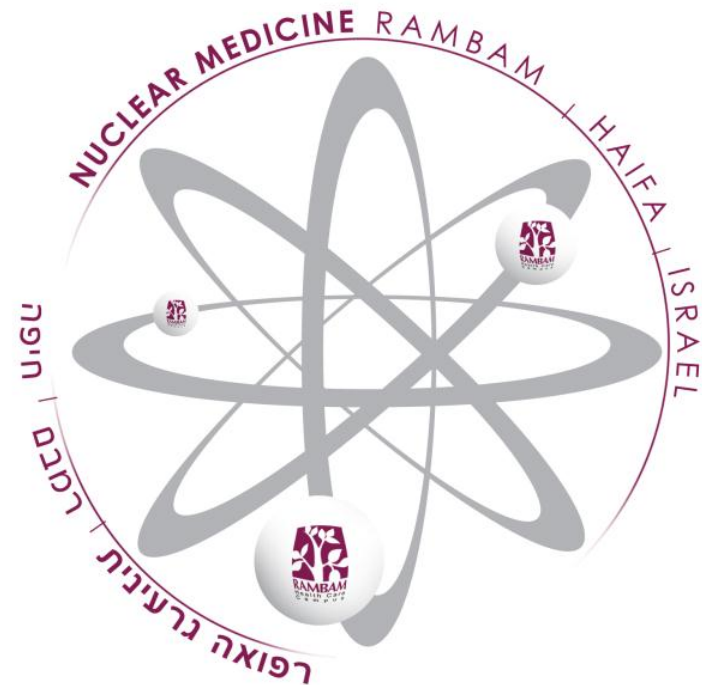


FDG-PET/CT in Breast Cancer

IAEA PET/CT Workshop: Improving Patient Care
Midrand, November 2010

Ora Israel, MD

Department of Nuclear Medicine
Rambam Health Care Campus
Technion, Haifa, Israel



Outline

- Clinical overview
- The role of FDG-PET/CT for:
 - diagnosis of breast ca (FDG-avid incidentaloma)
 - staging of breast ca
 - diagnosis of loco-regional recurrence
 - diagnosis of occult recurrence
 - prediction & monitoring response to treatment
- Diagnosis of bone metastases
 - FDG vs. Fluoride imaging of bone mets
- Limitations of FDG
- Guidelines for FDG Imaging of Breast Cancer



Breast Cancer - Introduction

- Breast cancer - most common malignancy in women (1/8) in the western world
- 2007: ~180,000 newly diagnosed; >40,000 death (15% female cancer deaths)
- Role of FDG-PET/CT:
 - Diagnosis: limited value , poor performance in small size, non invasive, slow-growing tumors
 - Preoperative staging: in high risk patients for assessment of distant metastatic spread
 - Recurrence: to identify distant sites of disease
 - Prognostic indicator



FDG-PET/CT for Diagnosis of Breast Cancer

- Sensitivity 88%, specificity 80%
- FN rate 12%

FDG-PET/CT: not routine for diagnosis of breast cancer
(low spatial resolution, suboptimal performance in small tumors)

High FDG-avidity: infiltrating ductal

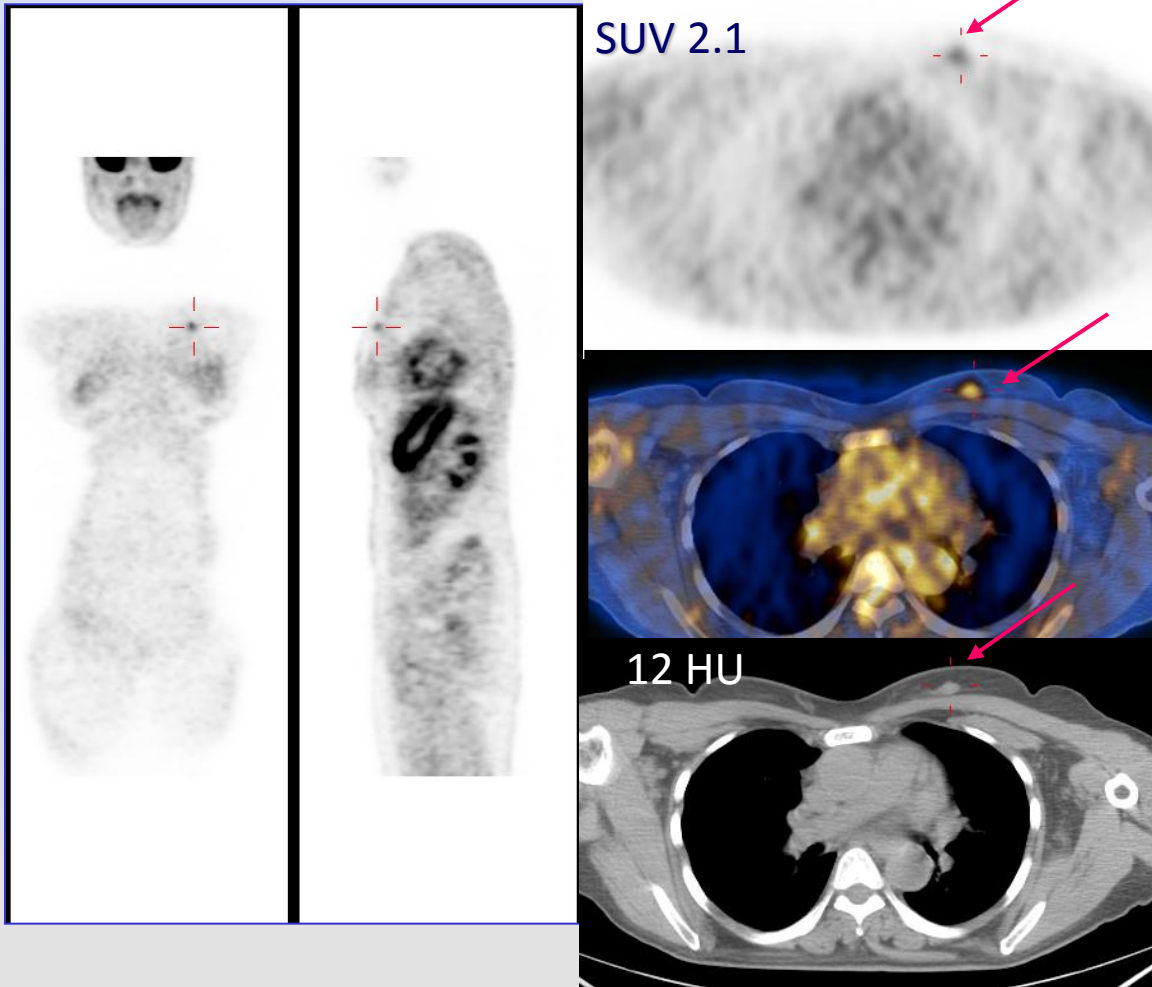
Dedicated FDG Imaging

PEM (positron emission mammography)

- Better in smaller primary tumors
- Limited: posterior located tumors



Breast FDG-avid Incidentaloma - Unexpected Breast Cancer



F, 60y, Thyroid Ca

Focal FDG uptake in Lt. hemithorax, localized by PET/CT to Lt. breast

Lt. invasive ductal breast cancer

Breast FDG-avid Incidentaloma

(Litmanovitch et al, EJNMMI 2009)

- Whole-body PET/CT FDG-avid incidentaloma in 1-3% of cancer patients
- Most common sites: GIT, thyroid gland, lung

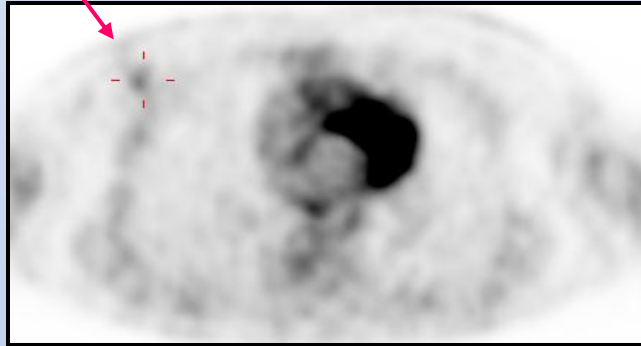
FDG-avid breast incidentaloma

- 33/4,038 female patients – incidence: 0.82%
- 43% - malignant (primary breast ca, lymphoma, metastases)
- 57% - benign (e.g. fibroadenoma , ductal hyperplasia, mastitis)
- SUVmax (malignant vs. benign): 3.54 ± 2.39 vs. 1.83 ± 1.1 , $p < 0.03$



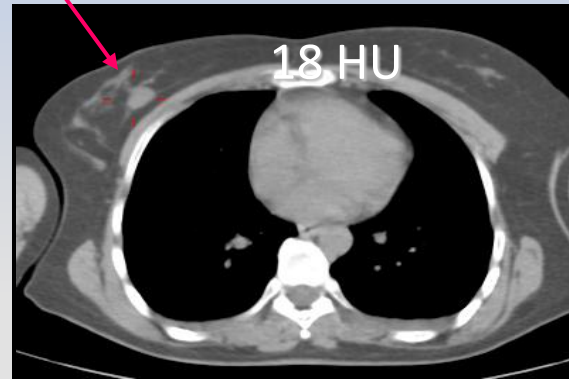
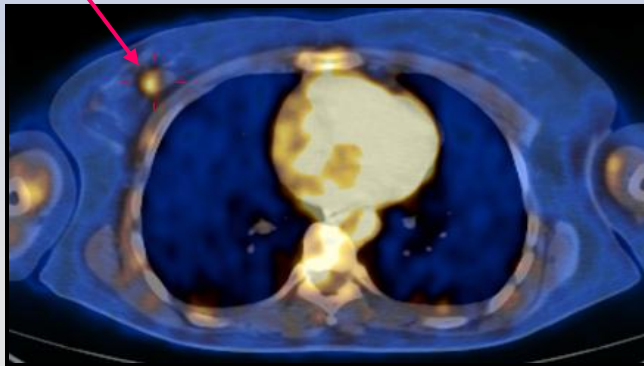
Breast FDG-avid Incidentaloma – Benign Lesion

SUV_{max} 0.6



F, 43 y, Ca of Parotis

Fibroadenoma of rt. breast

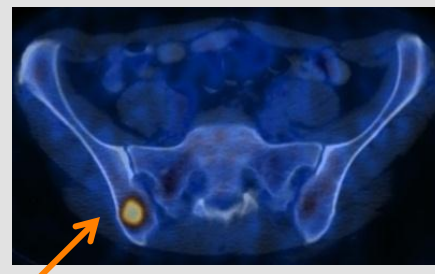
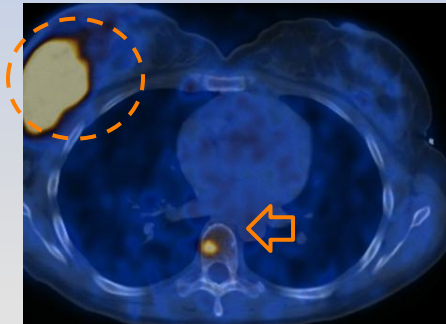
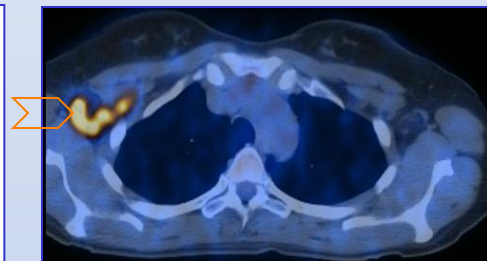


TNM Staging of Breast Cancer

- T: Primary tumor:
 - T0 : no evidence of primary tumor
 - Tis: primary tumor *in situ*
 - T1-T3: tumor size <2 cm, 2 - 5 cm, >5 cm
 - T4: any size & extension to chest wall, skin
- N: Nodal status (LN) :
 - Nx: cannot be assessed
 - N0: no regional LN metastasis
 - N1: ipsilateral axillary LN (s)
 - N2: ipsilateral fixed axillary or internal mammary LN (s)
 - N3: infraclavicular, internal mammary, axillary, supraclavicular
- M: Metastases (M):
 - M0 (no distant metastases)
 - M1 (distant metastases)



Locally Advanced Breast Cancer, Staging



F, 35y, newly diagnosed invasive duct rt. breast ca with vascular invasion.

Palpation: enlarged axillary LNs

Bone scan: equivocal in spine and pelvis

- **rt. breast cancer**
- **mets in rt. axilla & rt. internal mammary LNs**
- **mets. in bone: thoracic vertebra & rt. ilium**

FDG-PET/CT Staging of Breast Cancer

T-staging

- size & histology dependent
- High: invasive infiltrating ductal breast ca: sens 90%, spec 93%
- Tumor size-related sens: 25% for <1 cm, 84% 2cm, 92% >2cm
- FDG is predictive of likelihood & pattern of Rx failure

Limitations:

- Small tumors
- Low-grade tumors



FDG-PET/CT Staging of Breast Cancer

N-staging

- CT criteria: shape, size, density, contrast enhancement
~ 20% normal size – malignant & ~40% enlarged – benign
- FDG-PET/CT : number of LN (single/multiple) & localization

Better performance in:

- high-level axillary, supraclavicular & internal mammary LN
(changes in planned RxT fields or surgical approach)
- Axillary vs. Internal mammary LN:
sens 60%, spec 80-100% vs. sens 85%, spec 90%

Limitations:

- inability to detect small LN & micromets (sentinel node)
- False positive: FDG+ muscle, brown fat ; non-malignant LN



FDG-PET/CT Staging of Breast Cancer

M-staging

- A *true* whole body technique
- Metabolic changes can precede anatomic changes
- Better than conventional modalities to detect occult mets

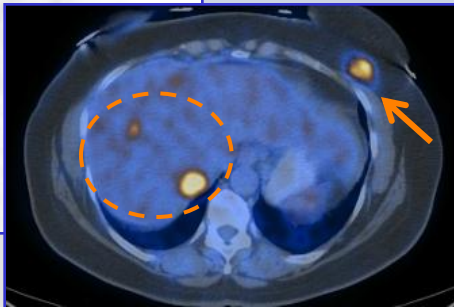
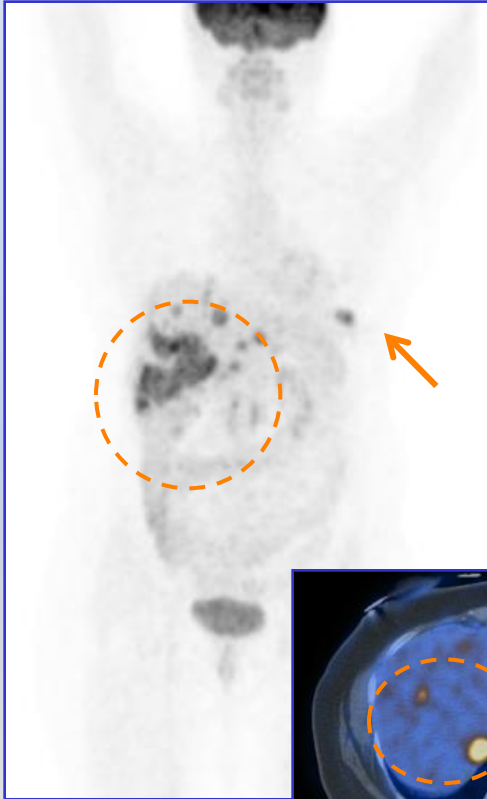
Radical changes in Rx approach

- Distant mets: FDG-PET/CT vs. conventional imaging
sens 100%, spec 98%, NPV > 90% vs. sens 60%, spec 83%
- High sensitivity: mets in bone, pleura, mediastinum, abdomen
- Most frequent site of occult mets: skeleton
- FP/TP higher in low-stage breast ca



FDG-PET/CT in Breast Ca

Diagnosis of Distant Mets



F, 65y, newly diagnosed invasive duct lt. breast ca

Diffuse abdominal pain

US & CT: fatty liver infiltration

FDG uptake in lt. breast tumor

Multiple FDG-avid liver mets.

- > 50% pts with breast ca develop liver mets, usually late, after other organs
- FDG-PET/CT can improve characterization of equivocal hepatic lesions on CT

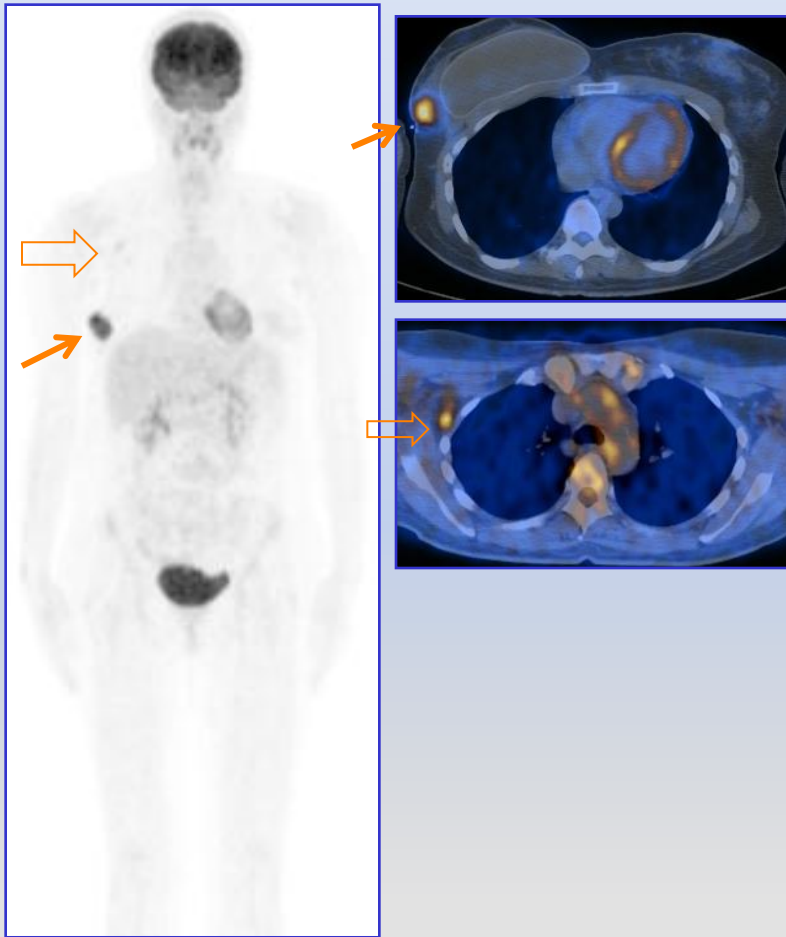
FDG-PET/CT in Breast Cancer

Loco-regional Recurrence

- Local or regional recurrence occurs in 7-30% of patients with breast cancer.
- Most frequent site: breast, chest wall
- Multiple therapeutic options (related to distribution & burden of disease): surgery, chemo, radiation, hormonal
- FDG-PET/CT: sens 85%, spec 98%, accuracy 97%
- FDG-PET/CT: affects management in up to 44% pts
Mainly: restaging prior to aggressive local therapy



FDG-PET/CT in Recurrent Breast Ca



F, 44y, invasive duct rt. breast ca, s/a mastectomy & breast reconstruction, non-compliant to chemotherapy.

New mass in rt. breast on palpation.
Biopsy: recurrent breast ca

FDG-avid mass in rt. breast,
adjacent to implant.

FDG uptake in 12 mm rt. axillary LN.

- **Recurrent rt. breast ca**
- **Rt. axillary LN met**

Loco-regional Recurrence



FDG-PET/CT in Suspected Occult Recurrent Breast Ca

- Early diagnosis and accurate restaging (localization and assessment of extent): important for further patient management, mainly defining the most appropriate therapeutic strategy.
- In asymptomatic patients with breast cancer FDG-PET has an accuracy of 87-90% vs. 50-78% for CT for the detection of metastases.
- Median sensitivity 93% (patient), 92% (site)
- Median specificity 82% (patient), 89% (site)

Suarez et al. Q J Nucl Med 2002; 46:113-121

Gallowich et al. Invest Radiology 2003; 38:250-256

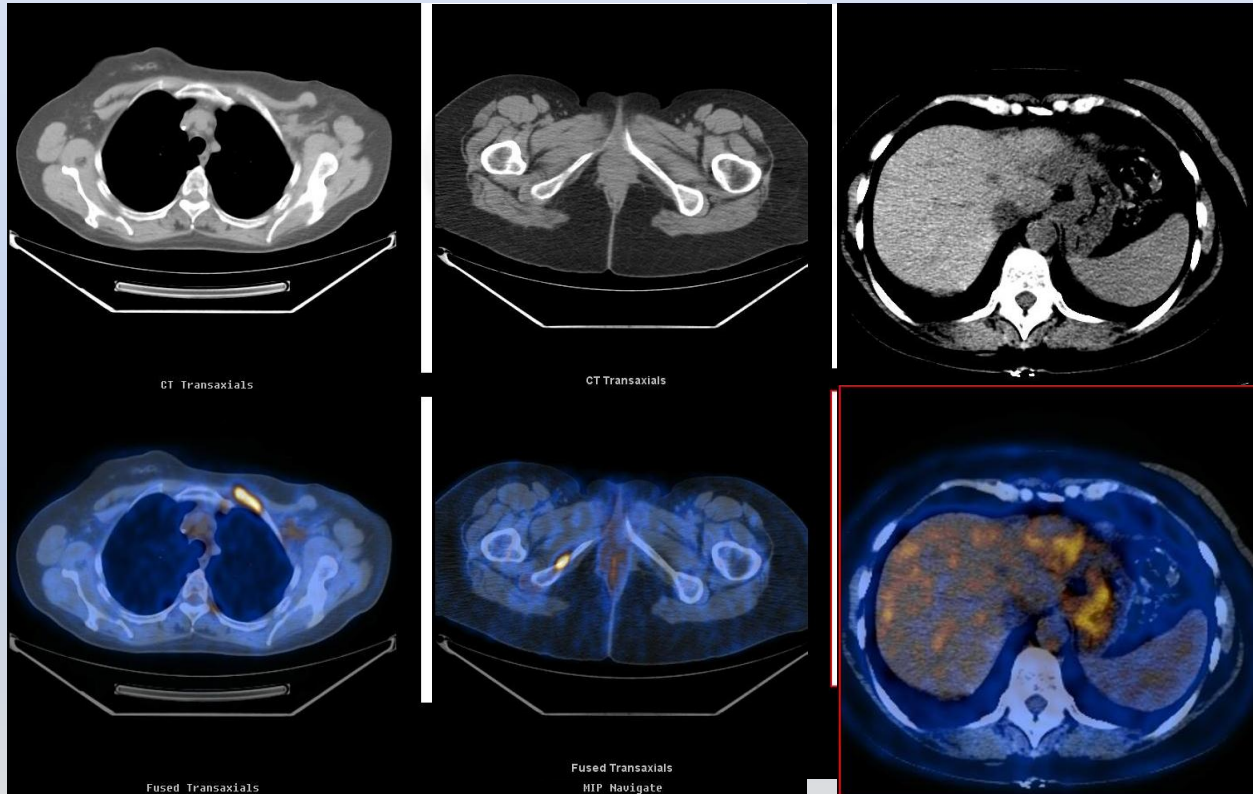
Isasi et al. Breast Cancer Res Treat 2005; 90:105-11

Tatsumi et al. EJNMMI 2006; 33:254-262



FDG-PET/CT in Breast Cancer

Rising Serum Markers - Occult Recurrence?



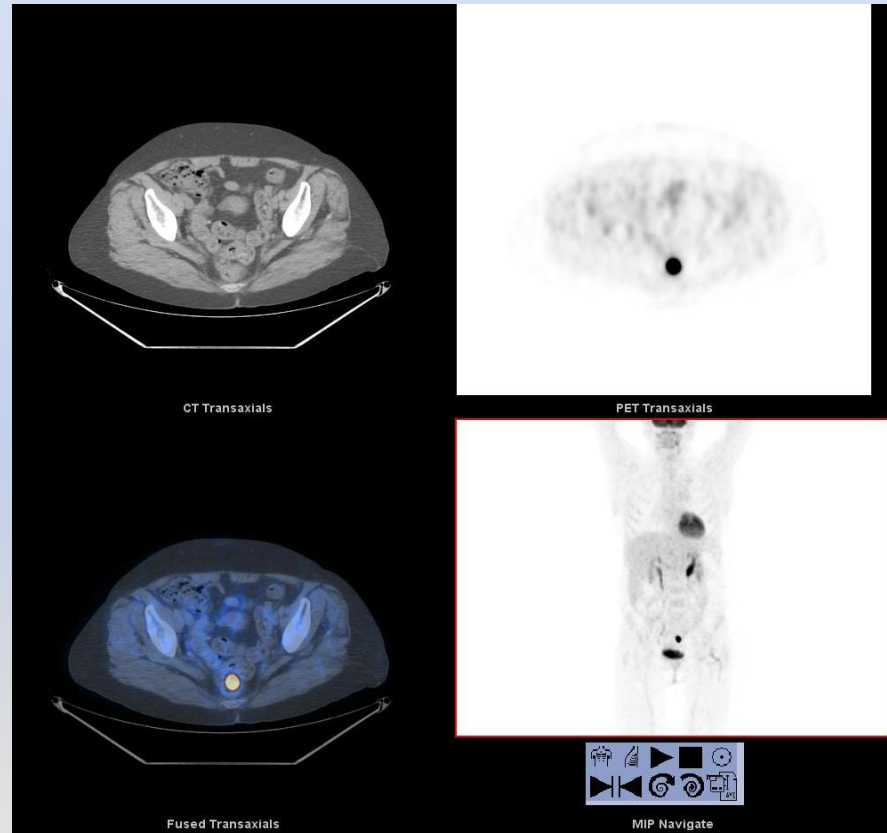
F, 43y, breast ca with liver mets, s/a chemo
Rising Ca 15-3 & hypodense liver lesion on CT

Bone mets in Lt. 2nd rib and rt. ischium
No FDG uptake in liver lesion – fibrosis



FDG-PET/CT in Breast Cancer , Rising Serum Markers Occult Recurrence? The Significance of GIT Incidentaloma

Israel et al, JNM 2006



F, 62y, Breast ca, s/a surgery 2 yrs
Rising CEA

Intense focus of increased FDG uptake in the rectum.
Biopsy: adenocarcinoma



FDG-PET/CT in Breast Ca & Rising Serum Markers

Radan et al, Cancer 2006

- In asymptomatic patients with breast cancer FDG-PET has an accuracy of 87-90% vs. 50-78% for CT for the detection of metastases,
- Sensitivity 93% , Specificity 82%
- False positive: uptake in inflammatory processes
- False-negative: small subcentimeter lesions
- Uptake in malignancy other than breast cancer

- Sensitivity 90%
- Change of management: 51% patients
 - Started chemo- or radiotherapy
 - Change in treatment modality (more extensive disease)
 - PET/CT guided biopsy



Breast Ca - Monitoring response to treatment

- Therapeutic strategies: rapid progress over past decade
- Breast-conserving surgery
- Primary systemic therapy (chemo prior to surgery)

Early detection of non-responders to primary chemo spares further ineffective treatment

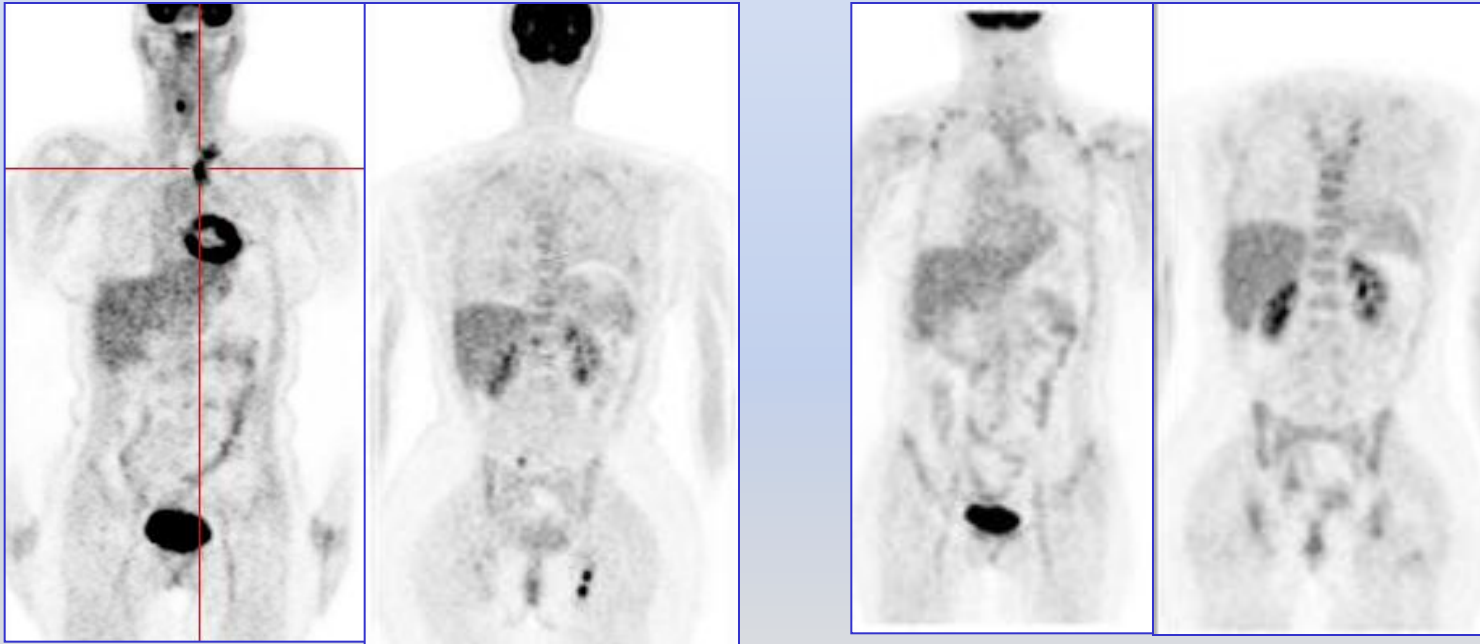
- Less adverse effects
- Earlier administration of more effective treatment
- Lower costs

Degree of response – important prognostic info (pathologic CR is associated with longer survival)



FDG-PET/CT in Breast Ca

Monitoring response to treatment



Breast Ca with nodal mets - Good response to treatment

- Baseline: FDG + cervical, mediastinal, pelvic & inguinal LN mets.
- After treatment: FDG- study – all abnormal foci have disappeared

FDG-PET/CT in Breast Ca

Monitoring response to treatment

- FDG-PET/CT: more accurate than anatomic imaging for predicting outcome of breast ca after treatment
- Specific response assessment criteria still need to be defined & validated
- Low FDG uptake preRx (=low metabolic rate) not likely to achieve histopathologic response
- Stratification with single postRx FDG study:
survival FDG (-) 24 mo vs. FDG (+) 10 mo ($p < 0.001$)

Cachin et al, JCO, 2006



Serial FDG-PET/CT in Breast Ca

Monitoring Response to Neoadjuvant/Primary Systemic Rx

- Early response with FDG preRx & after 2 cy:
 Δ SUV 40%: responders/non-response: sens 77%, spec 80%

Duch et al, EJNMMI 2009

- Serial FDG-PET/CT: predictive of response (change in SUV)
 - PPV and NPV: FDG 93% , 84% vs. CT: 85%, 59%
 - Prognostic accuracy: 90% for determining response
- Early/mid-treatment study – predictive of microscopic CR
Changes in FDG uptake precede morphologic changes
- Early marker for resistance to treatment



FDG-PET/CT in Bone Metastases

- Bone mets in breast cancer: osteolytic and osteoblastic
- High detectability rate for bone metastases
- Sclerotic vs Lytic
 - Variable FDG-avidity (lytic & sclerotic mets)
 - Survival is lower with lytic disease
- Progressive Disease & Previous Treatment
 - Following treatment, previously lytic lesions may become sclerotic and be metabolically inactive – factors which may affect FDG uptake



FDG-PET & CT in Bone Metastases

Cook, J Clin Oncol 1998

Metastases	BS lesions	PET lesions
Sclerotic	3.7	2.7
Mixed	5.0	13.3
Lytic	11.9	21.8

- Lesion detectability: FDG-PET > Bone scan (mainly for lytic and intramedullary lesions)
- Detectability of blastic lesions: FDG-PET < Bone scan
- SUV: lytic lesions > blastic lesions
- Survival: pts with lytic lesions < blastic



Bone Scan & FDG-PET & CT in Breast Ca with Bone Metastases

Nakai et al, EJNM, 2005

CT BS/FDG-PET

Blastic 100/55.6%

Lytic 70/100%

Mixed 84/94.7%

Invisible 25/87.5%

BS
PET

Sens	Spec	Acc
78.2%	82.4%	79.8%
80.0%	88.2%	83.1%



FDG & CT in Bone Metastases

Treatment-related Changes

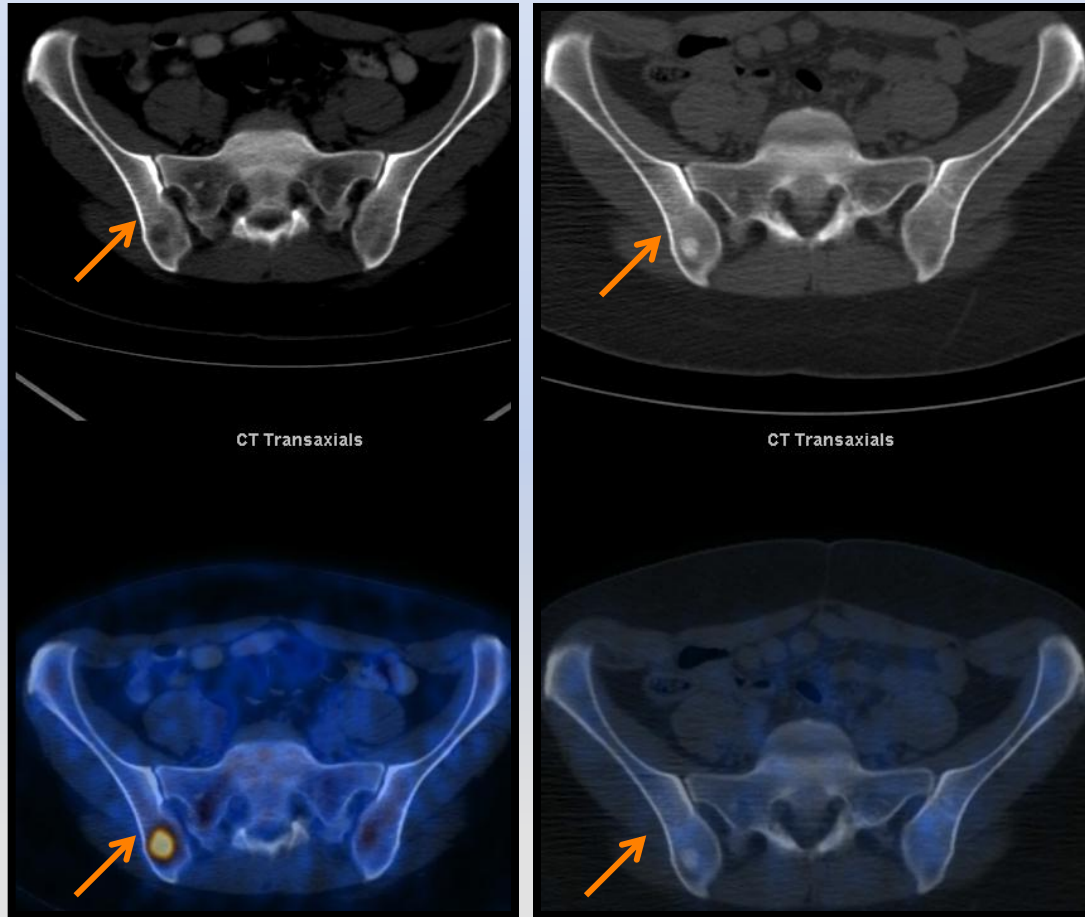
Israel et al, EJNM 2006

	Total	FDG +	CT +
Untreated	82	74/82 [90%]	77/82 [94%]
Treated	218	95/218 [46%]	209/218 [96%]
p		<0.001	ns



FDG-PET/CT in Breast Ca with Bone Mets

Monitoring Response to Treatment



Bone Metastasis
Good Response to Rx

F, 35, newly diagnosed
invasive duct rt. breast ca
Chemo instituted following
diagnosis of bone mets at
staging.

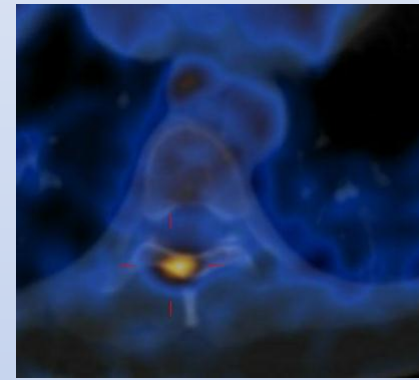
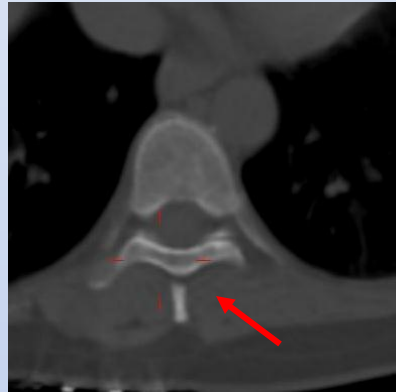
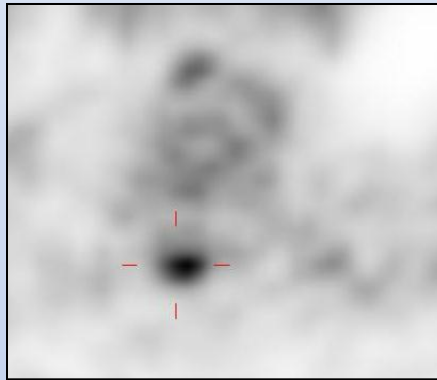
Response assessment after
6 mo of chemo:

FDG-avid osteolytic bone
mets in rt. Ilium.

Lesion in rt ilium is
sclerotic & FDG negative

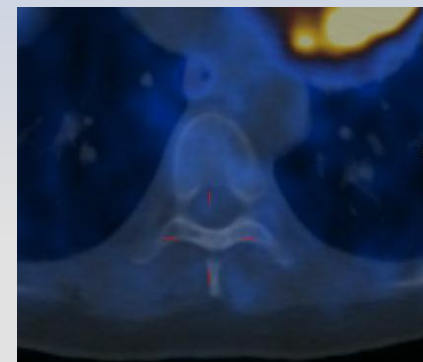
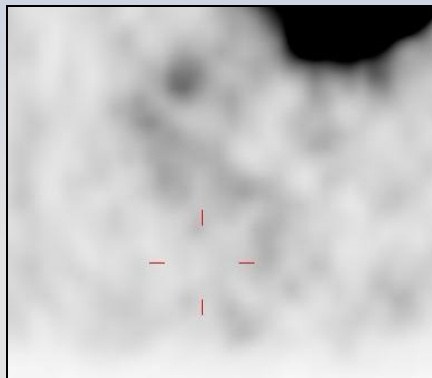


FDG-PET/CT in Breast Ca with Bone Mets



F, 40, newly diagnosed breast cancer, back pain

Before treatment: FDG-avid vertebral metastasis, negative CT



After chemo: sclerotic lesion on CT with no FDG uptake

FDG-PET/CT in Breast Ca with Bone Mets

- FDG-PET/CT has a high sensitivity, up to 100%, for detection of lytic bone metastases, vs. 70% for Tc-MDP bone scintigraphy.
- After treatment most lytic FDG-avid lesions in patients who respond to treatment become sclerotic and FDG-negative.
- FDG-avid sclerotic bone metastases showing persistent FDG uptake also demonstrate an increase in size on CT, and these findings are consistent with disease progression .



18F-Fluoride PET/CT for Bone Metastases

- Uptake mechanism - similar to Tc-agents
 - High bone turnover & remodelling (blood flow & osteoblastic activity)
 - renal excretion
 - chemisorption onto mineralising bone surfaces
 - exchange with OH^- in bone crystal – fluoroapatite
- F18 vs. Tc-labeled agents
 - Superior pharmacokinetics
 - Higher bone uptake (1st pass extraction 100% vs.60%)
 - Faster blood clearance
 - Better lesion contrast – higher target/background

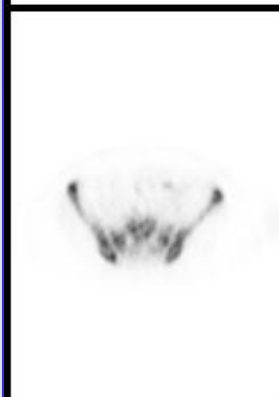


18F-Fluoride PET/CT of the Skeleton Imaging Protocol

- Dose: 8-12 mCi (296-444 MBq)
- Time of uptake: *45 min*
- Increased hydration & Voiding
- *Walking & physical activity – decreases background*
- Acquisition:
 - Time: 2-3 min/FOV
 - Inclusion of *lower limbs* (based on clinical indication)
- Radiation doses:
 - Bone: 0.0120 mGy/MBq vs.0.035 for Tc-agents
 - Bladder wall: 0.19 mGy/MBq vs. 0.03 for Tc-agents



F-18 fluoride Bone PET



Fluoride Uptake in Benign Bone Lesions Osteophytes in the Thoracic Spine

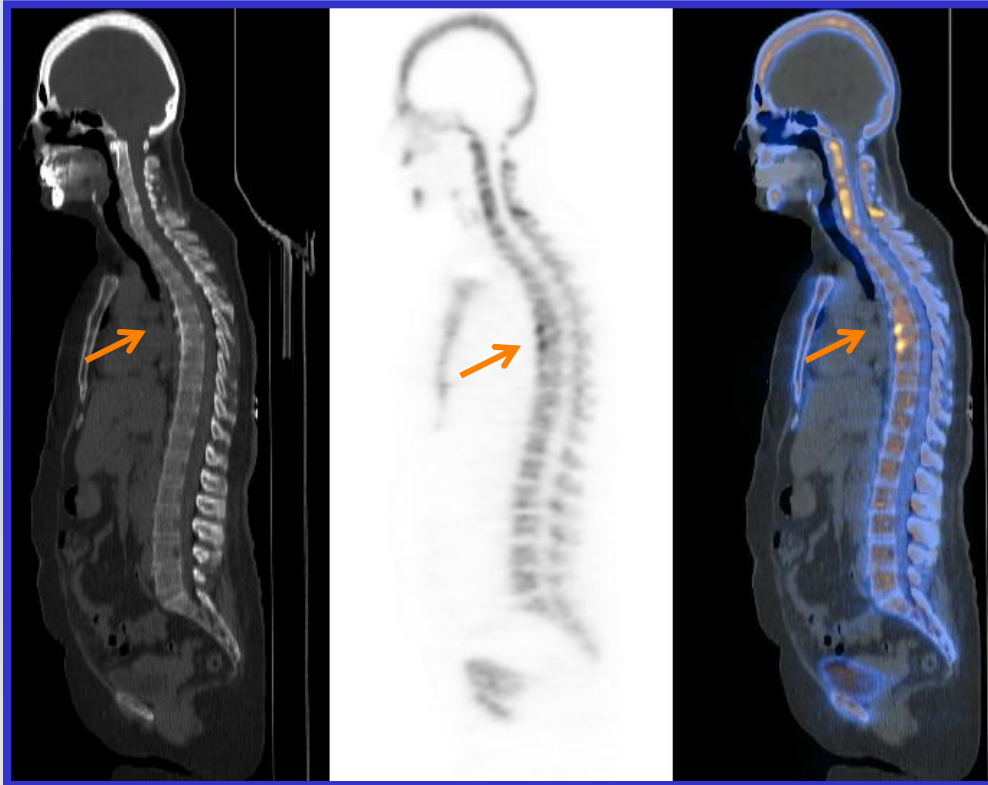
F, 65y, newly diagnosed lt. breast ca metastatic to the liver.

Fluoride PET/CT in search for skeletal mets

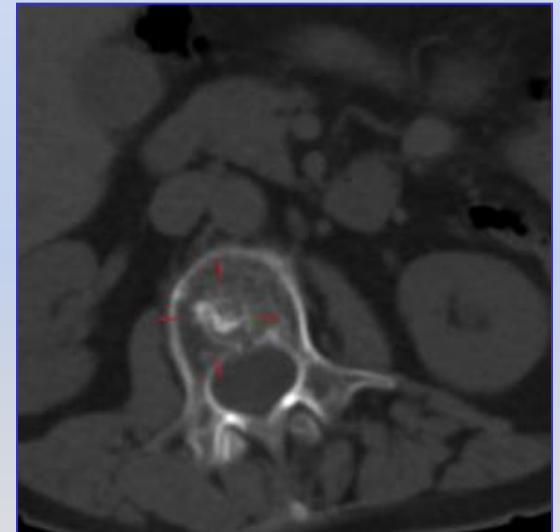
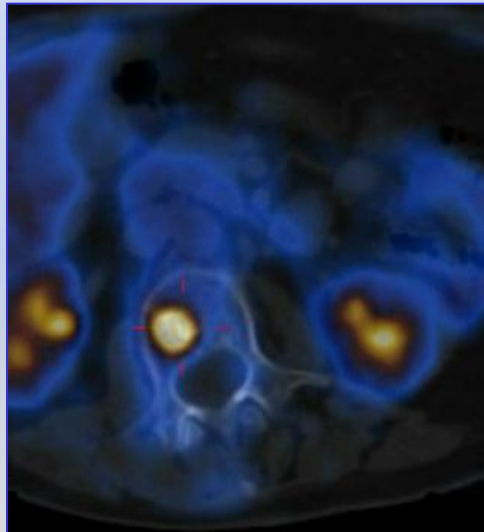
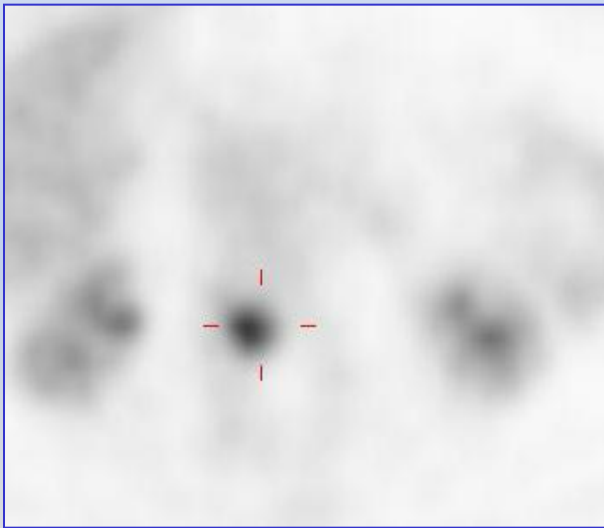
Increased Fluoride uptake, moderate intensity in thoracic spine - localized to osteophytes in the anterior aspect of the T5 and T6 vertebral bodies.

Osteophytes in thoracic spine

No evidence for bone mets

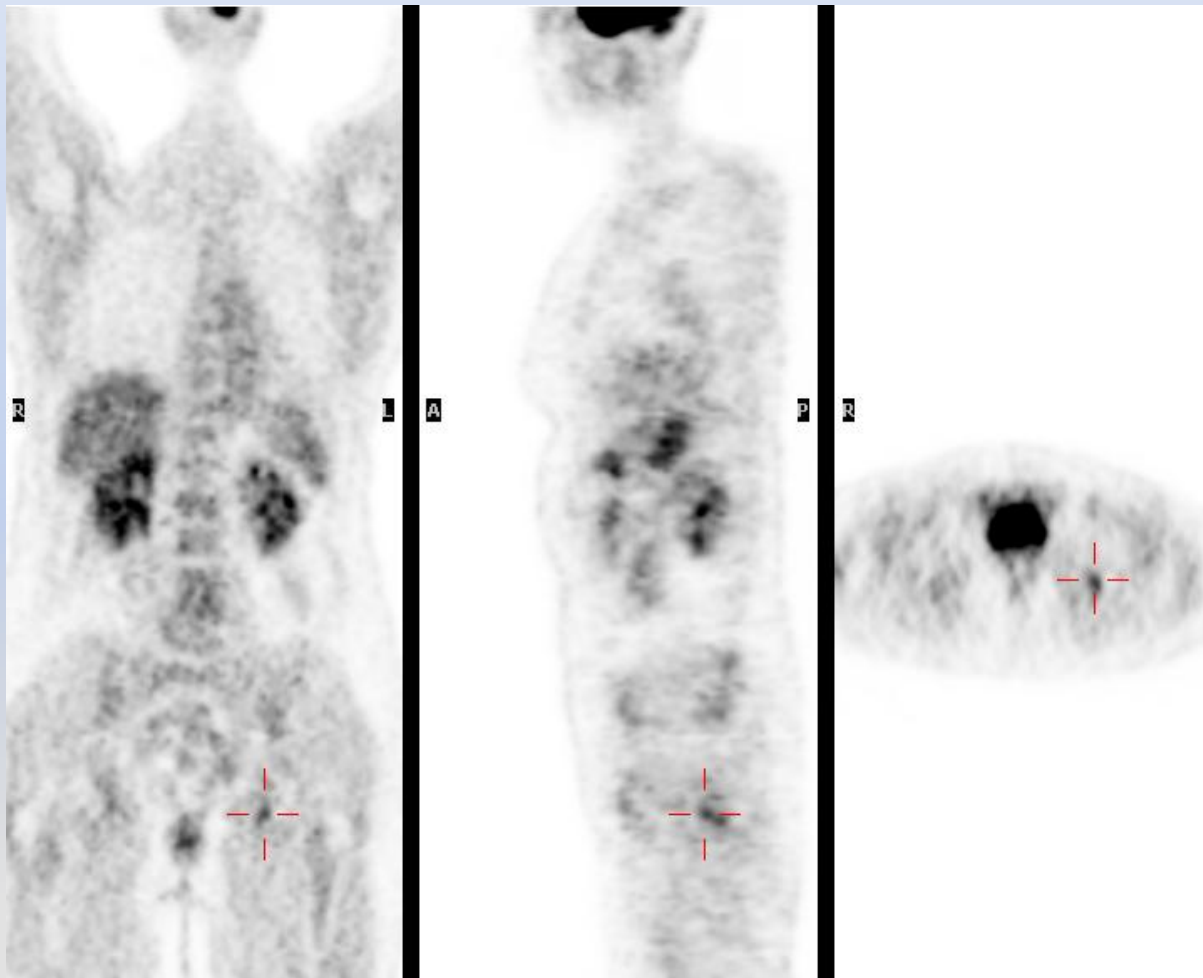


FDG-avid Benign Bone Lesions degenerative changes with & w/o sclerosis



F, 65, Breast cancer, S/a chemo- & radiotherapy
Schmorl's nodule in body of L3

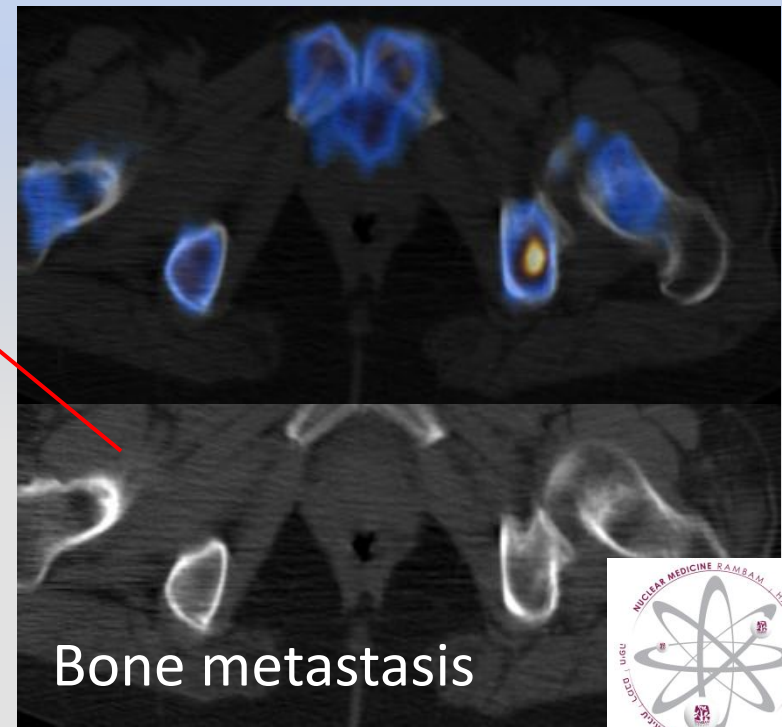
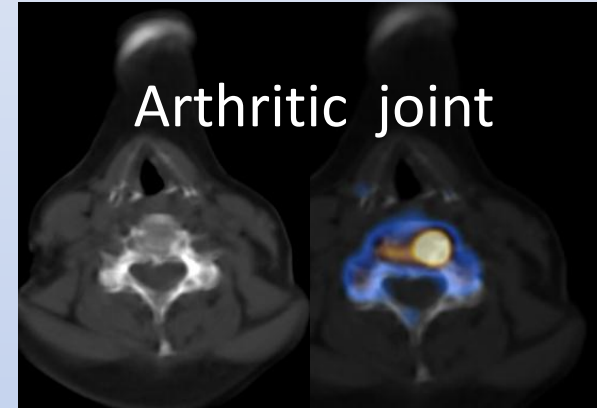
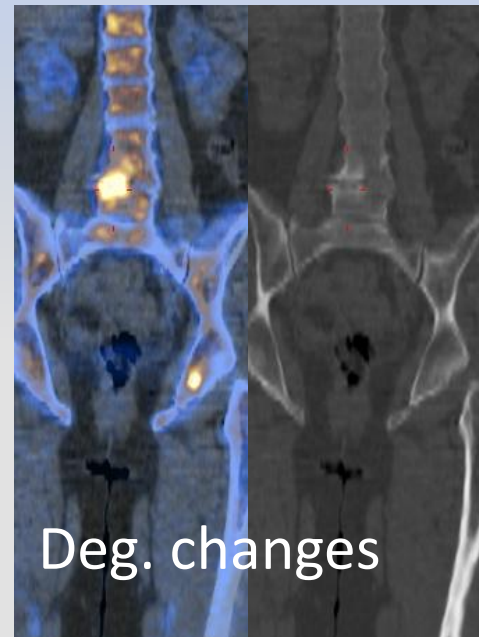
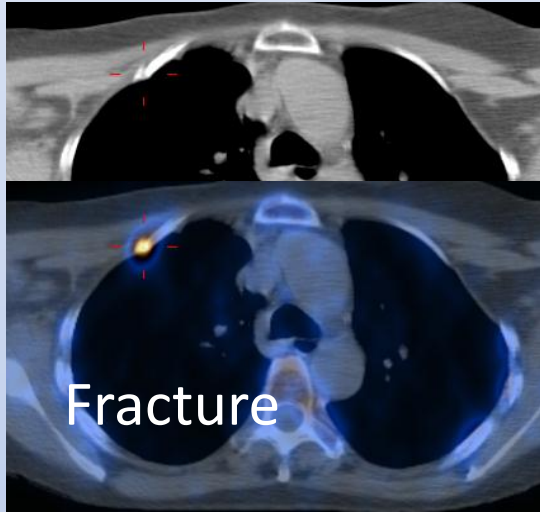
FDG-PET/CT in Breast Cancer



Lesion in Lt. ischium (by PET/CT) – Equivocal



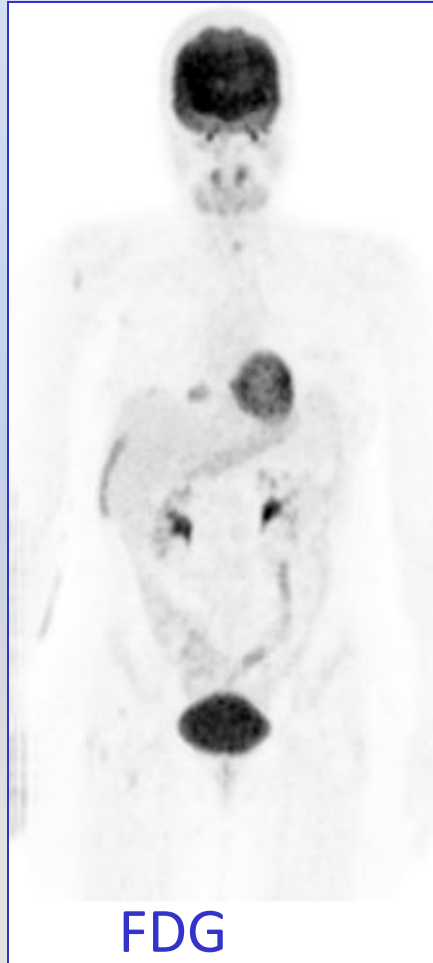
F18-fluoride PET/CT in Breast Cancer



FDG & Fluoride Imaging of Metastatic Breast Cancer



F18-fluoride



FDG

F, 44y, locally advanced invasive lobular
lt. breast ca, s/a mastectomy &
neoadjuvant chemo

Diffuse skeletal pain & equivocal bone
scan

FDG: uptake in rt humerus, upper
thoracic spine, rt rib & rt femur.

**Fluoride: additional foci in skull,
thoracic vertebrae, rt scapula & ribs**

FDG PET/CT in Breast Cancer

- Complementary to mammography in specific populations:
 - Dense breasts
 - fibrocystic disease
 - post-therapy
 - breast implants
- PET can not detect nodal micrometastases: SNB is superior for axillary node detection
- Detection of distant metastases : Superior to bone scan in osteolytic lesions

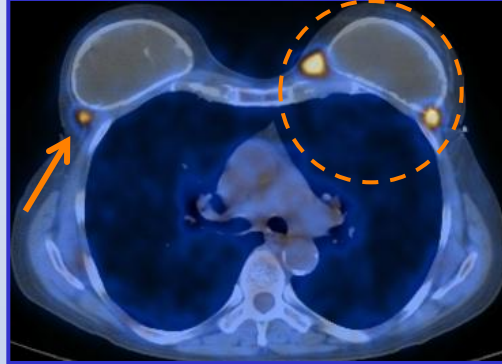
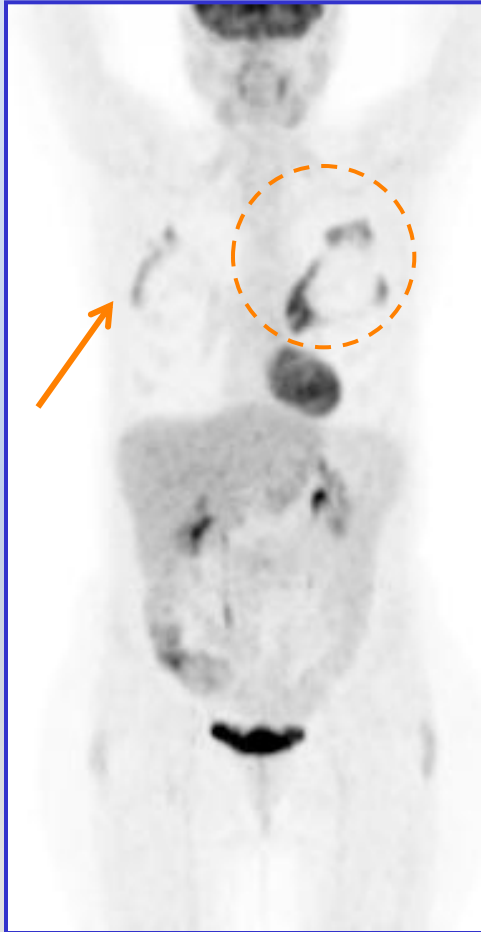


Limitations of PET/CT [for Staging & Beyond]

- FP: FDG-avid non-malignant processes
(eg: granulomatous mastitis, rapid growing fibroadenoma;
physiologic uptake: muscle, adipose tissue)
- FP: FDG-avid procedure/treatment-related
(eg: inflammatory reaction s/a FNA, CNBiopsy – 2 wk interval!)
- FN – technology related: limits of resolution
- FN – patient/tumor related:
 - hyperglycemia;
 - Histology (better differentiated, slow-growing, non-invasive)
- Pitfalls:
 - misregistration (respiration, patient movement)
 - truncation artefacts



FDG Breast Uptake Unrelated to Cancer Inflammatory Reaction



F, 69y, COPD

New single pulmonary nodule in
LUL on CT

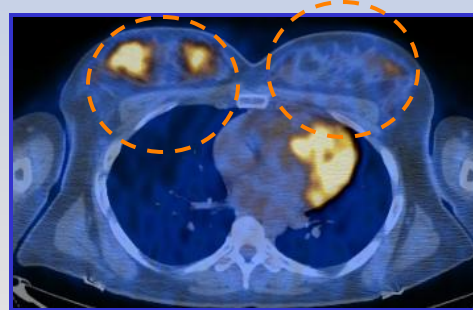
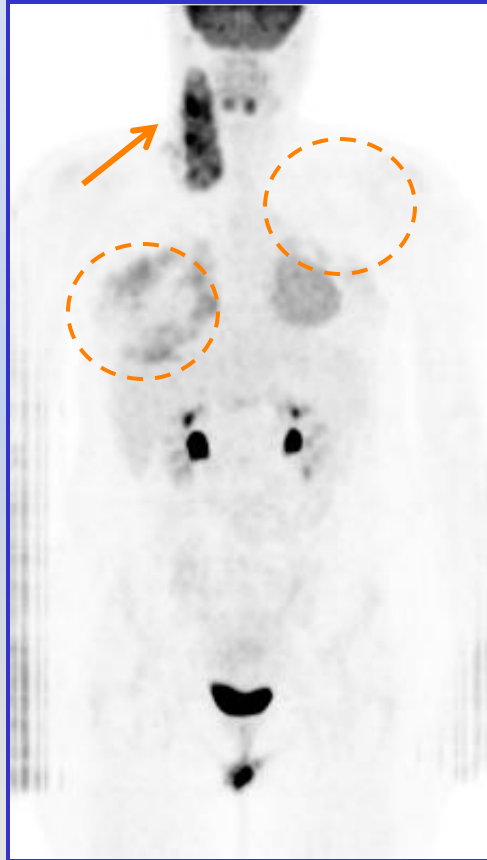
Linear and focal FDG-avid areas
in anterior aspect of the chest
wall localized to the borders of
breast implants.

**FDG uptake in hypermetabolic
inflammatory reaction
surrounding breast implants.**
(s/a bilateral mammoplasty 7
years prior to current
examination).



FDG Breast Uptake Unrelated to Cancer

Lactating Breast & Breastfeeding



F, 27y, Hodgkin's diagnosed during pregnancy. (Large mass in her right neck.)

A large area of FDG uptake in right cervical and supraclavicular LNs.

Diffuse inhomogenous FDG uptake in the breasts, more prominent on the right.

Hodgkin's disease stage IIA (cervical and supraclavicular LNs).

FDG uptake in lactating breasts, following rt. breast feeding just prior to tracer injection.



FDG Imaging & Breast Feeding

- FDG breast uptake increases during lactation but is not excreted in the milk in significantly amounts.
- Increased radiation exposure in breastfeeding infants occurs mainly because of close contact to persons injected with FDG, and not because of breast feeding after tracer injection.
- Current guidelines recommend to discontinue breastfeeding for several hours following injection of FDG



FDG-PET/CT in Breast Cancer

Guidelines & Recommendations

(NCCN 2007, multidisciplinary panel – JNM 2008)

Recommended :

- Adjunct for assessment of recurrent/metastatic disease

Promising:

- Loco-regional staging in locally advanced disease
- Early response to systemic therapy
- Rx response in metastatic disease (mainly bone)

Not recommended:

- Screening or detection of primary tumor
- Staging early stage disease
- Post-treatment follow up



Thank You

