PET imaging of inflammation and infection

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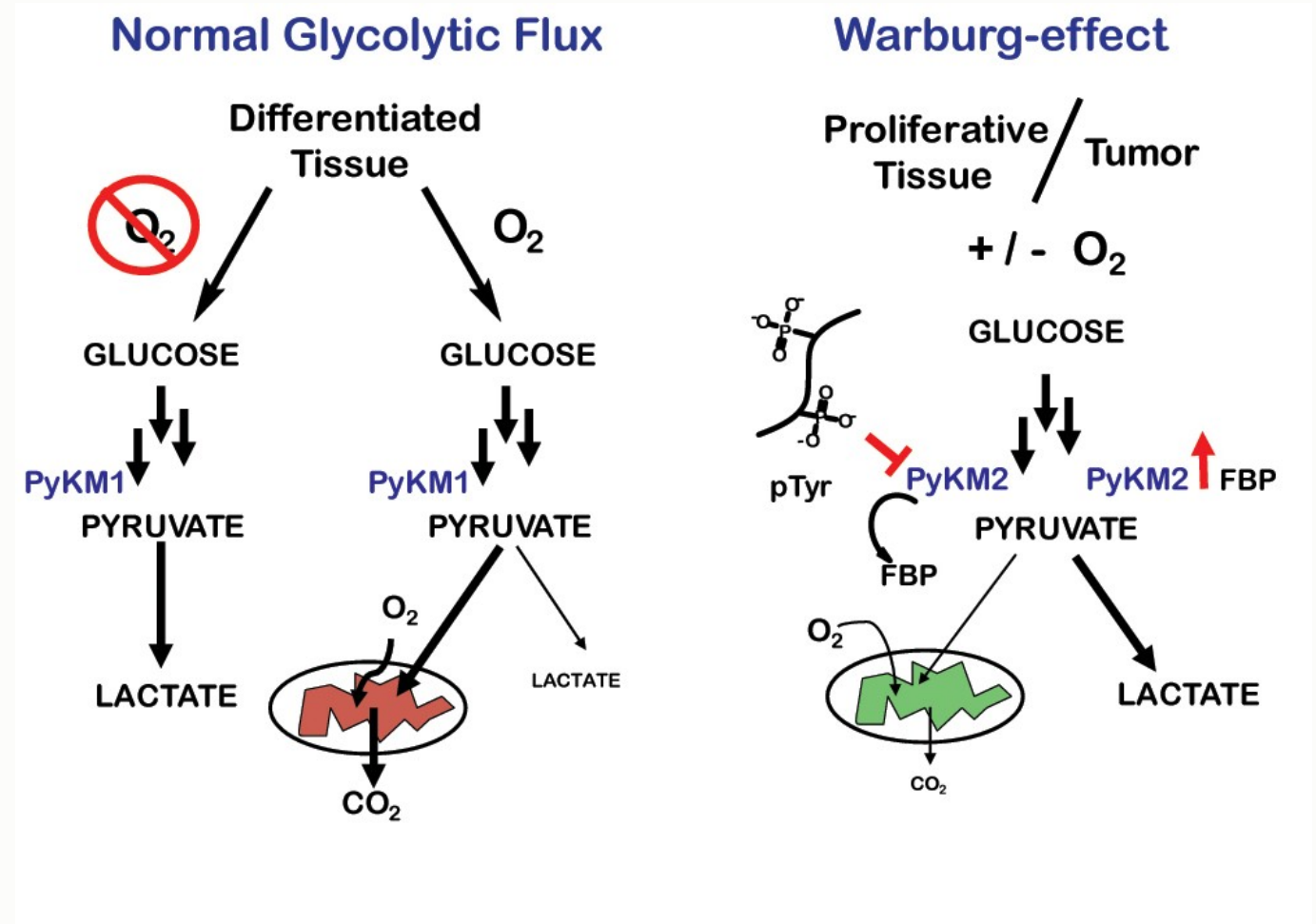
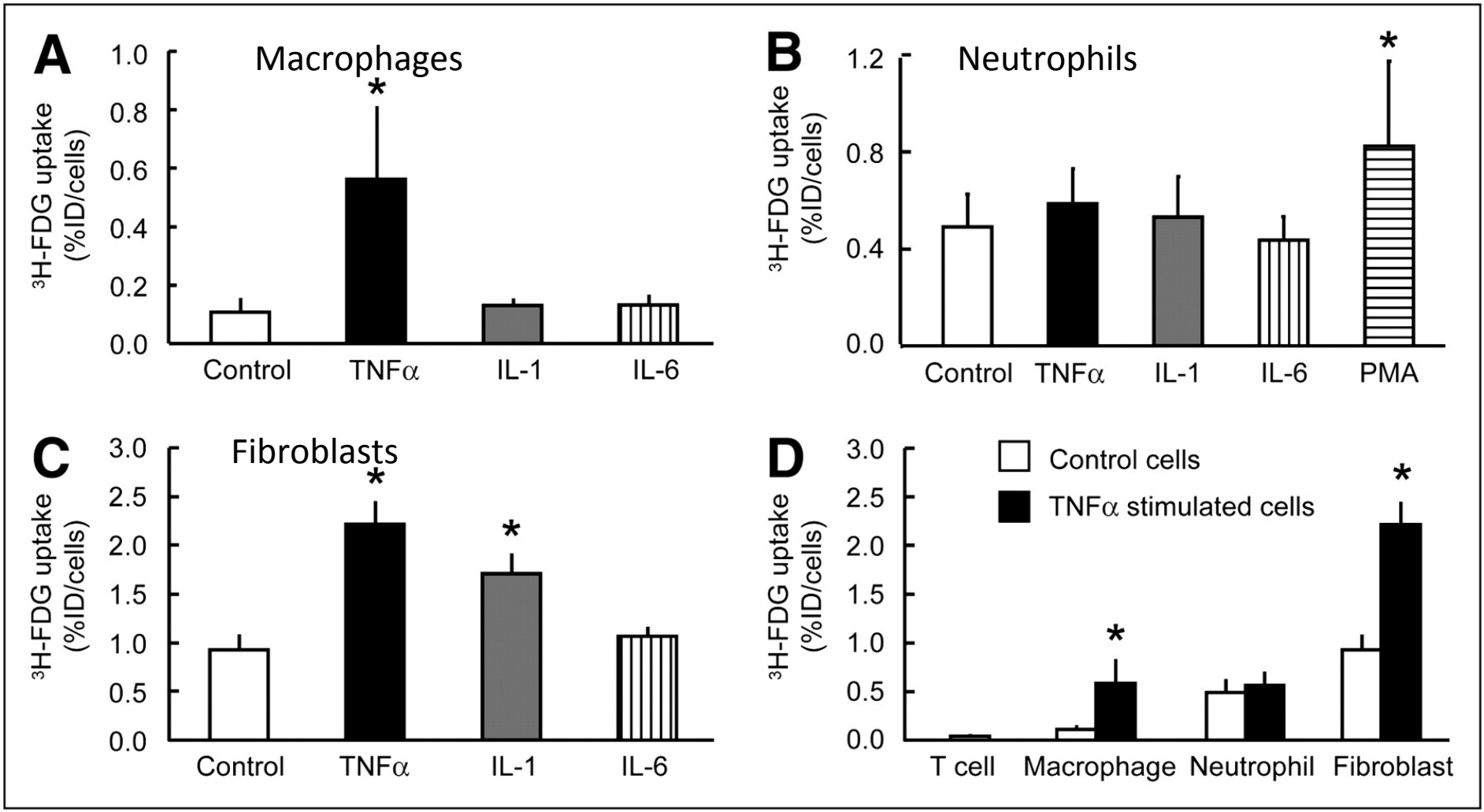
Glucose uptake into tumours



FDG and inflammation

- Increased uptake of FDG occurs when lymphocytes activated. Ishimori JNM 2002
- Uptake not just related to perfusion but active uptake when FDG related to FLT where no increased uptake van Gaarde JNM 2004
- Uptake of FDG related to hypoxia and presence of cytokines Matsui JNM 2009

Uptake and cytokines-Matsui



Sarcoid

- Disseminated inflammatory disease
- Characterised by granuloma
- Various patterns
  - Salivary/lacrimal glands
  - Lymph nodes
  - CNS
  - Skin
  - Joint
  - Pulmonary- the most dangerous

Imaging in sarcoid

- Normally diagnosis clinical followed by biopsy
- 50% of patients have raised serum ACE
- If lymph nodes involved may see symmetrical enlarged mediastinal/hilar nodes the lambda pattern
- Since 1966 Ga-67 citrate used
  - Not very trendy
  - High radiation dose

Ga-67 in sarcoid

Panda sign, lacrimal and salivary glands

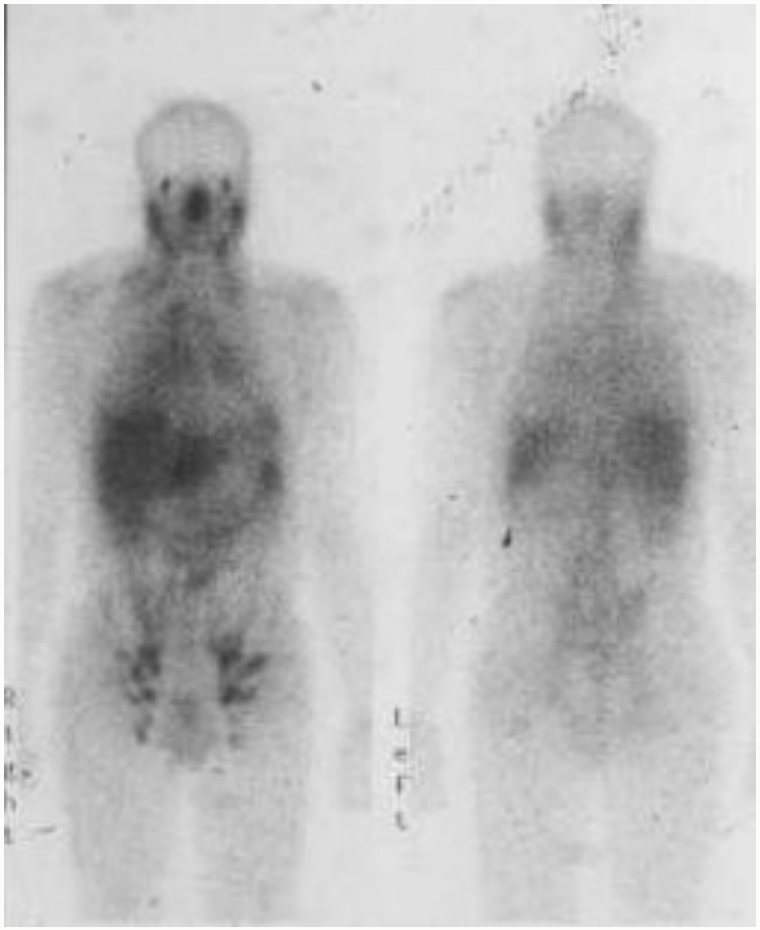
Lamba sign mediastinum and hilar nodes

Diffuse lung uptake

Lymphadanopathy (symmetrical)

Joints

Liver-diffuse

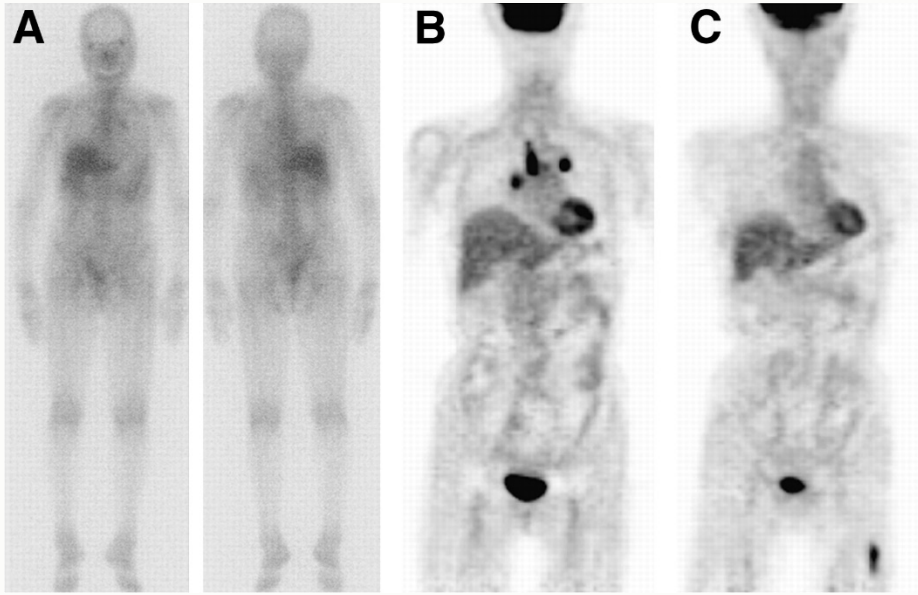


Use of F-18 FDG

- Lymphocytes very FDG avid
- Much improved resolution
- Lower radiation dose (5mSv vs 18mSv)
- Confirm sites of active disease esp in the abdomen
- Quantify uptake which may be useful in treatment monitoring

FDG vs Ga-67

- Nishiyama et el JNM 2006
- 18 sarcoid patients imaged with Ga-67 and FDG.
- Pulmonary disease Ga-67 81%, FDG 100% - mean SUVmax 7
- Extra-pulmonary disease Ga 48%, FDG 90% mean SUVmax 5



A= Ga-67
B= F-18 FDG
C= F-18 FDG post therapy

Using FDG to monitor therapy

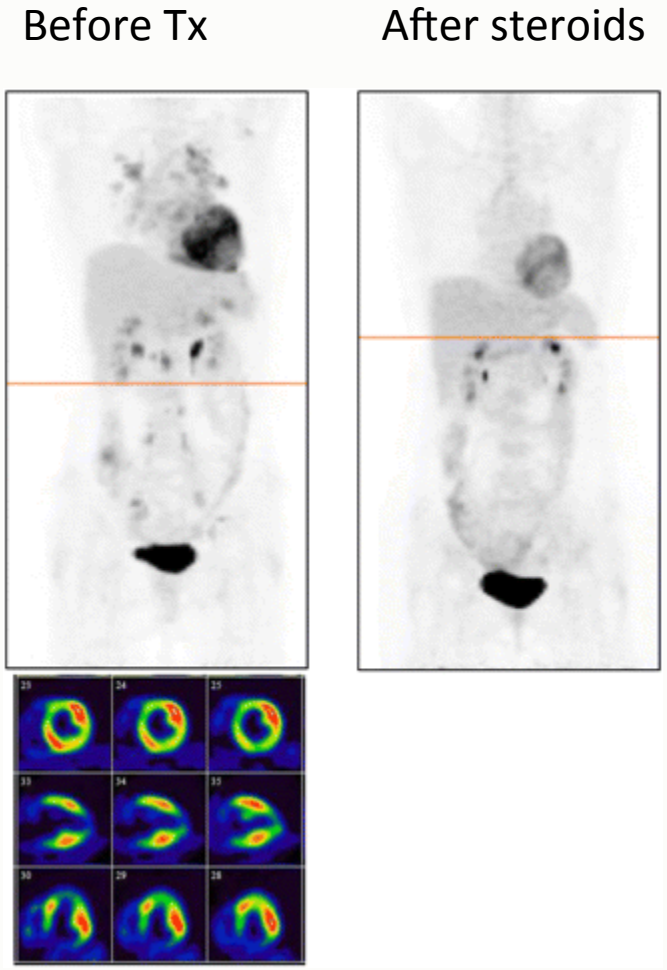
- Sobic-Saronovic, Clin Nucl Med 2013
- 30 patients imaged before and after steroids for active sarcoid
- Observed reduction in sites and intensity of activity
- Correlated well with clinical symptoms
- SUVmax 8.5 to 4.9 ($p<0.05$)
- Serum ACE did not predict response

Cardiac sarcoid

- Cardiac sarcoid may occur with other sites or be isolated
- Can result in heart failure and arrythmias
- Cause of unexpected cardiac death
- Recently a growing role for cardiac F-18 FDG
- Has been proposed both for diagnosis and to monitor any response to therapy

Imaging cardiac sarcoid

- Patient preparation vital
- Patient need 24hrs high fat/low carbohydrate diet
- IHD should be excluded by MIBI/Rb-82
- Images should be gated
- No myocardial uptake or diffuse uptake normal.
- Focal uptake is cardiac sarcoid



Review of FDG in cardiac sarcoid

- Youssef et al JNM 2012
- Systematic review of 7 studies of FDG in cardiac sarcoid
- 164 patients with sarcoid scanned 50% had cardiac involvement
- Sensitivity of FDG 89% (95% CI 76-06%)
- Specificity of FDG 78% (95% CI 68-86%)

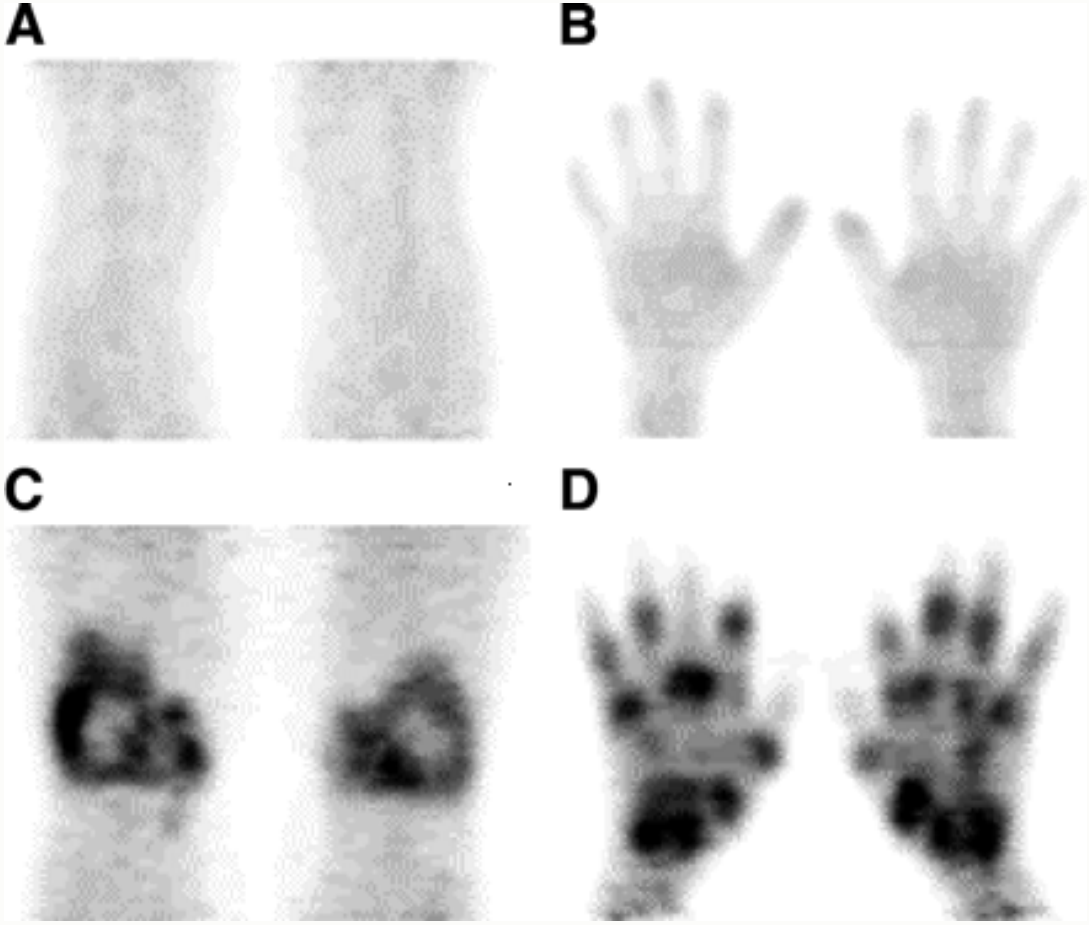
Using FDG in RA

- Beckers et al JNM 2004
- 21 patients with active RA
- FDG imaging with views of knees and hands
- FDG positive in 68% joints though 75% of joints swollen and 79% painful
- Good correlation with increased blood flow on Doppler ultrasound

FDG uptake in RA
Beckers et al JNM 2004

Normal

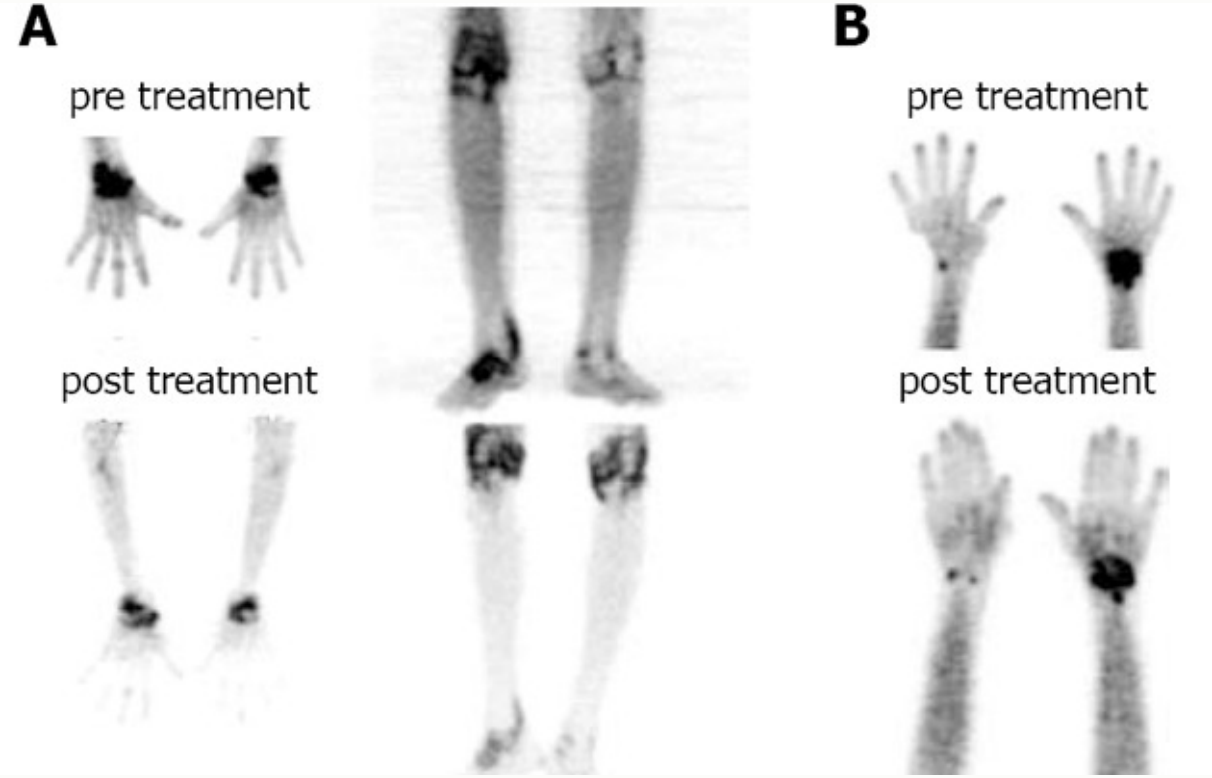
Patient with RA



Monitoring response

- Vijavant et al WJR 2012. 17 newly diagnosed RA and 11 newly diagnosed sero-neg arthropathy
- Good correlation between symptoms and sites of increased uptake of FDG
- Change in SUVmax correlated well with clinical response and change in CRP

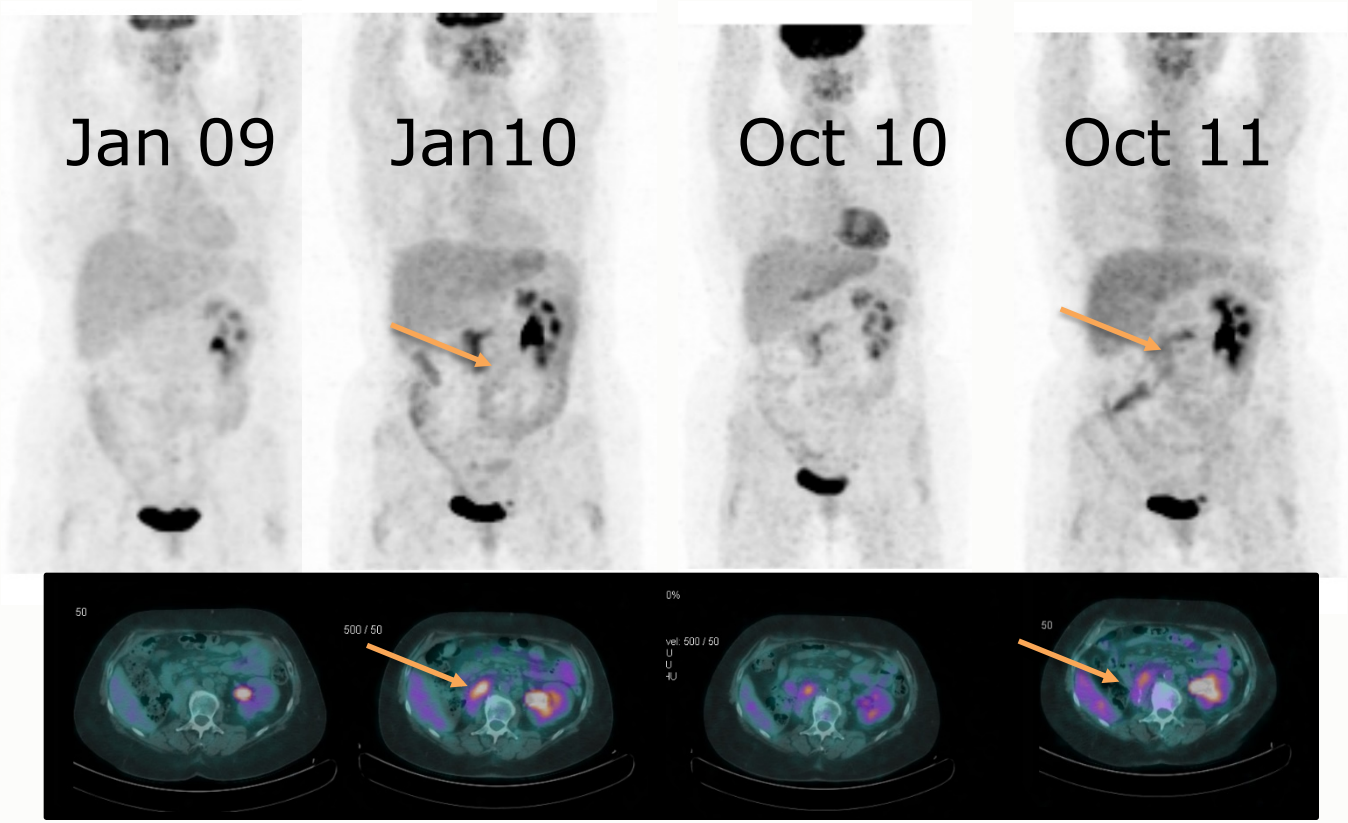
FDG before and after Tx
Vijavant et al WJR 2012



RA and PET in 2004-stll true 2013

- However, much work remains to be done to gain more detailed information and to clarify the impact of ^{18}F-FDG PET on diagnosis and therapy of RA, in comparison with state-of-the-art MRI, ultrasound, and three-phase bone scanning. Eventually, we may be able to define indications for ^{18}F-FDG PET to improve and adjust RA management.-*Wilfred Brenner*

F-18 FDG Imaging to monitoring treatment of unilateral RPF



on steroids off steroids on steroids on steroids

Case of Prof A Signore

FDG Imaging of Infection

Rationale

- **FDG** uptake is related to the glycolytic activity of cells responsible for the inflammatory response
- Cells involved in infection &inflammation (activated lymphocytes, neutrophils, macrophages), *similar to* malignant cells
  - express high levels of surface glucose transporter proteins with high affinity to FDG (mainly GLUT1 & GLUT3)
  - exhibit high intracellular levels of hexokinase and phosphatase activity promoting accumulation of FDG
- Enhanced glucose consumption (& FDG uptake) can be also the result of a stress reaction in response to cellular damage

FDG Imaging in Infection
Clinical Indications

- **Localized infection in chest & abdomen**
- **Fever of unknown origin (FUO)**
  - True FUO
  - Immune-deficiency & immune-compromised (AIDS)
- **Musculo-skeletal infections**
  - **Osteomyelitis**
  - **Spinal infection**
  - **Diabetic foot**
  - Infected orthopedic prostheses
- **Vascular**
  - **Infected vascular graft**
  - **Vasculitis**
  - Inflammatory vulnerable plaques
- Inflammation
  - **Sarcoidosis**
  - Foreign body reactions
- Inflammatory bowel disease

EANM/SNMMI Guideline for ^{18}F-FDG Use in Inflammation and Infection

F. Jamar, J. Buscombe, A. Chiti, P. Christian, D. Delbeke, K. Donohoe, O. Israel, J. Martin-Comin, A. Signore

J Nucl Med Mol Imaging 2013

FDG Imaging of Infection
Pros & Cons

Advantages

- F-18: good physical properties
- FDG: good tracer kinetics
- PET: high spatial & contrast resolution

  good image quality
- CT: anatomic information
- Study duration:1.5 – 2h
- Short physical T1/2: lower radiation
- No blood handling

Limitations

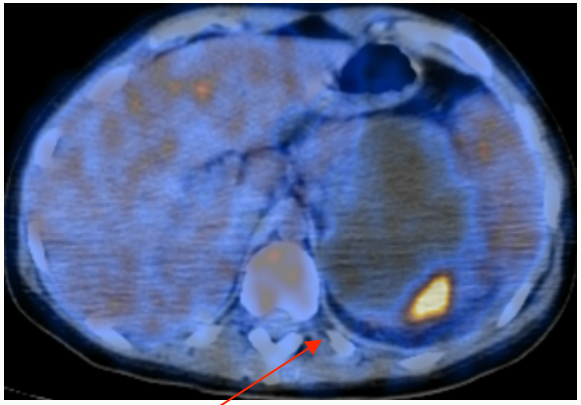
- Nonspecific uptake:
  - Physiologic
  - Malignancies
  - Foreign body reaction
- Availability & Waiting list
- Cost & [lack of] reimbursement

FDG Imaging in Infection

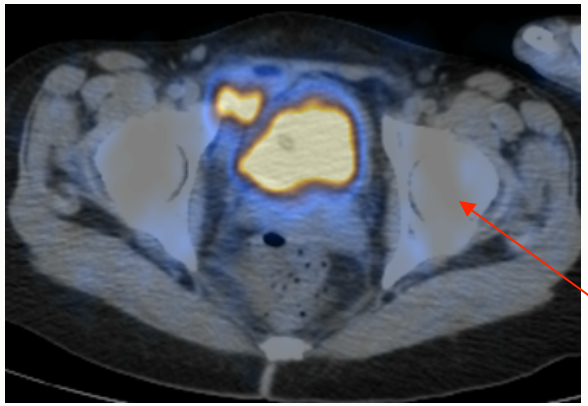
FUO in Immune - Compromised Patient

F, 21, FUO, Polycystic kidneys

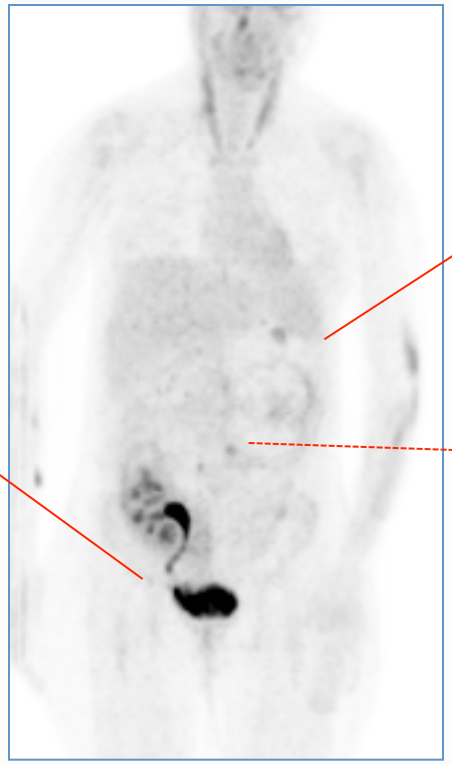
1 month after renal transplant

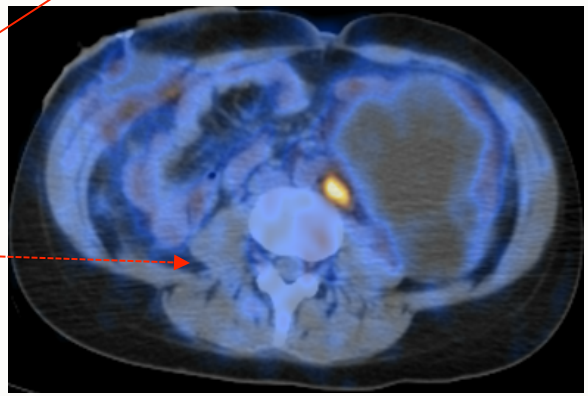


Infected renal cyst



Pelvic Abscess





Reactive LNs

Pre-FDG Examination for Suspected/Assessment of Infection and Inflammation

Prior to the study

- avoid physical exercise within 24 hours
- fast for 6 hours
- ensure hydration and promote diuresis
- Diabetics: schedule 3-4 hours after breakfast
- Provide all clinical and radiological documentation related to the clinical question

Pre-injection – record:

- Patient weight and height
- Date of last menstruation
- History of diabetes
- Specific medication: antibiotics, immunosuppressives, steroids, insulin, oral anti-diabetics
- Recent invasive diagnostics or surgery (4 weeks); radiation therapy (3 months)
- History of cancer, recent chemotherapy

Pre-injection preparation

- Check blood glucose levels
- Patient relaxation (muscle uptake)
- Waiting room with adequate temperature (brown fat uptake).

FDG Imaging of Infection

Imaging Protocol

- Administered dose:
  - 185-370 MBq/kg (5-10 mCi/kg) in adults

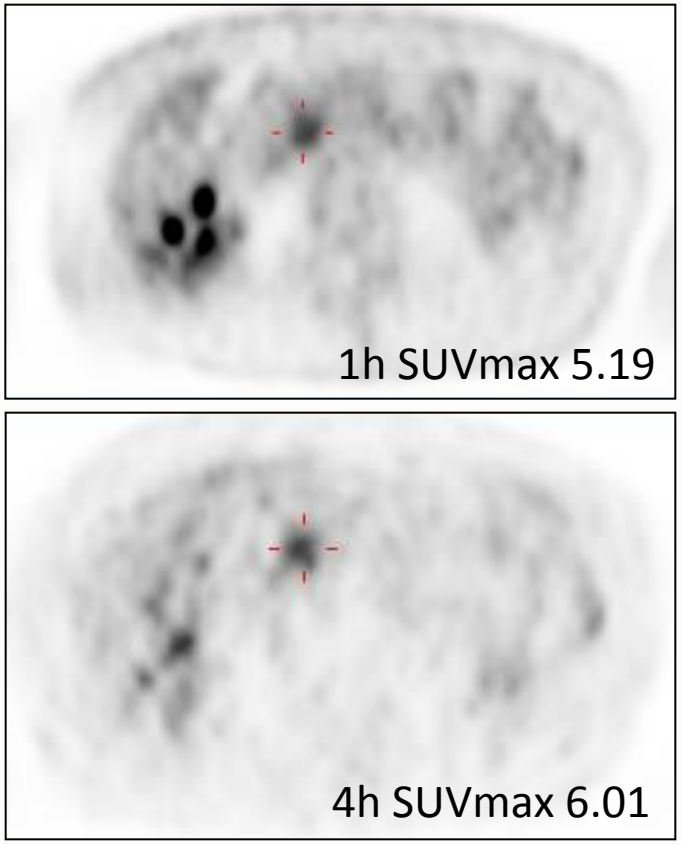
    higher in BMI>30
- Uptake period: ≥60 min
- PET image acquisition:
  - Limited FOV: diabetic foot, infected graft or prosthesis
  - Whole body imaging: FUO, sarcoid, etc
- Careful positioning *& immobilization* - review for potential misregistration
- *Questionable: dual-time point acquisition*
- *Use of iv contrast*

Dual-time Point FDG Imaging
Can it differentiate inflammatory from malignant lesions?

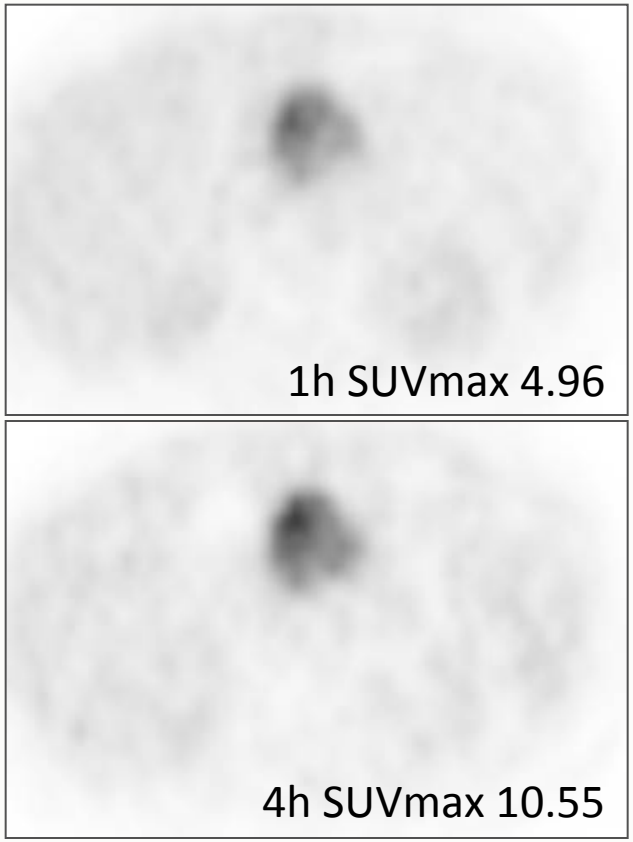
- Malignant lesions: increase in uptake over time
- Inflammatory/infectious process: decrease or stable uptake (SUV) over time
- Mechanism: ? faster glucose washout from benign lesions

- Potentially significant overlap of FDG uptake dynamics
- ? limited/no value in infection
- At present - not enough evidence to differentiate between malignant and inflammatory lesions

Dual-time Point FDG Image Acquisition
Infection vs. Cancer



Pancreatitis



Pancreatic Cancer

FDG Imaging in Infection
Image Analysis

- Physiological FDG distribution
  - Mainly: brain, heart, kidneys, urinary tract,
  - Variable: muscles, GIT, lymphoid tissue, thymus, brown fat, bone marrow
- Qualitative analysis:
  - Pattern: focal, linear, diffuse
  - Intensity
- Quantitative SUV analysis: *not validated for infection & inflammation*
- Localization of abnormalities according to the anatomical CT map
- Assessment of CT for non-FDG avid abnormalities
- Interpretation in relationship to:
  - Clinical question & history
  - Previous test results

FDG Imaging [in Infection]

Pitfalls and Limitations

Miss – Mask - Mimick

"…PET imaging[may] not [be] for the faint hearted! However, recognition of the limitations of PET along with its strengths is the best way to avoid pitfalls"

Barrington & O'Doherty, EJNM 2003

"Limitations of PET for imaging lymphoma"

Not only a 3-D but also a 3-M modality

Through PET/CT – knowledge of new patterns
Solutions for most interpretation dilemmas

FDG Imaging in Infection
Image Interpretation

False negative:

Technical

- *Blood glucose levels at time of FDG injection*
- *Administration of **drugs** interfering with FDG uptake*

Disease-related

- Size (small)
- Low **metabolic rate**

Location-related (masked by adjacent highly FDG-avid structures)

- Brain uptake – of CNS lesions
- Heart uptake – of mediastinal & paracardiac sites
- Liver, Bowel – of hepatic, abdominal & pelvic processes
- Kidneys, bladder – of abdominal & pelvic processes

FDG Imaging in Infection
Image Interpretation – False Positive

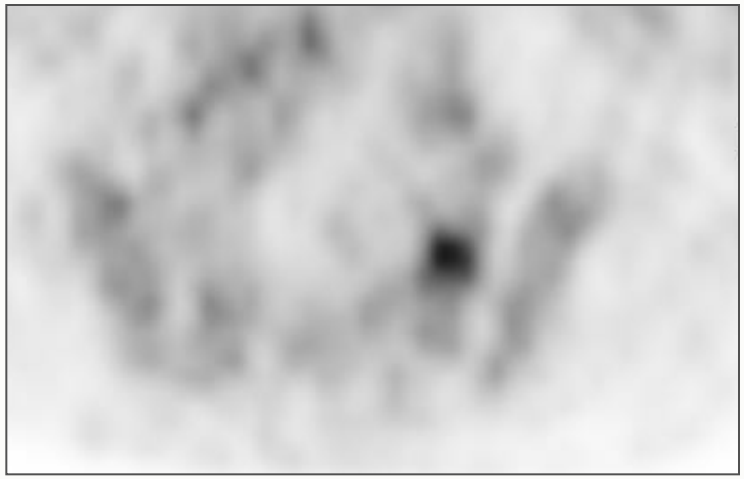
Physiologic FDG uptake

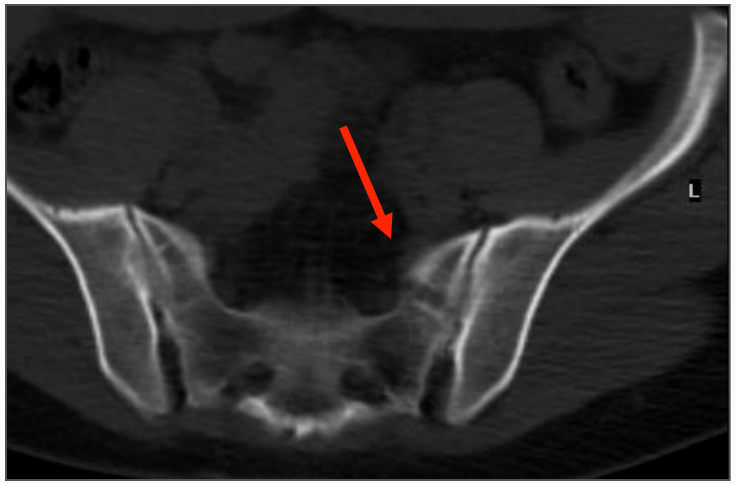
- oropharynx, vocal cords
- Cervical muscle, fat uptake (vs. LN)
- GIT (focal or segmental)
- Ureter
- Salivary glands, lymphoid tissue
- LN proximal to tissue injection
- Skin folds & sweat gland in axilla
- Bone marrow uptake
- Ovarian & endometrial uptake
- Brown Fat
- Lactating Breasts

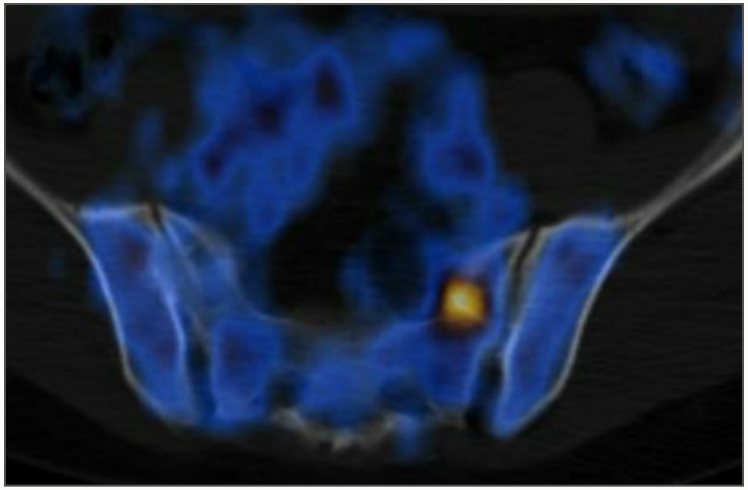
Benign FDG uptake & artifacts

- **Artifacts** (e.g. injection, AC, contamination, metallic devices)
- Benign bone lesions (fracture, degenerative changes)
- Uptake in **foreign body** aseptic reaction (e.g. implants, grafts, stents)
- **After treatment** (e.g. healing scar, chemo/radiation & distorted anatomy
- Uptake in [un]known **malignancies**

FDG Uptake in Benign Process – Bone Fracture







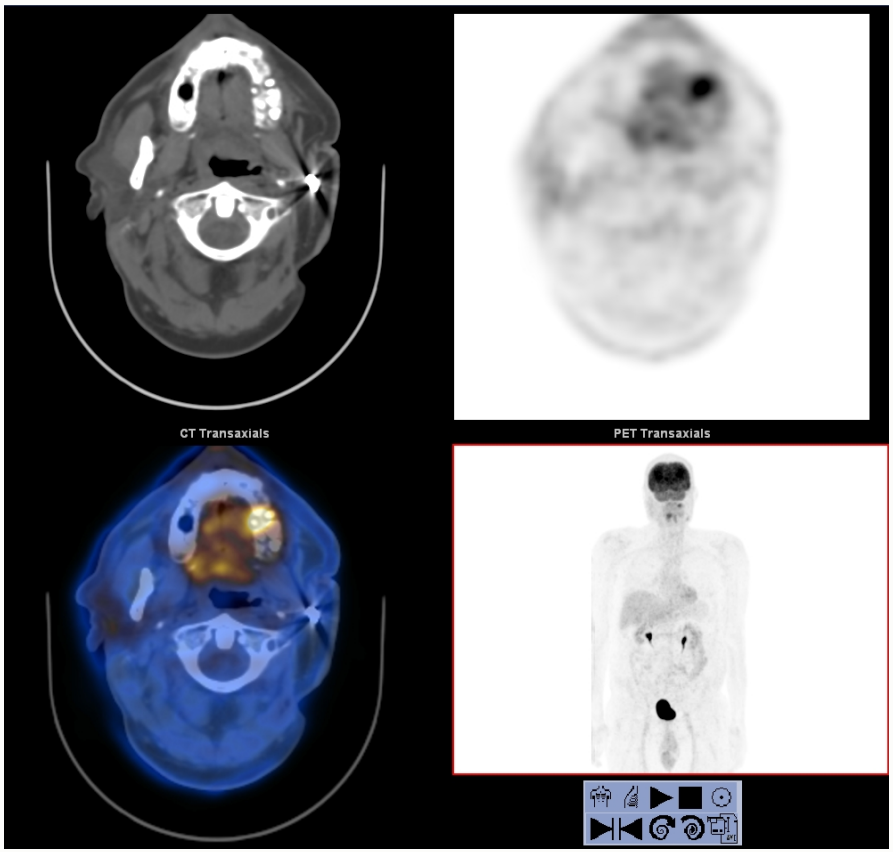
FDG-avid fracture

in left sacro-iliac region

FDG Imaging of Infection
Pitfalls Associated with Adminstration of Drugs

- Antibiotics - thought to lower FDG uptake in infection (no studies confirming this)
- Metformin (antihyperglycemic) - associated with intense diffuse FDG uptake in small & large bowel, could mask infectious/inflammatory lesions (=FN) or be misinterpreted as severe colitis (=FP). Resolved by 2 days discontinuation.
- Steroids - may result in FN, should be avoided or on low dose if possible. Potential mechanisms:
  - resolution of inflammation
  - Inhibition of peripheral glucose uptake (reduce GLUT expression on cell surface)
  - effect on liver uptake with lower FDG availability

FDG Imaging in Infection



M, 67, advanced parotid ca treated by total parotidectomy & radiotherapy (1y)
FUO

Focal FDG uptake in lt. maxilla

Dental abscess

FDG-PET/CT Pitfalls in Specific Infectious or Inflammation Entities - 1

Imaging vasculitis

- Diameter of vessels - limited to aorta & medium sized arteries
- Pattern & location: differential diagnosis vs. infection & atherosclerosis

Imaging cardio-vascular Infections

(heart valve endocarditis, vascular graft reconstruction)

- Variable physiological uptake in left ventricle (level of glucose metabolism in fast)
- Motion-related mis-registration: cardiac, respiratory, involuntary movements (limbs)
- Postsurgical inflammatory changes - persistent for weeks or months
- Chronic aseptic reaction to synthetic implants
- Pattern recognition: diffuse vs. focality, intensity
- Adjacent FDG+ findings: outside device boundaries, regional lymph nodes, vegetations, abscesses, aneurysms, fistulas

FDG-PET/CT Pitfalls in Specific Infectious or Inflammation Entities - 2

Imaging MSK infection:

- FDG avidity by other skeletal lesions: tumour, recent surgery, fractures, osteophytes, enthesopathy, degenerative changes
- Artefacts generated by FDG uptake adjacent to prostheses
- Children: symmetrical FDG uptake in epiphyseal growth plates

Pitfalls in Imaging fever of unknown origin (FUO)

- Timing: late in the course of disease - increase in FN due to antibiotics, steroids
- Relationship to blood infection parameters (ESR, CRP): unclear results with normal values

Diabetes & Infection

- Diabetics – increased propensity to infections
- Unclear if hyperglycemia is an independent risk factor
- Host-specific factors predisposing diabetics to infection:
  - impairment of immune response induced by hyperglycemia
  - vascular insufficiency (local tissue ischemia)
  - neuropathy (unnoticed, ignored skin ulcers, urinary stasis)
  - skin & mucosa pathogens (Staph, candida)
- Frequent type of infections:
  - **Foot**
  - Urinary tract
  - Fungal, **malignant otitis externa**
  - Cholecystitis , Pyomyositis, Necrotizing fasciitis

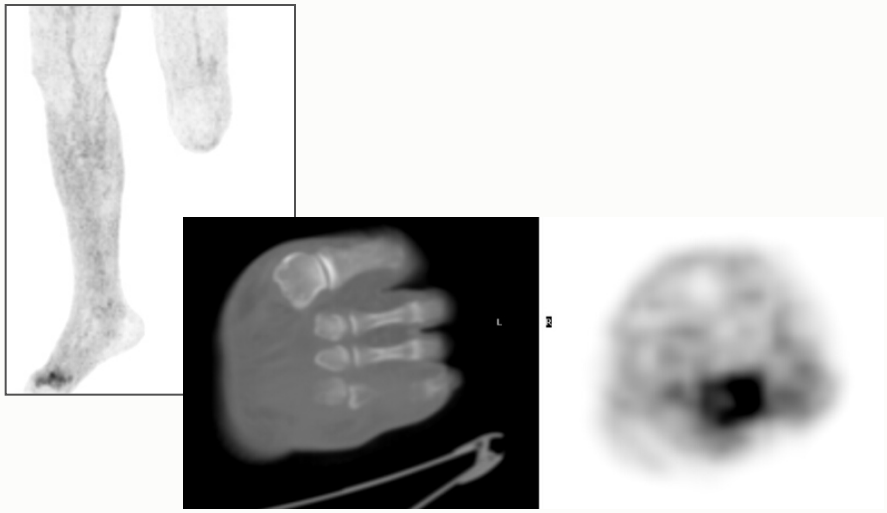
FDG Imaging in Infection

Diabetes & Hyperglycemia, Specific Considerations

Diabetic foot

blood glucose - 190 mg/dl

TP study

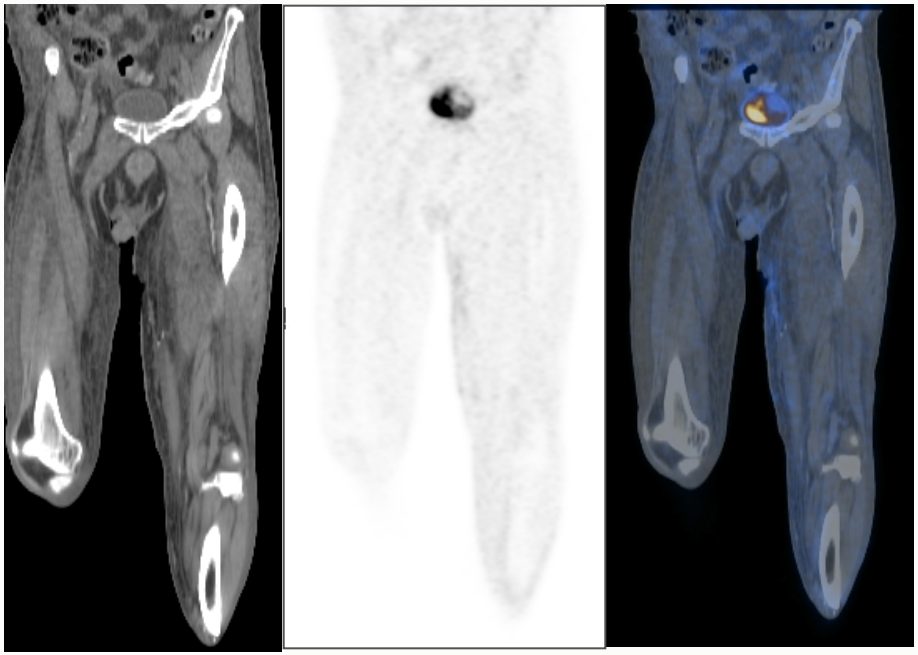


Osteomyelitis 4th metatarsus

Diabetic patient, vascular graft

blood glucose - 84 mg/dl

FN study



Infected surgical wound

Diagnostic Accuracy of FDG-PET/CT in Hyperglycemia & Diabetes [n=443 Patients]

Rivkin et al, JNM 2010

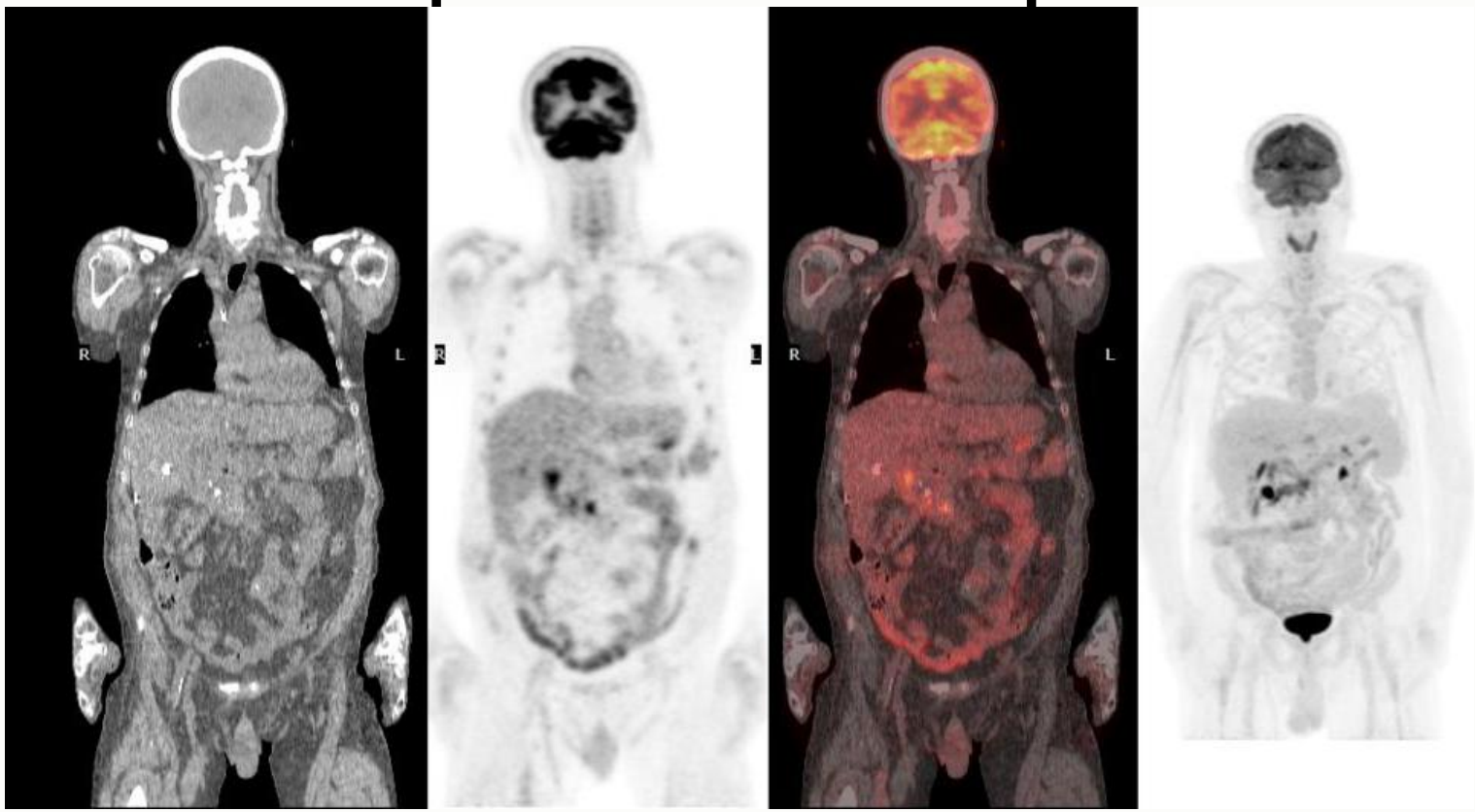
	Infection & Inflammation		Cancer		p
	No. pts	False negative rate	No. pts	False negative rate	
Hyperglycemia	19/123	0/11 (0%)	84/320	6/56 (10%)	NS
Normo-glycemia	104/123	4/54 (7%)	236/320	7/181 (4%)	NS
P		NS		P<0.05	
Diabetes Mellitus	42/123	2/26 (8%)	183/320	8/122 (7%)	NS
No diabetes	83/123	2/39 (5%)	137/320	5/115 (4%)	NS
P		NS		NS	

- Hyperglycemia but not DM affect FDG-PET/CT detection rate of cancer ($p<0.05$)
- Neither DM nor hyperglycemia had a significant impact on false negative rate of FDG imaging in infection

An urgent case

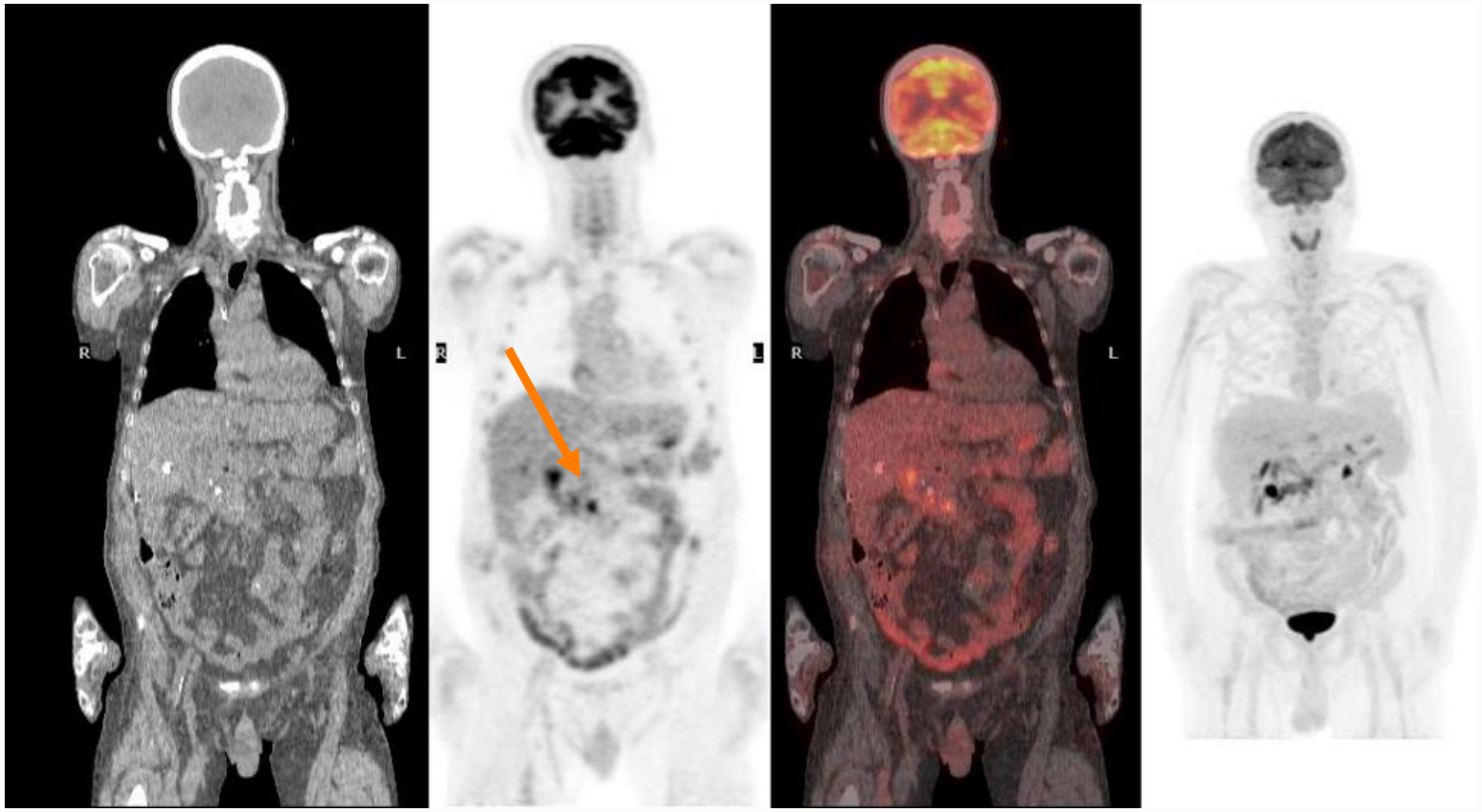
- 45 year old female
- Awaiting cholecystectomy for gall stones
- Admitted with high fever and upper abdominal pain
- Surgeon wants a quick answer
- What kind of study would you suggest?
- What could you do to provide a quick answer?

Time of flight FDG PET-CT image 90 minutes post 367MBq F-18 FDG



What do you think?

FDG PET-CT shows 2 sites of focal uptake in the pancreas-abscesses



Summary

- FDG has increasing role in infection and inflammation
- Accuracy of reporting related to clinical situation
- How can we pay for this extra use of PET