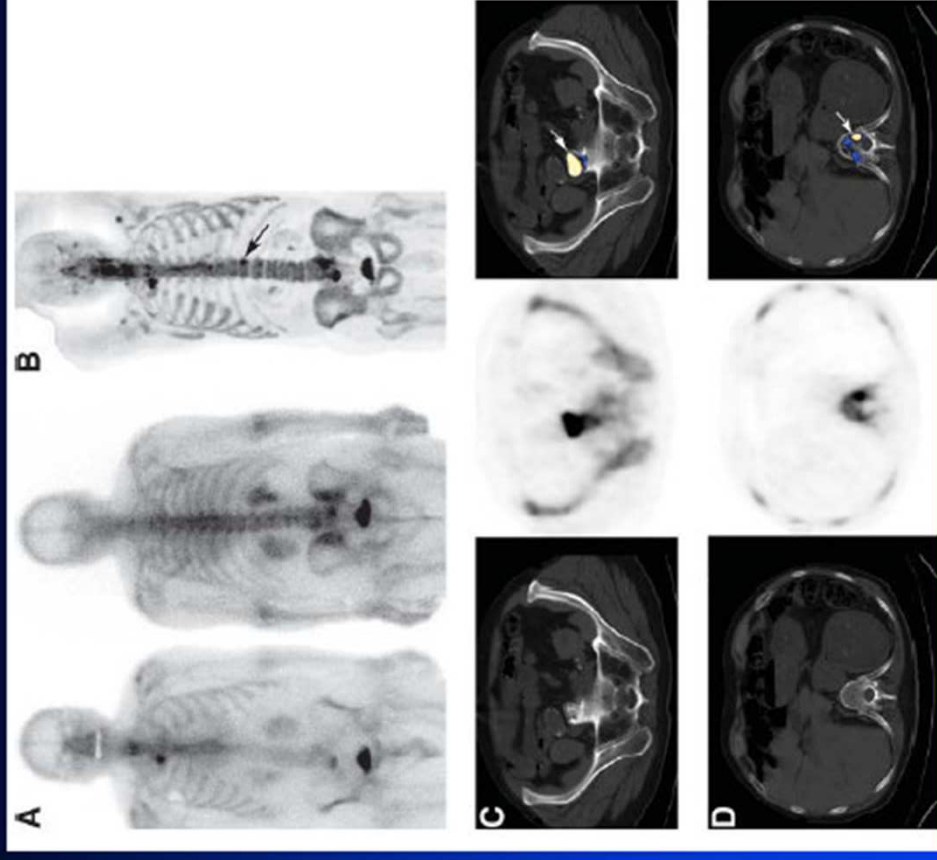
^{18}F -Fluoride-PET

Prostate Cancer

81 y/o patient with rising PSA.

BS & ^{18}F -PET showed increased uptake in sacrum and right sternoclavicular joint (sites of DJD on CT)

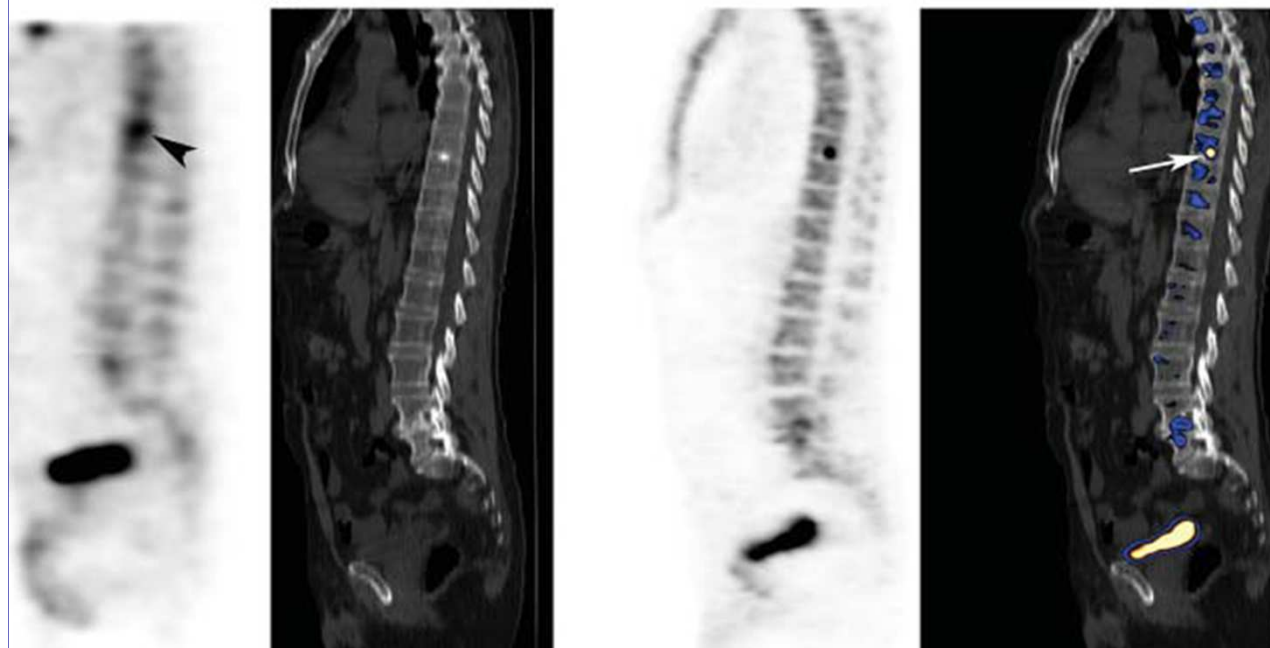
^{18}F -PET detected additional site of uptake in left aspect of T12

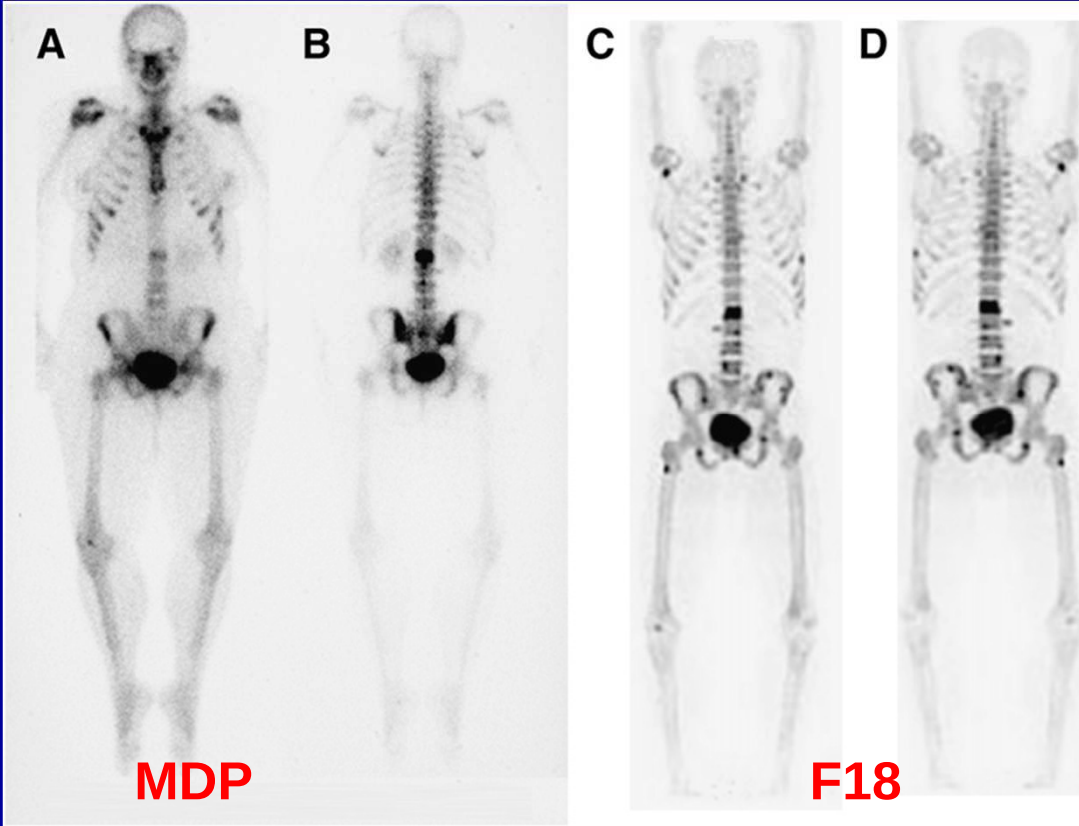




**F18 Fluoride pet
Bone scan**

C



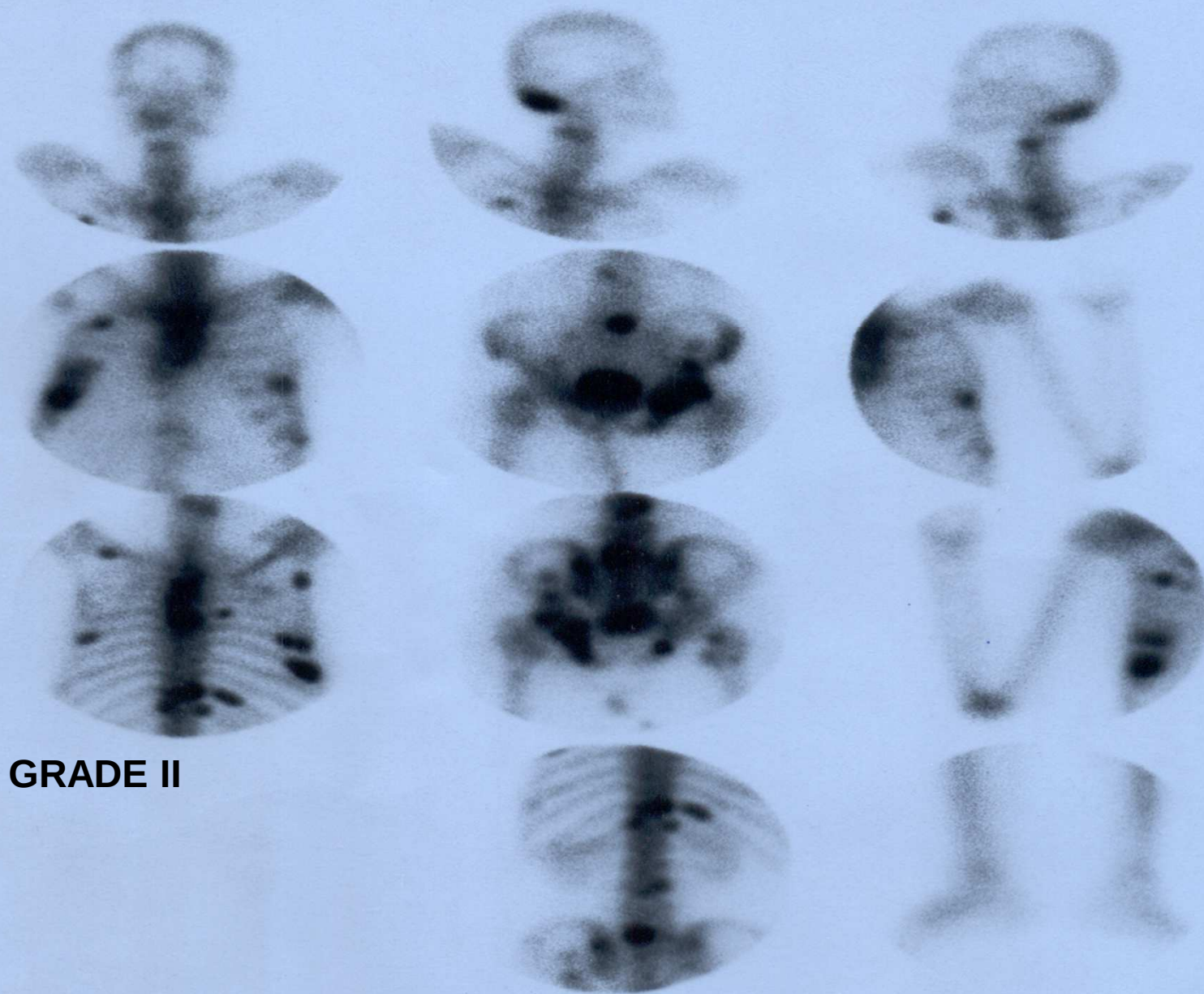


Grading - 2 year survival

94 %	Grade 1(1 to 6 metastatic foci,with each focus less than size of vertebral body)
74%	Grade 2(6 to 20 metastatic foci)
68%	Grade 3(more than 20 metastatic foci but not a superscan)
40%	Grade 4 (superscan or more than 75% involvement of the ribs, vertebra and pelvis)

- *Soloway etal*

Multiple Metastasis



GRADE II

GRADE III

SAINT, EVERETT

Bone Scan

02/24/94



Anterior



Posterior



Anterior

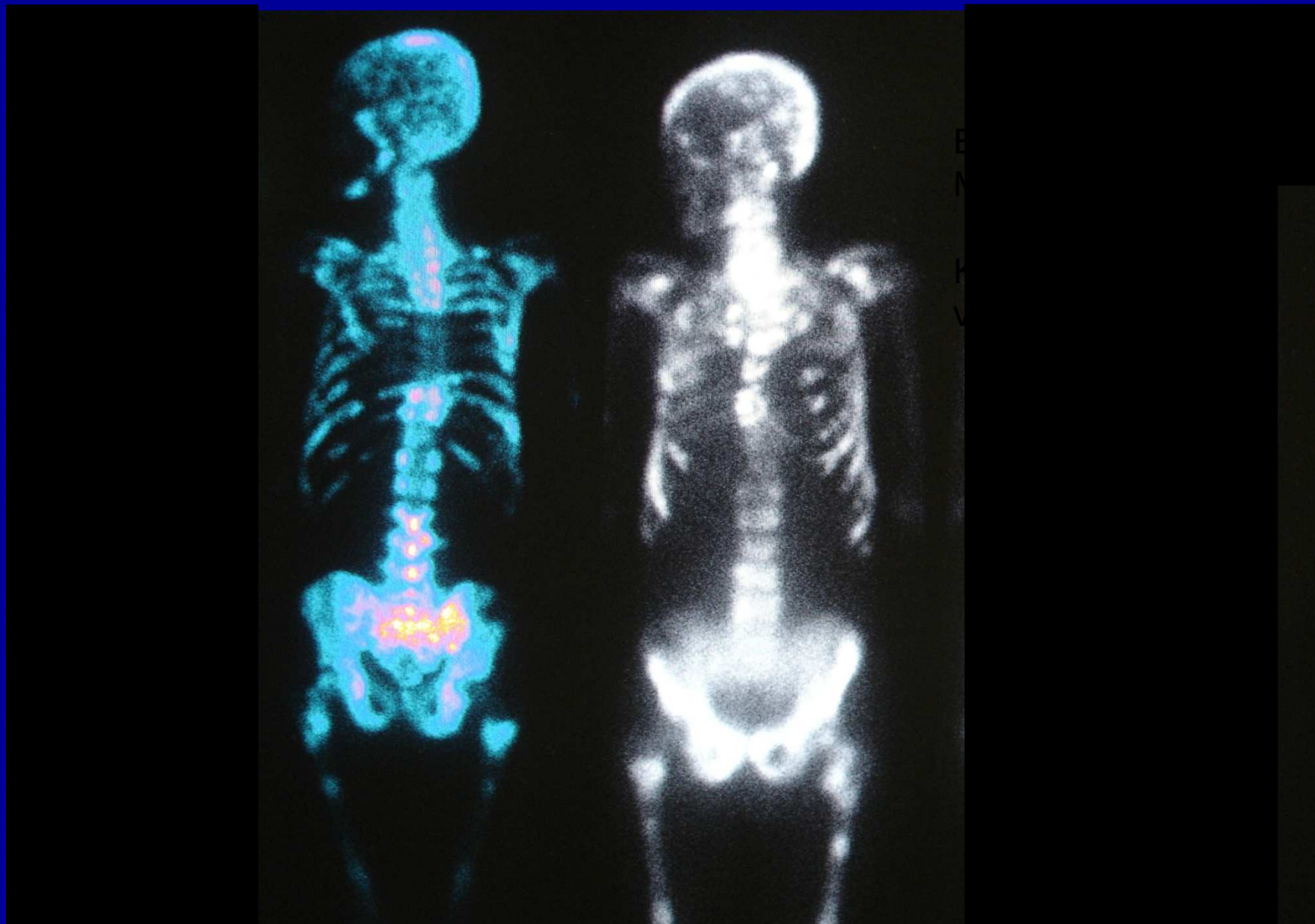


Posterior

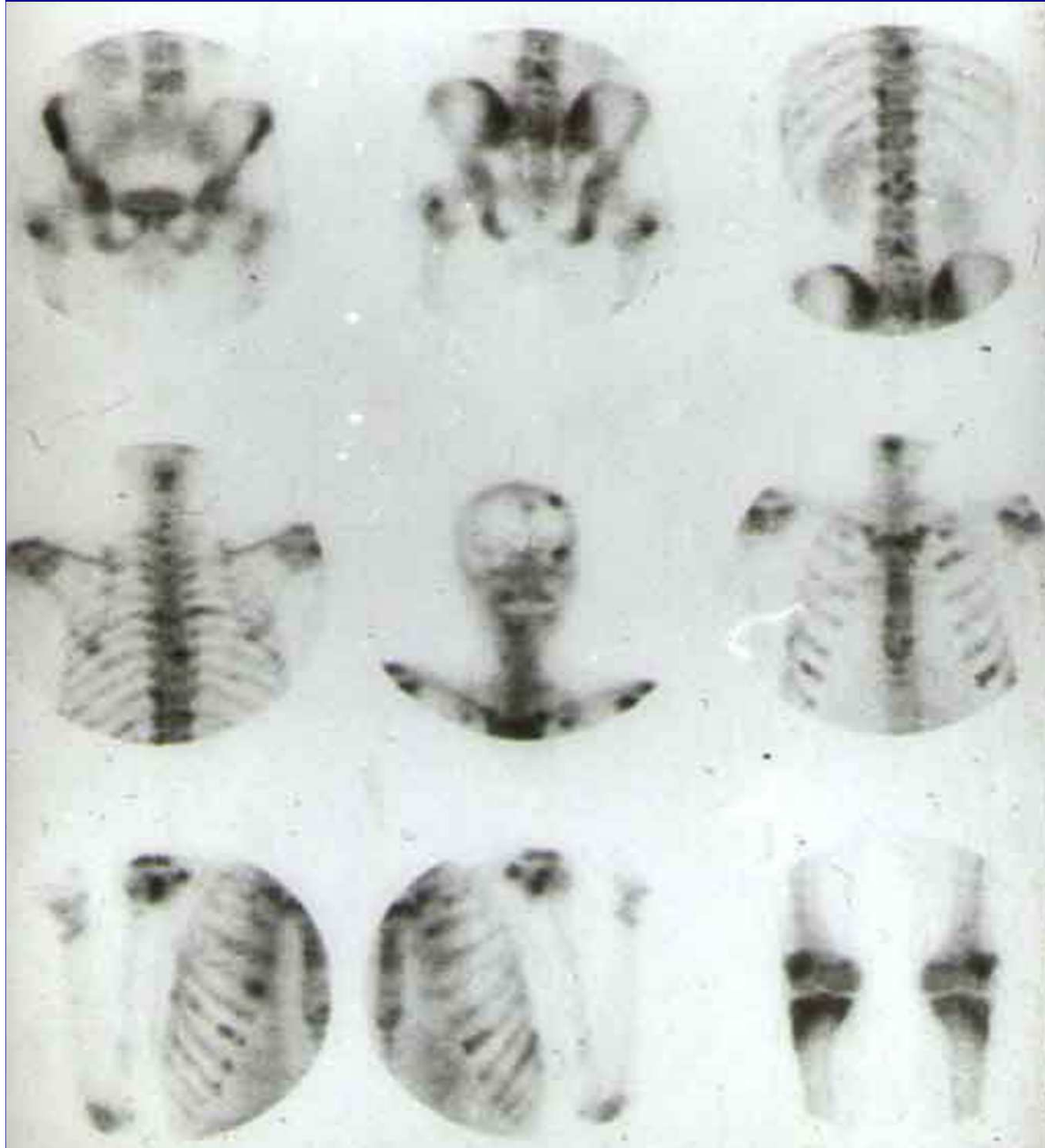
Multiple Metastasis

SUPERSCAN .

GRADE IV



MULTIPLE SKELETAL METASTASES

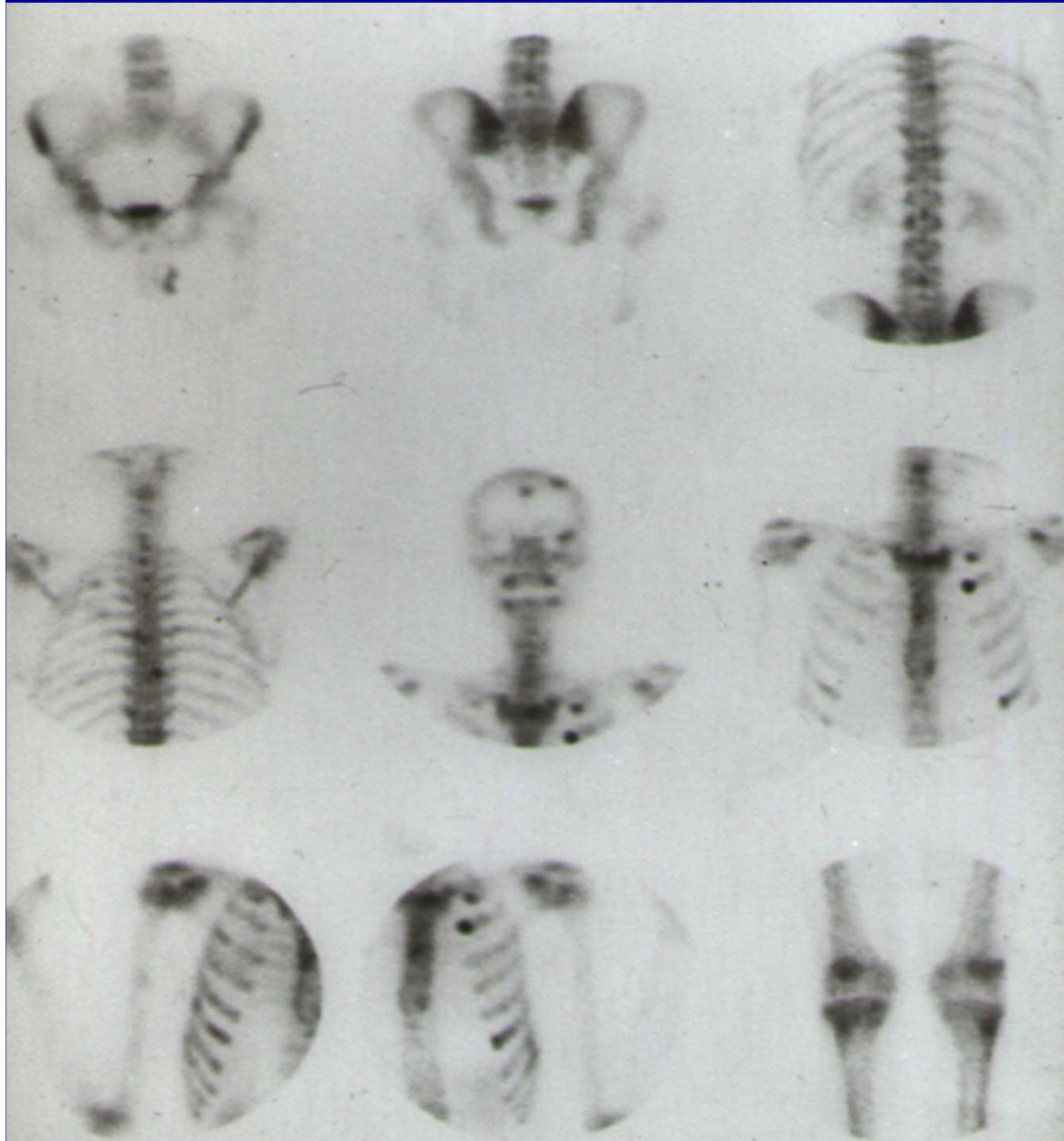


EASY TO DO

**WHOLE SKELETAL
SURVEY DONE**

**FREQUENTLY
USED TO MONITOR
RESPONSE TO
THERAPY**

MONITOR THE RESPONSE TO THERAPY



**COMPARED TO
PREVIOUS BONE
SCAN SOME
LESIONS HAVE
DISAPPEARED
AFTER FEW MONTHS
OF FLUTAMIDE
TREATMENT.**

Summary: Prostate Cancer

- ^{18}F -fluoride-PET
 - Superior to bone scintigraphy - greater bone uptake
 - Nonspecific - benign vs. malignant
 - PET/CT improves specificity
 - Availability and costs

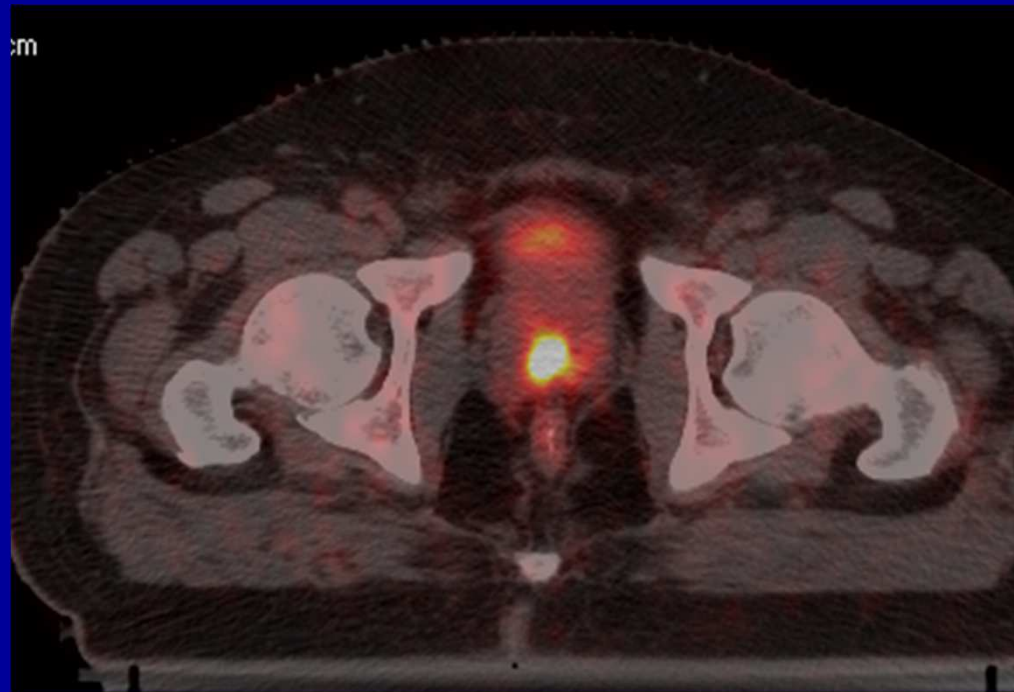
Oncologic PET Beyond FDG:

- **Driven by the goal of more individualized therapy**
 - More specifically targeted, less toxic
- **PET will play a role in choosing therapy**
 - Measure therapeutic targets
 - Identify resistance factors
- **Better response monitoring will be key**
 - Earlier measures of treatment efficacy
 - More specific measures of drug action
 - Quantitative surrogate endpoints for clinical trials

Carcinoma prostate (recurrent),
post chemotherapy surveillance.



Radiotherapy plan.



Management Strategies in Pain Syndromes Secondary to Bone Metastases

Analgesics	Pharmaceuticals	Interventions	Radiation
Nonnarcotic analgesics	Chemotherapy	Surgery	Single fraction RT
NSAIDS	Hormones	Inteventional Anesthetics	Multiple fraction RT
Narcotic analgesics	Steroids	Psychological support	Wide field RT
		Acupuncture	Unsealed source Radiopharmaceutical therapy

Radiation Therapy

Local RT

Hemibody RT

Whole body RT

Mechanism of action

Osteoclast inhibition

Reduction in number of viable tumor cells

Removal of tumor from bone enables osteoblastic repair.

Duration of palliation

Variable

In 25% of cases relief starts as early as 48 hours

In 80% of cases single dose of RT achieves pain relief within 4-6 weeks.

Radiotherapy contd..

Upper hemibody RT : 6 Gy single fraction

Lower Hemibody RT : 8Gy single fraction

Sequential hemibody RT : Allow 4-6 weeks gap

Side effects :

Nausea,
vomiting,
Bone marrow suppression

Brachytherapy

- * Iodine-125 seeds

- * Iridium

External RT to prostate bed

- * IMRT or IGRT

Indications for Radiopharmaceutical Therapy

Patient has cancer metastasis to bone

Positive bone scan

Bone pain

Recurrent pain in a radiotherapy field.

Multiple sites of pain

Pain in more than one site requiring radiotherapy in most painful site.

Pain in more than one site requiring opiate analgesia.

Radiopharmaceuticals for Palliative Therapy

Radionuclide	Pharmaceutical	Half life (days)	Max Beta MeV	Mean beta E- MeV	Max range in tissue(mm)	Gamma Photon KeV(%)
Sr 89	Chloride	50.5	1.46	0.583	6.7	—
P 32	Orthophosphate	14.3	1.71	0.695	8	—
Re 186	HEDP	3.8	1.07	0.349	4.7	137(9)
Sm 153	EDTMP	1.95	0.8	0.224	3.4	103(28)
Sn 117m	DTPA	13.6	(con elect)	0.129 0.153	0.3	159(86)

Abbr-HEDP,hydroxyethylidene diphosphonate;EDTMP,ethylenediaminetetramethylene phosphonate ;DTPA ,diethylenetriaminepentacetic acid

Radiopharmaceutical therapy.

Since multiple sites of osseous metastases are common and some patients have multifocal bone pain, systemic targeted treatment of the skeletal metastatic sites offers the potential of pain relief with minimal side effects. Radiopharmaceuticals developed for the treatment of painful bone metastases use the following radionuclides: ^{32}P , ^{89}Sr , ^{186}Re , ^{188}Re , ^{153}Sm , and ^{177}Lu . All agents have advantages and side effects. The agents differ in terms of efficacy; duration of pain palliation; tumoricidal effects; ability to repeat treatments; toxicity, and expense. Most studies with these agents have been conducted in prostate and breast cancer patients.

“Ideal” Radiopharmaceutical for palliative therapy

Selective uptake at metastatic sites relative to normal bone

Rapid clearance from soft tissue and normal bone.

Simple production process

Stable and easy to transport

Cost effective and ready availability

$E_{\text{max}} > 0.8 \text{ MeV}$ and $< 2.0 \text{ MeV}$

Distribution should be predicted from $^{99\text{m}}\text{Tc}$ MDP bone images

Contraindications to Radiopharmaceutical Therapy

Platelet count < 100000(relative)

Platelet count < 60000(absolute)

White count < $2.5 \times 10^6/l$

Rapidly falling blood counts

Evidence of disseminated intra vascular coagulopathy

Impending pathological fracture

Impending cord compression

Less than two months projected survival

Prior to myelosuppressive chemotherapy

Extensive soft tissue metastases

MECHANISM OF ACTION

The sources of radiation within bone differ with the radiopharmaceutical used: The metallic chelated radiotracers tend to chemically adsorb to the trabecular surface, whereas ^{32}P and ^{89}Sr (as the chloride) distribute more widely throughout bone.

Due to the heterogeneity of radiopharmaceutical uptake, tumor and marrow distribution, there is variation in dosimetry

P-32

^{32}P is a reactor-produced, pure β -emitting radionuclide

Physical half-life of 14.3 d.

The maximum and mean β -particle energies are 1.71 and 0.695 MeV, respectively, with the mean and maximum particle range in tissue of 3 and 8 mm, respectively.

Response rate

The response rates were between 59% and 93% for prostate cancer and between 52% and 94% for breast cancer, with overall response rates of 77% and 84%.

Pain palliation occurs within 14 days, with a range of 2 days to 4 wk.

Sr - 89

Strontium is an element that behaves biologically like calcium.

It localizes in bone primarily in areas of osteoblastic activity.

^{89}Sr has a physical half-life of 50.5 d and emits a β -particle with a maximum energy of 1.46 MeV and an average soft-tissue range of 2.4 mm.

The usual therapeutic dose is 148 MBq (4 mCi).

Transient increased bone pain (painful flare) may occur in the first 2–3 d after treatment. This is usually mild, self-limited, and controlled with analgesics.

A flare usually heralds a good treatment response.

Patients can be retreated after 90 days, though multiple therapies may lead to greater marrow toxicity.

Although the agent is useful for osseous pain palliation, there is no survival benefit, even when a dose of 399.6 MBq (10.8 mCi) is used .

However, in patients with androgen-independent prostate cancer and severe bone pain , combined treatment with ^{89}Sr and doxorubicin resulted in a mean survival of 28 mo compared with 17 mo for patients treated with doxorubicin alone.

The use of ^{89}Sr can help reduce the lifetime health-care costs by decreasing both the need for radiotherapy and the need for narcotics and hospitalization.

Samarium 153- EDTMP

^{153}Sm , a nuclide with a physical half-life of 1.9 d, decays by β -emission.

The β -particle has a maximum energy of 0.81 MeV, a mean energy of 0.23 MeV, and an average soft-tissue range of 0.6 mm.

The β -ray is accompanied by a 103-keV X-ray, which is 28% abundant.

^{153}Sm is complexed with ethylenediaminetetramethylene phosphonic acid to form $^{153}\text{Sm-EDTMP}$.

The distribution of ^{153}Sm -EDTMP is identical to that of bone-seeking radiopharmaceuticals such as $^{99\text{m}}\text{Tc}$ -MDP

^{153}Sm -EDTMP is usually administered at a dose of 37 MBq/kg (1 mCi/kg). An initial dose-escalation study demonstrated dose-limiting myelotoxicity, with a maximum tolerated dose of 37 MBq/kg (1 mCi/kg)

Platelet nadir occurs between days 16 and 45 (median, 28 d).

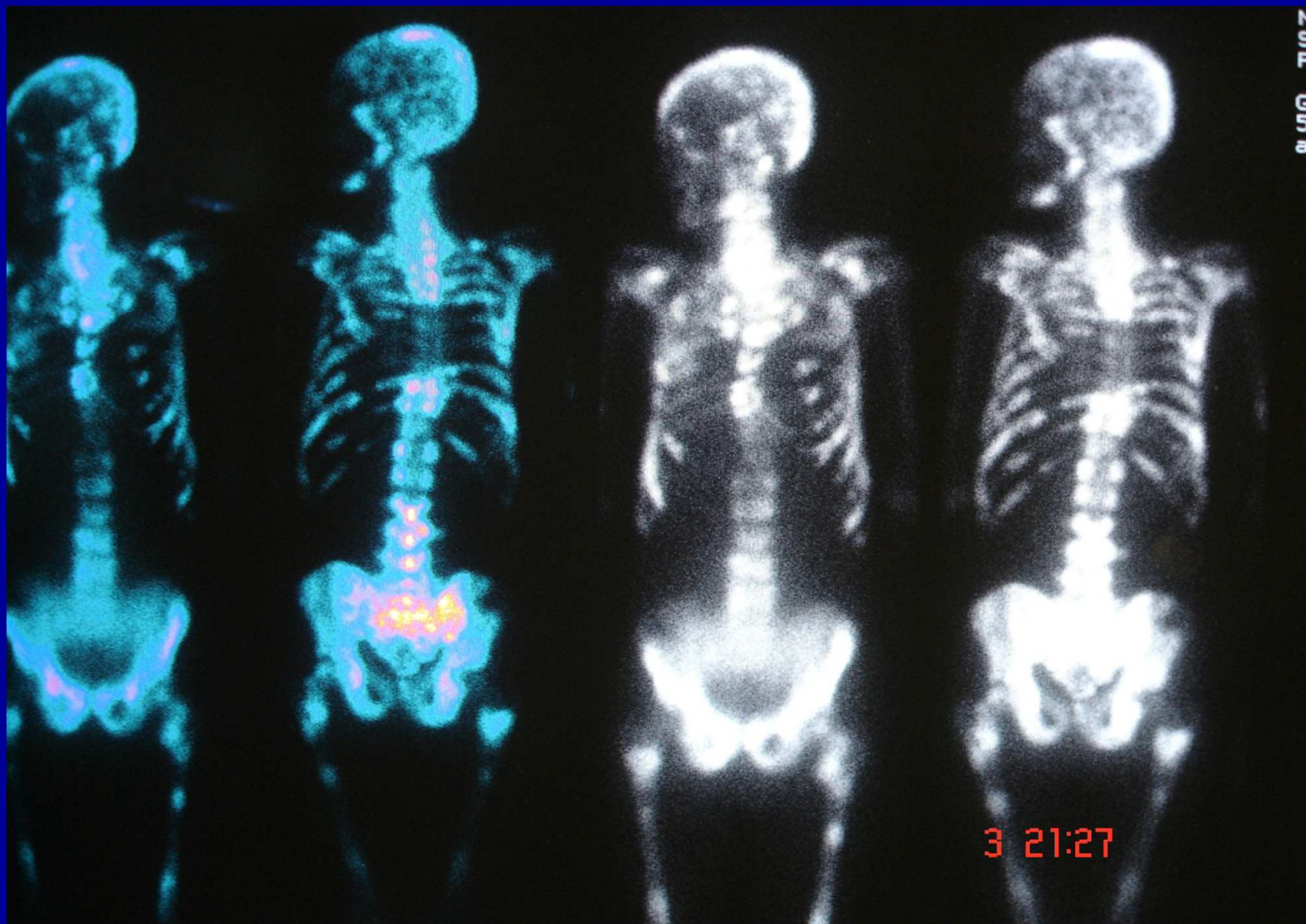
Pain palliation occurs in 62%–74% of patients

Rhenium – 186 HEDP

^{186}Re -Labeled 1,1-hydroxyethylidene diphosphonate (^{186}Re -HEDP/ ^{186}Re -(Sn)HEDP or etidronate) and ^{188}Re are investigational radiopharmaceuticals for bone pain palliation.

^{186}Re has a physical half-life of 3.7 d and emits a β -particle with a maximum energy of 1.07 MeV, a mean energy of 0.349 MeV, and an average soft-tissue range of 1.1 mm.

Sam-153 Post therapy scan shows excellent accumulation of the isotope.



^{117m}Sn –DTPA.

The chelate ^{117m}Sn -diethylenetriaminepentaacetic acid (^{117m}Sn -DTPA) is an experimental radiopharmaceutical undergoing evaluation for treatment of painful bone metastases.

^{117m}Sn , a nuclide with a physical half-life of 13.6 d, decays by isomeric transition with emission of the dominant γ -ray at 156 keV. The γ -ray undergoes conversion and it is the conversion electrons that have the therapeutic potential.

The energetic conversion electrons have a very short range in soft tissue (0.2–0.3 mm),

^{117m}Sn -DTPA contd...

In reported studies, the pain palliation rate is approximately 75%.

The onset of pain relief is also much earlier than that with the other agents.

At doses of >444 MBq (>12 mCi) (per 70 kg body weight), pain palliation has been noted as early as <1 wk after treatment

Thank you