Conventional Nuclear and PET Imaging of Suspected MSK infections

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Why Image Suspected MSK Infection?

- History, subjective symptoms, biochemistry, and physical findings often inconclusive
  - Especially early disease
- Bone biopsy relatively low yield & invasive
  - Complications, especially prostheses
  - Costs can mount
MSK Infections

- Acute osteomyelitis
- Diabetic foot infection
- Spondylodiscitis
- Post-traumatic bone infection
- Inflected orthopedic prosthesis
- Chronic osteomyelitis
Anatomic Imaging of MSK Infections

• **Radiography** is *moderately Sn* for *early OM*
  – X-ray not Sn for OM until 10 to 21 days because to be radiographically visible bone density loss must reach 30-50%

• **CT & MRI** also *moderately Sp* for *OM* when complicated by **hardware**
  – Metallic implants cause artifacts on CT
  – Can’t do MRI on traditional metal implants
  – *Conventional functional imaging* also *moderately Sn* because of increased non-specific accumulation due to implants
Comparing Modalities in MSK (OM)

Table 2 – Diagnostic Imaging Studies for Osteomyelitis

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography</td>
<td>67</td>
<td>50</td>
<td>Generally should not be used in osteomyelitis evaluation</td>
</tr>
<tr>
<td>Leukocyte scintigraphy</td>
<td>61 to 84</td>
<td>60 to 68</td>
<td>Combining with technetium-99 bone scintigraphy can increase specificity</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>78 to 90</td>
<td>60 to 90</td>
<td>Useful to distinguish between soft tissue and bone infection, and to</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>determine extent of infection; less useful in locations of surgical</td>
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<td></td>
<td></td>
<td></td>
<td>hardware because of image distortion</td>
</tr>
<tr>
<td>Plain radiography</td>
<td>14 to 54</td>
<td>68 to 70</td>
<td>Preferred imaging modality; useful to rule out other pathology</td>
</tr>
<tr>
<td>(anteroposterior, lateral,</td>
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<tr>
<td>and oblique views)</td>
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<tr>
<td>Positron emission tomography</td>
<td>96</td>
<td>91</td>
<td>Expensive; limited availability</td>
</tr>
<tr>
<td>Technetium-99 bone scintigraphy</td>
<td>82</td>
<td>25</td>
<td>Low specificity, especially if patient has had recent trauma or surgery;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>useful to differentiate osteomyelitis from cellulitis, and in patients in</td>
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<td></td>
<td></td>
<td></td>
<td>whom magnetic resonance imaging is contraindicated</td>
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</table>

Conventional Nuclear Imaging of MSK Infections
Tc-99m MDP Bone Scan

• Tc-99m labeled bisphosphonates (MDP and HDP) demonstrate **osteoblastic** activity

• In general, **Sn** of Tc-99m MDP for osteomyelitis is > 90% but **Sp** depends
  – If bony structure **not** complicated by fracture or hardware, **Sp is > 90%**
  – If post-traumatic or post-surgical, **Sp is ~35%**
Tc-99m MDP Bone Scan

- 740 MBq (20 mCi) of Tc-99m MDP injected IV
- Imaging on LEHR collimator
  - Photopoeak set at 140 keV
- Effective dose: 6.3 mSv
- 3 phases to increase Sp
  - 1\textsuperscript{st} phase: flow
  - 2\textsuperscript{nd} phase: blood pool
  - 3\textsuperscript{rd} phase: delayed (3-4 hours post injection)
Gallium Scan

• In general, Ga-67 has high Sn for acute and chronic infection and non-infectious inflammation

• But Sp for infection is low

• Other shortcomings
  – Need for delayed imaging beyond 24 hours
  – Can’t administer high dose activity (high effective dose, 15 mSv, and long half life of Ga-67, 78 hrs)
  – Limited spatial resolution because low counts
  – Physiologic bowel and soft tissue uptake
Gallium Scan

• 150-220 MBq (4-6 mCi) of Ga-67 Citrate injected IV
  – Up to 330 MBq (9 mCi) for larger patients

• Imaging on MEGP collimator
  – Photopeaks set at 93 and 184 (and 296) keV

• Effective dose: 15 mSv

• Images acquired 24-72 hrs after injection
  – 4- or 96-hr images help abdomen interpretation
Sulfur Colloid Marrow Scan

- In general, Tc-99m sulfur colloid correlates with red bone marrow
- 300-370 MBq (8-10 mCi) of Tc-99m sulfur colloid injected IV
- Imaging on LEGP collimator
  - Photopeak set at 140 keV
- Effective dose: 2.1 mSv
- Images acquired 30 min after injection
Radiolabeled WBC Scan

• In the **proper clinical context**, Tc-99m and In-111 labeled WBC have **Sp > 90%**
  – Sn is excellent in peripheral skeleton (Sn > 95%)
• But **Sn of radiolabeled WBC for infection in central skeleton is poor**
• Other shortcomings
  – Laborious preparation, requiring specialized equipment & handling of possibly infected blood
  – Poor spatial resolution – can’t always separate bone from soft tissue infection
  – Normal bone marrow can cause False Positives
  – Not useful in leukopenic patients (granulocytes < 2K/mL)
Radiolabeled WBC Scan

- 40 mL of patient’s blood is drawn and labeled with In-111-Oxine (or Tc-99m-HMPAO)
- 18-24 MBq (0.5-0.6 mCi) In-111 WBC injected IV
  - 185-370 MBq (5-10 mCi) Tc-99m HMPAO IV
- MEGP with photopeaks at 174 and 247 keV
  - LEGP with 140 keV photopeak for Tc-99m HMPAO
- Effective dose: 6.7 mSv for In-111 WBC
  - 8.1 mSv for Tc-99m HMPAO
- Acquisition immediately if preferred, always 18-24 hours later
Radiolabeled WBC Scan

**Radiolabeled WBC Scan**
- Acquisition by **24 hours**
- Great Sn and higher Sp for **acute** infections than Gallium Scan
  - Not as Sn as Gallium Scan for **chronic** infections
- **Less variable physiologic uptake** (especially In-111 WBC)
- **Concurrent antibiotics & photopenic central skeleton lesions produce FP & FN**

**Gallium Scan**
- Acquisition by **48 hours**, sometimes longer
- **Excellent Sn** for infection, inflammation and neoplasm
- **Lot of variability of physiologic uptake**, which is usually in GI tract, GU tract and soft tissues
Radiolabeled WBC Scan

**In-111 WBC**
- Does **not** concentrate in GI tract, GU tract or GB, thus better for abdominopelvic infections
- Longer half-life of In-111 (67 hours) allows **better delayed imaging** than Tc-99m
- Obligates us to use lower administered dose, causing grainier images

**Tc-99m-HMPAO WBC**
- Labeling less stable than In-111 WBC
  - Tracer in GIT, GUT and GB
- 6 h H.L. of Tc-99m leads to higher dose, thus more counts and **better quality images**
- Faster uptake in infection sites, thus **better earlier imaging**
- Better visualization of small anatomy
- Low absorbed radiation doses make it more suitable than In-111 for **infants & children**
Bone + Radiolabeled WBC Scan

- Palestro’s team at Long Island Jewish Medical Center studied 24 patients with a variety of suspected OM (prosthetic joint, long bone, and diabetic foot)
  - Also screened with antigranulocyte scan, In-111 WBC scan & bone scan

Bone + Radiolabeled WBC Scan

- **11 cases** (5 DM foot OM and 6 infected joint prostheses) proven by histopath

- Radiolabeled WBC scan was TP in 10 cases, but FP in 4 cases
  - 1 FP but 5 TP in knee prostheses

- Thus, Sn was 91% but Sp 62%

Example of false positive, as this was read as hip prosthesis infection

Other false positives included soft tissue infection and gangrene

Bone + Radiolabeled WBC Scan

• Bone scan was 100% Sn, thus excellent NPV
  – But Sp was 38%

• Adding bone scan to radiolabeled WBC scan improved Sp to 77%
  – Sn remained 100%

A case where bone scan prevented a false positive. The photopenic defect on bone scan proved to be gangrene.

Bone + Radiolabeled WBC Scan

- In diabetic foot, seems best to combine bone scan with radiolabeled WBC scan
- Bone scan is 100% Sn, but Sp low largely because of neuropathic joint disease
- In French study, 75 diabetics with 83 foot ulcers were scanned for suspected OM

Bone + Radiolabeled WBC Scan

- 41 (of 83) ulcers diagnosed as OM by histopathology (15) or follow-up x-rays
- Concordant findings: positive for infection
- Discordant findings: negative
  - Focus on radiolabeled WBC scan but correlation to bone on bone scan

OM of the Right 1st toe

Bone + Radiolabeled WBC Scan

- Bone + radiolabeled WBC scintigraphy was TP in 38 cases → Sn of 93%
- Among 42 ulcers not associated with OM, combination scintigraphy had 41 TN → Sp 98%

Bone + Radiolabeled WBC Scan

• Bessette’s group in Milwaukee reviewed 32 patients with suspected sternal OM
  • Group composed of 12 patients with biopsy-proven sternal OM
  • All scanned with CT and radiolabeled WBC + bone scans

• CT positive for sternal OM in 7 patients - 5 bony erosions & 2 severe demin (Sn 58%)
  • Combination scintigraphy positive in 11 patients (Sn 92%)
    – 1 case of FP due to concurrent IV antibiotics which was not seen on radiolabeled WBC scan

Radiolabeled WBC & Vertebral OM

• Palesto’s team in NY reviewed 71 patients where radiolabeled WBC scan performed for possible vertebral OM
  – 57 had bone scan too (31 were two-phase)
  – Final diagnosis based on variety of endpoints
• 28 patients identified with vertebral OM
  – 24 cases confirmed

• In many cases, radiolabeled WBC scans were photopenic in confirmed infection sites

Radiolabeled WBC & Vertebral OM

- 15 (of 28) cases of vertebral OM had absent or ↓ radiolabeled WBC activity
  - Sn 54% and Sp 52%
- Of 12 with ↑ vertebral activity, 11 had confirmed vertebral OM
  - Sp 98%, but Sn 39%
- 26 scans had “normal” vertebral uptake
  - 2 had confirmed OM

TABLE 3
Comparison of Leukocyte and Bone Scintigraphy for Diagnosis of Vertebral Osteomyelitis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Sen</th>
<th>Spc</th>
<th>Acc</th>
<th>+PV</th>
<th>−PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte (I)</td>
<td>39%</td>
<td>98%</td>
<td>76%</td>
<td>92%</td>
<td>73%</td>
</tr>
<tr>
<td>(n = 76)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Leukocyte (D)</td>
<td>54%</td>
<td>52%</td>
<td>53%</td>
<td>39%</td>
<td>66%</td>
</tr>
<tr>
<td>(n = 76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte (I or D)</td>
<td>93%</td>
<td>50%</td>
<td>66%</td>
<td>52%</td>
<td>92%</td>
</tr>
<tr>
<td>(n = 76)</td>
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<td></td>
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</tr>
<tr>
<td>Two-Phase bone (I)</td>
<td>47%</td>
<td>71%</td>
<td>58%</td>
<td>67%</td>
<td>53%</td>
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<tr>
<td>(n = 31)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Delayed bone (I)</td>
<td>86%</td>
<td>49%</td>
<td>63%</td>
<td>51%</td>
<td>85%</td>
</tr>
<tr>
<td>(n = 57)</td>
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</table>

Sen = sensitivity; Spc = specificity; Acc = accuracy; +PV = positive predictive value; −PV = negative predictive value; I = increased; and D = decreased.

FIGURE 2. The principal limitation to labeled leukocyte imaging in vertebral osteomyelitis is the nonspecificity of skeletal photopenia, present in 54% of the cases of osteomyelitis in our series. We were unable to distinguish the skeletal photopenia seen in infection from other causes of skeletal photopenia: (A) Thoracic vertebral osteomyelitis in a 57-year-old male symptomatic for 6 mo (purulence only was present in biopsy specimen—no organisms were cultured). (B) Prostate carcinoma metastases to the lower thoracic spine in a 73-year-old male (photopenia involving a right lower posterior rib is also evident). (C) Lumbar spine compression fractures in a 66-year-old female. (D) Paget’s disease involving L5 in a 61-year-old male.

Radiolabeled WBC & Skull OM

- In Seabold’s study at the U. of Iowa, 26 patients with suspected cranial OM (16 were post-operative)
- Variety of studies including CT & MR with contrast and SPECT bone and radiolabeled WBC scan

Radiolabeled WBC & Skull OM

Radiolabeled WBC & Skull OM

- **If no prior intervention in skull** (with minimal bone marrow), **CT and bone scan** most Sn for OM
- **In skull base** without prior intervention, **MR and bone scan** most Sn for OM
- **MR is best imaging to assess extent of soft tissue involvement**
- **In skull with pre-existing abnormality** (e.g., post-surgery), **combined radiolabeled WBC & bone scans** most Acc for OM
- **Abnormal findings revert back to normal sooner** with **radiolabeled WBC scan vs MRI and CT** in successfully treated patients

Radiolabeled WBC + Marrow Scan in Hardware Infections

- In painful prostheses, radiolabeled WBC hard to interpret because poor Sp
  - WBC accumulate in normal marrow via phagocytosis
  - Bone scan also poor Sp
- Radiolabeled WBC + Tc-99m sulfur colloid (marrow) scans investigated since 1990
- Combination of WBC & marrow scans is positive for HW-associated infection when positive WBC scan finding has no corresponding activity on marrow scan (i.e., incongruent)

Radiolabeled WBC + Marrow Scan in Hardware Infections

Radiolabeled WBC + Marrow Scan in Hardware Infections

Neuropathic Arthropathy

Uninfected Hardware

Radiolabeled WBC + Marrow Scan in Hardware Infections

• Vexing issues with this combination
  – If no WBC activity (like central skeleton when photopenic defect corresponds to infection), marrow scan no help
  – Photopenic defect on marrow scan may not be present in 1st week after onset of OM
  – Sulfur colloid degrades 2 hours after preparation, causing erroneous conclusions

Radiolabeled WBC + Marrow Scan in Hardware Infections

• 92 hip arthroplasties studied by Palesto’s team at NY Mount Sinai Center
  – Arthroplasties considered infected if operative cultures grew organisms (n=19) or gross purulence at surgery (n=4)
• Among 42 with only In-111 WBC scan, Sn best in femoral head zone, 87%, and Sp 94%
• Among 50 with combined radiolabeled WBC/marrow scans, Sn was 100% and Sp 97% using criteria of incongruence

Radiolabeled WBC + Marrow Scan in Hardware Infections

• Love’s team in NY reviewed 59 patients with painful prosthesis who had FDG, marrow and radiolabeled WBC scans
  – Also had histopath and/or microbiology dx
  – Only non-AC FDG PET images reviewed

Radiolabeled WBC + Marrow Scan in Hardware Infections

- Radiolabeled WBC + marrow scans very Sn (100%) and Sp (91%) for infected prosthetic joints
  - Sn/Sp 100% for painful knee prostheses (n=19)
- Acc 95% vs 61% for FDG PET
- Tracers are different
  - Neutrophils present in acute infection but absent in loosening, thus high Sp/Sn
  - FDG into activated inflamm cells, thus high FP

Radiolabeled WBC + Marrow Scan in Hardware Infections

- Van Acker’s team in Belgium prospectively studied 21 patients with 3-phase bone scan to exclude TKA infection
- Radiolabeled WBC scan with Tc-99m HMPAO; SPECT 4 hours & planar 24 hours post-injection
  - Used 0-4 grading scale for uptake, and uptake at bone-prosthesis interface (BPI) considered positive
- Compared to FDG PET

- Focal radiolabeled WBC activity alone was 53% Sp
- Sp became 93% when correlated with “hot spot” on bone scan
  - 4 FP (loosening) on WBC scan ↓ to 1 because of bone scan
  - Radiolabeled WBC 100% Sn
- Focal FDG uptake alone was 73% Sp
- Sp became 80% when correlated with “hot spot” on bone
  - FDG scan 100% Sn

Radiolabeled WBC SPECT/CT

- Filippi’s team in Rome studied 15 patients with suspected OM and 13 patients with suspected HW infection
- Planar 99m-Tc HMPAO images taken ½, 4 & 24 hr post injection
- 99m-Tc HMPAO SPECT/CT taken 6 hr post injection

Radiolabeled WBC SPECT/CT

- **100% Sp** of SPECT + planar alone (no CT)
- But **Sn poor**: 7 FNs & 3 false extent of disease (soft tissue & bone)
- **SPECT/CT improved localization** of focal radiolabeled WBC activity in **35%** of 28 cases
- **Sn** and **Sp** of SPECT/CT for diagnosing infection was **100%**

Tc-99m MDP Bone SPECT/CT Case

• 46-year-old man with history of bilateral amputations presents with long-standing chronic non-healing wound at the left below knee amputation (BKA), sustained after a crush injury

• Referred for bone scan to exclude osteomyelitis of left stump

Tc-99m MDP Bone SPECT/CT Case

On Tc-99m MDP bone SPECT/CT, increased tracer accumulation corresponds to heterotopic ossification on CT, not to bone, thus excluding OM with high degree of Sn.
Adding CT to SPECT

• Disadvantages
  – Lower count rate versus planar imaging (as it is reconstructed and not truly tomographic imaging)
  – Lower spatial resolution than planar imaging
  – Takes longer to acquire good-quality images

• Advantages
  – Localizes “hot spot,” thus showing whether it is at site of interest or outside of it
  – Regardless of tracer or disease entity, scintigraphy’s Sp goes up when CT added
  – Improves inter-reader agreement & management of patients


Summary of Gamma Imaging of Suspected MSK Infections

• **Bone Scan** has excellent Sn but poor Sp
• **Radiolabeled WBC Scan** has good Sp & Sn in peripheral skeleton
  – Poor Sn in central skeleton
• **Bone + Radiolabeled WBC scans** improve Sp (and thus accuracy)
  – But in diabetic foot ulcer/OM, neuropathic joint disease is problem
  – Good Acc in infected knee & hip prostheses
Summary of Gamma Imaging of Suspected MSK Infections

• Radiolabeled WBC + Marrow scans improve accuracy
  – Better in diabetic foot OM/ulcer
  – Perhaps better Acc in infected knee prostheses

• Impact of SPECT and SPECT/CT
  – Improves accuracy and localization
F-18 FDG PET Imaging of MSK Infections
F-18 FDG

• FDG enters cells via glucose transporters
  – Active transport mediated by GLUT 1-10, but primarily by GLUT 1 & 3
  – Active transport by Na\(^+\)-glucose transporter (primary mechanism for kidney epithelial & intestinal cells)
  – Passive diffusion is minor compared to active
• FDG gets phosphorylated and not further metabolized
  – 2’-FDG-6 phosphate not substrate for glycolytic pathway or pentose-phosphate shunt
  – Low initial concentrations of FDG in normal fasting heart & brain, but uptake increases over time
FDG & WBC

• Accumulates much more in **activated** (versus inactive) lymphocytes and especially **neutrophils & macrophages**
  – 24 hours after activation of WBC, increased de novo synthesis of GLUT-1 & 3
  – **Blood glucose < 250 mg/dL**, FDG uptake into inflammatory cells **not** impaired

• **Radiolabeled WBCs** are different, going **wherever WBC are**, activated or not
  – FDG relatively **low accumulation in normal marrow**

Patient History & FDG PET

• Positive PET findings have to be interpreted in context of patient history
  – FDG PET is a non-specific tracer
  – Active inflammation present for months to year after orthopedic surgery
  – Inflammation related to bone remodeling after fracture or surgical intervention
F-18 FDG PET/CT Scan

- 370-740 MBq (10-20 mCi) of F-18 FDG by IV
- Imaging on PET/CT scanner
  - Low-dose CT for anatomic localization & attenuation correction
- Effective dose: 14.1 mSv
- **Partial body** PET/CT to reduce radiation dose
- Image acquisition starts about 45 min after injection and lasts **35 minutes** (3-5 min for CT)
FDG PET & Chronic OM

• In acute OM, FDG PET adds no value over CT, MRI and combination scintigraphy
  – *Conventional Imaging has > 90% accuracy*

• FDG PET useful in chronic OM (COM), where these modalities are limited
  – **COM**: > 6 weeks of ongoing bone infection whether or not signs & symptoms are present
  – Anatomic imaging: low Sp of X-ray, CT & MR (most Sn?) for various reasons
  – Functional imaging: low Sp (bone & gallium scans) or low Sn (radiolabeled WBC scan), also potential for suboptimal preparation, lots of time and costs
FDG PET & Chronic OM

- Zhuang’s team studied 22 patients at Penn
  - 6 diagnosed with **COM but no criteria** defined (except 1 year follow-up)
- All 6 COM cases diagnosed by 3 readers using **FDG PET** (no CT), thus **Sn 100%**
  - 2 patients had False Positive diagnosis by PET (both osteotomy-related inflammation), thus **Sp not good**
FDG PET & Chronic OM

- Guhlmann’s team prospectively studied 51 patients, 28 proven COM
  - Recurrent or OM sx > 6 wks
- FDG PET detected COM in 27 of 28 → Sn of 96%
- Excluded COM in 22 of 23 patients → Sp 96%
- AGAb scan (+ bone scan) had Sn/Sp 82%/88%

Case 1

- Man in his 50s complains of long standing central chest pain ("for years")
  - PCP localizes it to sternum, which is TTP and worse with exertion
  - Remote history of trauma to sternum, but no surgical intervention
  - Labs were relatively normal

- Seen at VA in 2009 from OSH, then again in 2011
Radiolabeled WBC Scan 9/2009
Case 1

- PCP relied on negative WBC study
  - Recall that this has poor to moderate Sn for chronic infections
- CT-guided aspiration biopsy was negative
  - Sensitivity of procedure is moderate (73-87%), on lower end if on antibiotics
- New PCP reviewed reports and wants bone scan because patient’s sternal complains slightly worsening

FDG PET & Post-traumatic OM

• Hartmann’s team in Switzerland reviewed 33 partial body FDG PET/CT in post-trauma patients suspected to have COM
  • 18 had metallic implants
  • Histopathology or culture was standard reference

• Radiolabeled WBC/Marrow scans study of choice for post-traumatic infection imaging
  – MRI & CT susceptible to safety issue & beam-hardening artifact
  – Bone scan susceptible to post-traumatic bone remodeling

FDG PET & Post-traumatic OM

FDG PET & Post-traumatic OM

- Of 33 partial PET/CT, 17 were TP (and 2 FP) → **Sn 94%**
- 13 were TN (and 1 FN) → **Sp 87%**
- **Axial (or central)** skeleton: 88% Sn and 100% Sp
- **Appendicular** skeleton: Sn 100% and Sp 85%

FDG PET & OM of Diabetic Foot

• Schwegler’s Swiss team prospectively studied 20 DM patients with chronic foot ulcer (> 8 weeks) but no signs of OM

• 7 biopsy-proven OM in unsuspected foot

• MRI: TP in 6 patients

• FDG PET (no CT): TP in 2 patients

• Both TN in 12 of 13 patients

Schwegler B et al. Unsuspected osteomyelitis is frequent in persistent diabetic foot ulcer and better diagnosed by MRI than by 18 F-FDG PET or 99m Tc-MOAB. J of Int Med 2007; 263; 99–10.
Keidar’s Israeli team prospectively studied 18 pedal sites in 14 diabetic patients

- **PET** found 14 foci
- **PET/CT** localized 8 foci to bone (4 patients)
  - 1 case characterized findings as neuropathic arthropathy
FDG PET & OM of Diabetic Foot

- PET/CT read by NM docs & skeletal radiologist
- Of 8 OM findings on PET/CT (4 pts), 5 in metatarsal bones
  - CT characterized 5 ‘likely OM’ (of which 3 normal)
- All 4 patients PET/CT positive patients confirmed to have OM (3 histopath, 1 clinical + x-rays hx)

**FIGURE 2.** PET/CT-based exclusion of osteomyelitis and localization of infection to soft-tissue abscess in 43-y-old woman with nonhealing ulcer and cellulitis in lateral aspect of right foot. (A and B) 18F-FDG PET coronal (A) and transaxial (B) images show area of increased 18F-FDG uptake in lateral aspect of mid foot. (C) PET/CT localizes abnormal 18F-FDG uptake to soft tissues. (D) CT shows soft-tissue swelling in same area. Patient underwent local drainage and short course of antimicrobial therapy with good clinical response. No evidence of osteomyelitis was found during a clinical and imaging follow-up of 12 mo.

FDG PET & Spondylitis (Vertebral OM)

• In Schmitz’ Germany study, PET scans in 16 patients with suspected spondylodiscitis
  – All had surgery

• 12 (of 16) had histopath confirmed SDitis

• FDG PET: all 12 TP

• FDG PET: 3 of 4 TN

FDG PET & Spondylitis (Vertebral OM)

• Of 15 patients with suspected central skeleton COM, Sn of FDG PET (*no CT*) was 95% and Sp 100%

• FDG PET is 96% accurate diagnosing COM of central skeleton (eg, chronic spondylitis)

FDG PET & Spondylitis (Vertebral OM)

• De Winter’s study used FDG PET in 33 patients with suspected central skeleton OM:
  – Sn 100% and Sp 90%
• Vertebral column: **10 TN & 2 TP**
  – No false findings
• 5 lesions complicated by **HW**
  – **4 TN & 1 TP**
    *(No False findings)*

TABLE III Advantages and Disadvantages of Fluorine-18 Fluorodeoxyglucose-Positron Emission Tomography for the Diagnosis of Musculoskeletal Infections

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Early (1-hr) imaging</td>
<td>High-cost</td>
</tr>
<tr>
<td>High target-to-background ratio</td>
<td>Possible lower sensitivity in diabetic patients</td>
</tr>
<tr>
<td>High resolution (±5 mm)</td>
<td>Patient must be sober for at least 4 hrs</td>
</tr>
<tr>
<td>High-count tomographic images</td>
<td>Technique is currently not widely available</td>
</tr>
<tr>
<td>Low bone and bone-marrow uptake</td>
<td>Differentiation between tumor and infection is not possible</td>
</tr>
<tr>
<td>Highly accurate in central skeleton</td>
<td></td>
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<tr>
<td>Not hindered by metal implants</td>
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<tr>
<td>No additional scans necessary, all-in-one technique</td>
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<tr>
<td>High interobserver agreement</td>
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<tr>
<td>Theoretically sensitive in low-grade infections</td>
<td></td>
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<tr>
<td>Use may be feasible in neutropenic patients</td>
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FDG PET & Infected Hip Prostheses

- In U. Penn study of 53 hip prosthesis, FDG PET had 11 TP of 12 pathology-proven infections (Sn 92%)
- Of 41 non-infected hip cases, PET was TN in 40 cases (Sp 98%)

**Criteria** to call FDG-avid finding an infection:
- Location, not intensity, determining factor
- FDG uptake at Bone-Prosthesis Interface considered positive
- Other publications showed BPI FDG uptake increases Sp
- FDG uptake in soft tissue was non-specific

FDG PET & Infected Hip Prostheses

Fig. 1. Coronal (A), sagittal (B), and axial (C) FDG PET images from a 44-year-old female who presented with painful right hip prosthesis. Arrows indicate increased activity in direct contact with the prosthesis in the region of the femoral component, corresponding to the bone-prosthesis interface. Histopathological examination of tissues obtained during revision arthroplasty was consistent with infection. Similar views (D, E and F) from a 53-year-old, asymptomatic male with a history of total hip arthroplasty 9 months prior to FDG PET imaging. In D, arrows indicate increased activity in the region of the femoral neck and greater trochanter, which is a non-specific finding and does not indicate infection.
FDG PET & Infected Hip Prostheses

• Of 12 pathology-proven knee prostheses infections, FDG PET was TP in 11 cases (Sn 92%)

• Of 24 non-infected knee prostheses, PET was TN in 18 cases (Sn 75%)

• In 15 patients with HW other than the knees, PET was TN in 11 cases and TP in 4 cases and zero False findings (100% accuracy)

FDG PET & Infected Hip Prostheses

FDG PET & Septic Hip Loosening

• In Aachen, Germany, Mumme’s team studied 70 hip prostheses with suspected loosening in 50 patients
  – 50 hip prostheses had micro & histopath evaluation; 20 prostheses did not
• 3-phase bone scan done to differentiate septic from aseptic loosening: 78% Sn & 70% Sp
• FDG PET (no CT): 91% Sn & 92% Sp
  – FDG uptake in B-P Interface & surrounding soft tissue is “inflammation” beyond loosening (category 5)
• Like Chacko’s study, SUV did not correlate well with infected versus non-infected prosthesis

FDG PET & Septic Hip Loosening

FDG PET & Septic Hip Loosening

Fig. 3a,b Histopathological findings from aseptic and septic arthroplasty loosening. 

a Polyethylene wear particles (small arrows) surrounded by macrophages and multinuclear giant cells (big arrows) (aseptic loosening); b polyethylene wear particles (small arrows) surrounded by leucocytes and parenchymal cell debris (stars) (septic loosening) as well as macrophages and multinuclear giant cells (big arrows) (polarization microscopy, ×100; H&E staining, iron reaction, ×100)

FDG PET & Infected Knee Prosthesis

- FDG PET not as accurate in knee prostheses
  - Unlike hip prosthesis where Sn & Sp are ~90%
- In Van Acker’s study of 21 patients with painful knee prostheses, PET was 100% Sn (using non-AC images), but 73% Sp
  - When abnormal FDG activity on PET corresponded to “hot spot” on delayed bone scan, Sp improved to 80%
  - 2 False Positives (even with bone scan) were due to aseptic loosening
- Non-specific focal FDG uptake seen 36 months after surgery in asymptomatic TKA

FDG PET & Infected Knee Prosthesis

Fig. 6a–d. Loosening of a TKA. a Focal MDP uptake of grade 4 around the tibial neck of the prosthesis; b congruent focal lesion on MDP SPET; c no focal uptake on WBC SPET; d false-positive congruent lesion on PET (grade 4, SUV 3.2)
FDG PET & Infected Knee Prosthesis

- Zhuang U. Penn team published that FDG PET better at diagnosing hip versus knee prosthesis infections
  - **Knee**: 10 TP of 11 knee prosthesis infections, but 7 FP among 25 non-infected knees (Sn 91% & Sp 72%)
  - **Hip**: 9 TP of 10 hip prosthesis infections, and 3 FP among 28 non-infected hips (Sn 90% & Sp 89%)

- In all 10 False Positive cases, surgery > 1 year before PET scan performed

- Study confirmed presence, not intensity, of FDG uptake at BPI is what best correlates to infection

FDG PET & Infected Knee Prosthesis

FIGURE 2. (A) Coronal image of 72-y-old woman with hip prosthesis. Periprosthetic infection on right side was identified (arrowheads). (B) Coronal image of 76-y-old woman with bilateral hip prostheses. Both infection (arrowhead) and loosening (arrows) were shown. (C) Coronal image of 78-y-old man with painful left hip prosthesis. Arrowheads indicate periprosthetic infection and osteomyelitis. (D) Coronal image of 76-y-old woman with bilateral hip prostheses. FDG uptake is noted only around neck of prosthesis (arrows). FDG PET diagnosis of loosening was confirmed after revision arthroplasty.

Case 2

• Man in his 60s complains of severe pain in L ankle
  – Recent of minor blunt trauma
  – Remote history of L ankle fracture s/p ORIF (“years ago,” at construction site)

• Seen at VA in late 2011 for ankle pain
  – WBC (especially neutrophils) & ESR high
Case 2

- Orthopedic team diagnosed patient with infected HW in L ankle
  - Plan to debride tissue and do HW Replacement
FDG PET False Positives & Prostheses

Fig. 1. Hip arthroplasty of the right side without any signs of loosening on the radiography. Note the prosthesis head localized eccentrically in the cup.

FDG PET False Positives & Prostheses

- **Positive FDG PET** at painful hip, but no infection on x-ray or bone scan
  - False Positive FDG PET
- **Biopsy**: macrophages & MNGCs around polyethylene particles

FDG PET False Positives & Other Cases

• **Uncomplicated** traumatic bone injury have abnormal FDG uptake up to **3 months post-trauma**
  – Fracture healing involves bone remodeling
• **Post-surgical bone** could have abnormal FDG uptake (but low) **greater than 1 year**
• Higher **FDG activity** ($\text{SUV}_{\text{max}} > 3$) raised likelihood of infection
  – In 21 patients suspected with OM, PET “showed high uptake of FDG within the infected tissue, with SUVs up to a maximum of 16.1. However, in fractures and pseudarthroses only very low FDG uptake, with SUVs of 0.2–1.1, was observed”
• **CT** (as in PET/CT) improves **Sp** (ie, reduces False Positives)

Summary of FDG PET of Suspected MSK Infections

• **FDG PET/CT** has the **best Sn and Sp** (ie, accuracy) in diagnosing **Chronic OM**
  – Any site, including **COM of vertebral bodies**

• No clear role for PET/CT in acute OM in **uncomplicated bone sites**
  – Dedicated MRI, bone + radiolabeled WBC scans or radiolabeled WBC + marrow scans are > 90% accurate
  – But **PET/CT** has **improved Sp** over MR and gamma modalities in **suspected acute OM of complicated bone**
Summary of FDG PET of Suspected MSK Infections

- **PET** has **excellent** negative predictive value (**NPV**) in **suspected diabetic foot infections**
  - Neuropathic arthropathy is still vexing issue (Radiolabeled WBC + Marrow scan may be better)
  - In patients with **high** clinical suspicion of diabetic foot OM, **FDG PET** as Sn and Sp as **MRI** (high)
  - When **low** suspicion, **MRI much better Sn**
Summary of FDG PET of Suspected MSK Infections

• In painful *hip* prostheses, FDG PET appears *most accurate* of all modalities
  – Best corresponding criterion for infected prosthesis is focal FDG at *Bone-Prosthesis Interface* (BPI)
  – Focal FDG uptake has good correlation, *SUV has none*
  – Debate still on whether focal FDG at *head & tip* also *highly Sp for infection*

• PET’s *Sn* is *excellent* for *knee* prosthesis infection, but *Sp is moderate*
  – May *need 2nd modality to reduce PET’s false positives* in suspected knee prosthesis infection
Summary of FDG PET of Suspected MSK Infections

• To ↓ False Positive in prostheses, 6 months isn't always sufficient between date of prosthesis implantation & date of PET, especially in knee prostheses

• Adding CT to PET data (as with SPECT) marginally improves Sn but significantly improves Sp (ie, significantly ↓ False Positives)
Best Nuclear Imaging for Suspected MSK Infections

• Suspected acute OM of the diabetic foot: Radiolabeled WBC + Marrow scans
  – Use Tc-99m HMPAO WBC (rather than In-111 WBC)
  – Ideally SPECT/CT
  – Consider MRI, Bone + Radiolabeled WBC scans

• Suspected acute OM of peripheral bones: Bone + Radiolabeled WBC scans
  – If complicated by HW or surgery, consider FDG PET/CT
  – Consider MRI if uncomplicated by prosthesis
  – Small bones: Tc-99m HMPAO WBC, not In-111 WBC
Best Nuclear Imaging for Suspected MSK Infections

- Suspected **acute OM of vertebral bodies** (spondylitis/spondlyodiscitis): **FDG PET/CT**
  - Consider MRI especially if not complicated by prosthesis or surgery

- Suspected **acute OM of skull**: **Depends**
  - No prior intervention in skull, **CT or bone scan**
  - Skull base without prior intervention, **MR or bone scan**
  - If prior intervention, **combined radiolabeled WBC & bone scans**
  - Role of FDG PET/CT unclear
Best Nuclear Imaging for Suspected MSK Infections

• Suspected **OM in post-fracture long bones:** *Unclear*
  • Consider any: MRI, CT, bone + radiolabeled WBC scans, or radiolabeled WBC + marrow scans and FDG PET/CT
  • Ideally SPECT/CT
  • If complicated by HW, consider FDG PET/CT

• Suspected **chronic OM:** **FDG PET/CT**
  – Especially central (skull and vertebral bodies)
  – Cases tend to be complicated by prostheses or sequestrum
Best Nuclear Imaging for Suspected MSK Infections

• Suspected infected knee prosthesis: radiolabeled WBC SPECT/CT + marrow scan
  • Consider MRI or bone + radiolabeled WBC scans
  • FDG PET/CT has excellent NPV but poor Sp in knee

• Suspected infected hip prosthesis: FDG PET/CT
  – Radiolabeled WBC SPECT/CT + marrow scan also highly accurate
  – Consider MRI or bone + radiolabeled WBC scans
Extended Bibliography & Thanks


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The End