The Painful Prosthetic Joint: Role of Nuclear Medicine

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Lower Extremity Prosthetic Joint Surgery

Year	Surgery	Hip	Knee	Total
2003	Primary	202,500	402,100	604,600
	Revision	36,000	32,700	68,700
	Total	238,500	434,800	673,300
2005	Primary	209,000	450,000	659,000
	Revision	40,000	38,000	78,000
	Total	249,000	488,000	737,000
2010*	Primary	253,000	663,000	916,000
	Revision	48,000	55,000	103,000
	Total	301,000	718,000	1,019,000

*estimated

Kurtz et al. JBJS 2007;89-A:780-785

Joint Replacement Surgery Complications

	Primary (%)		Revision (%)	
Etiology	TKA	THA	TKA	THA
Aseptic Loosening	≤ 8	2 - 14	10-15	10-15
Prosthetic Infection	≤ 2	≤ 1.3	6	3
Heterotopic Ossification	-	10- 50	-	15
Fracture	0.3	≤ 1	2	3
Dislocation	1 - 2	3	4	7

Campbell's Operative Orthopaedics (11th ed, 2008)

Complications of Joint Replacement Surgery

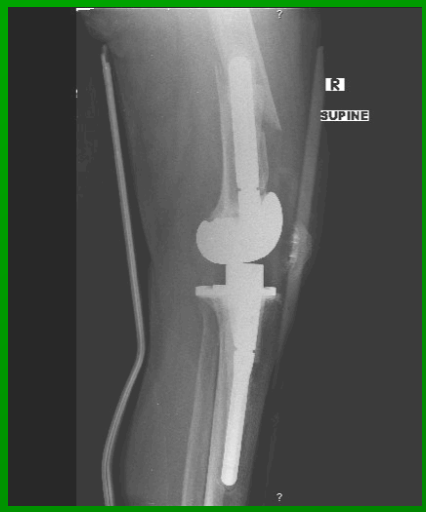
Fracture

Dislocation

Heterotopic ossification

Aseptic loosening

Infection



Aseptic Loosening

Surgical technique
Prosthetic components
Prosthetic design
Immune response

Immune Response

Related to prosthetic components

- Plastic liner
- Polymethylmethacrylate
- Metal

Aggressive process

- Synovial-like pseudomembranous structure
- Features of rheumatoid arthritis and foreign body reaction

Toumbis , Sem Arthritis Rheum, 1997; Wooley, Clin Orthop, 1996

Immune Response

Cellular composition

- Histiocytes (95%)
- Giant cells (80%)
- Lymphocytes/plasma cells (25%)
- Neutrophils (< 10%)

Toumbis , Sem Arthritis Rheum, 1997; Wooley, Clin Orthop, 1996

Aseptic Loosening

Cellular activation stimulates secretion of proteolytic enzymes & proinflammatory cytokines which damage bone & cartilage with resultant osteolysis & prosthetic loosening

Toumbis , Sem Arthritis Rheum, 1997; Wooley, Clin Orthop, 1996

Infection

Occurs in ≤ 2% of primary implants

Occurs in ≤ 6% of revisions

1/3 occur within 3 months after insertion

1/3 occur 3 months – 1 year after insertion

1/3 occur more than 1 year after insertion

Infection

Cellular composition

- Histiocytes
- Giant cells
- Lymphocytes/plasma cells
- ***Neutrophils invariably present***

Aseptic Loosening vs. Infection

Aseptic Loosening	Infection
Histiocytes	Histiocytes
Giant cells	Giant cells
Lymphocytes	Lymphocytes
Plasma cells	Plasma cells
	Neutrophils

Aseptic Loosening vs. Infection

- Aseptic loosening
  - Single stage exchange arthroplasty
    - One hospital admission
- Infection
  - Excisional arthroplasty
  - Antibiotic therapy
  - Revision arthroplasty
  - Multiple hospital admissions

Aseptic Loosening vs. Infection

- Differentiation can be challenging
  - Clinical signs of infection may be absent
  - Laboratory tests (WBC , ESR, CRP)
  - Lack sensitivity or specificity Joint aspiration with gram stain & culture
    - Definitive diagnostic test
    - Specificity 92% to 100%
    - Sensitivity 28% to 92%
    - Imaging studies often used

Sensitivity & Specificity

Sensitive but nonspecific test

- Multiple, expensive, operations when a single intervention may have sufficed

Specific but not sensitive test

- Results in additional surgical interventions because undiagnosed infection will cause any revision implant to fail

Imaging Modalities

Morphologic	Functional
X-ray	Bone scan
US	Gallium scan
CT	WBC imaging
MR	FDG-PET

Nuclear Medicine & Painful Joint Replacements

- Role
  - Screening test
  - Determine presence of infection
- Procedures
  - Bone scintigraphy
  - Bone/gallium scintigraphy
  - Leukocyte/marrow scintigraphy
  - FDG-PET

Bone Imaging

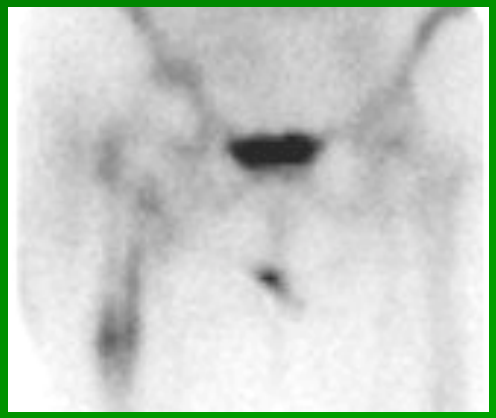
- ^{99m}Tc-MDP (methylene diphosphonate)
  - Binds to hydroxyapatite crystals
  - Uptake dependent upon
    - Blood flow
    - Rate of new bone formation

Periprosthetic Uptake Patterns

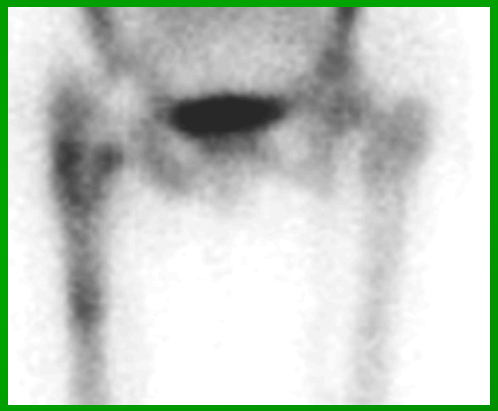
Loosening

Infection

Bone Scintigraphy



Infected

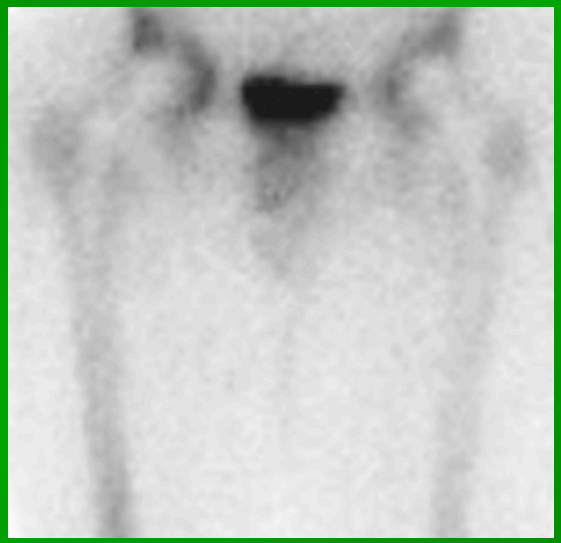


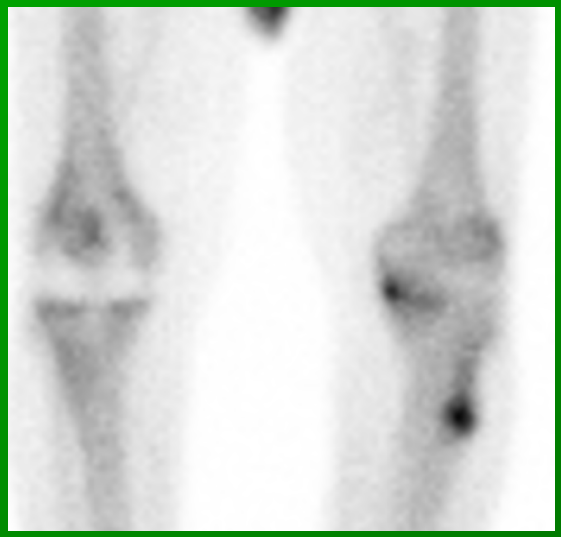
Aseptically Loosened

Bone Scan

Most useful when negative or when there are changes in periprosthetic uptake pattern over time

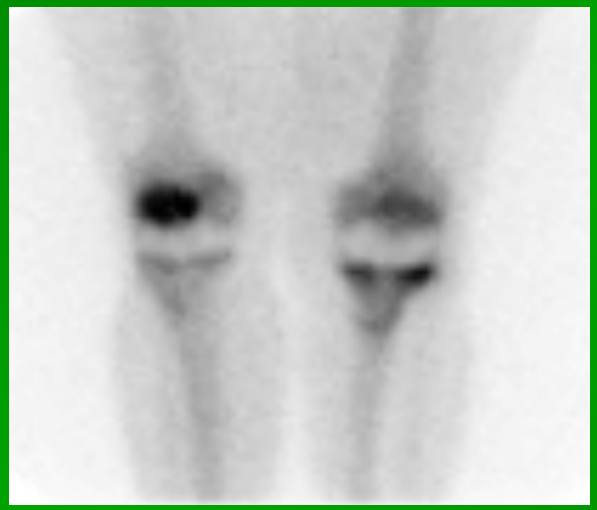
Normal: Periprosthetic uptake indistinguishable from adjacent non-articular bone





Painful Rt. Knee Replacement

Changes in periprosthetic uptake pattern over time



Rt: 7 yrs old

Lt: 1 yr old

Rt: 11 yrs old

Lt: 5 yrs old

Bone Scintigraphy in Joint Replacement Infection

Group	n=	Sen%	Spec%	Acc%
Tehranzadeh *(Radiology 1981)*	27	100	89	93
Mountford *(Nucl Med Comm 1986)*	50	100	46	58
Tehranzadeh *(Clin Nucl Med 1988)*	15	100	100	100
Magnuson *(Radiology 1988)*	49	100	18	53
Puskas *(Eur J Nucl Med 1992)*	43	92	24	48

150 Joint Replacements*
(All pts. had surgery)

- Patients (n=150)
  - 78 females, 72 males
  - Age 35-92 years
- 150 joint replacements
  - Age: 2 weeks – 22 years old
  - Hip (n=94)
  - Knee (n=56)

* Love et al., SNM 2008

94 Hip Replacements*

- Primary (n=70, THR:60, Hemi:=10)
  - Cemented (n=31)
  - Cementless (n= 21)
  - Hybrid (n=18)
- Revision (n=24)
  - Cemented (n=4)
  - Cementless (n=10)
  - Hybrid (n=10)

* Love et al., SNM 2008

56 Knee Replacements*

- Primary (n=43)
  - Cemented (n=40)
  - Cementless (n= 1)
  - Hybrid (n=2)
- Revision (n=13)
  - Cemented (n=10)
  - Cementless (n=2)
  - Hybrid (n=1)

* Love et al., SNM 2008

Final Diagnoses (n=150)*

	(n=)
Infected	67 (45%)
Aseptically loosened	67 (45%)
Miscellaneous	16 (10%)
Failed liners	*6*
Malpositioned components	*5*
Other	*5*

* Love et al., SNM 2008

67 Infected Prostheses

	(n=)
Organisms	56
Staphylococci	35
(MRSA)	*(9)*
Mixed flora	6
Streptococci	4
Candida sp	2
Enterococci	2
Other	7
Neutrophils	11
Total	67

Bone Scintigraphy in Joint Replacement Infection

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Puskas *(Eur J Nucl Med 1992)*	43	92	24	48
Love *(SNM 2008)*	150	78	28	50

Bone Scintigraphy in Joint Replacement Infection*

Prosthesis	Sensitivity	Specificity	Accuracy
All (150)	52/67 (.78)	31/83 (.37)	83/150 (.55)
THR (94)	20/34 (.59)	30/60 (.50)	50/94 (.53)
TKR (56)	32/33 (.97)	1/23 (.04)	33/56 (.59)

*Love et al., SNM 2008

Prosthetic Failure

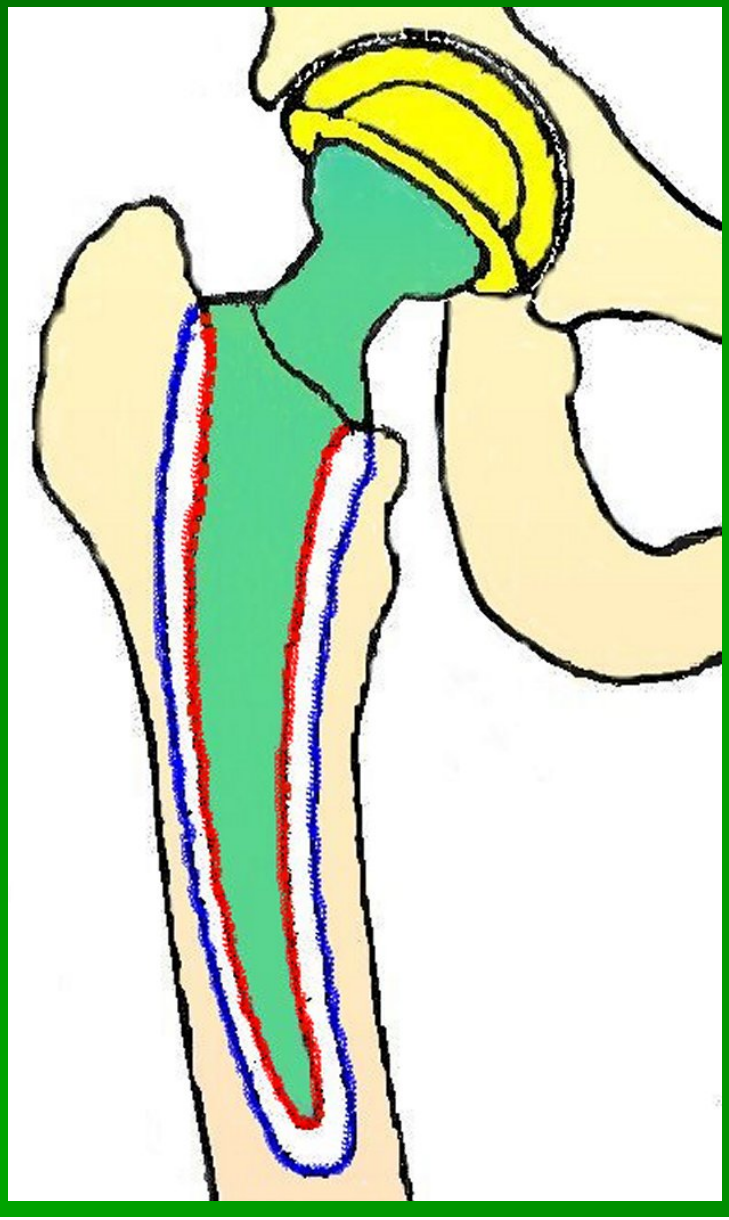
Loosening with infection

Loosening without infection

Infection without loosening

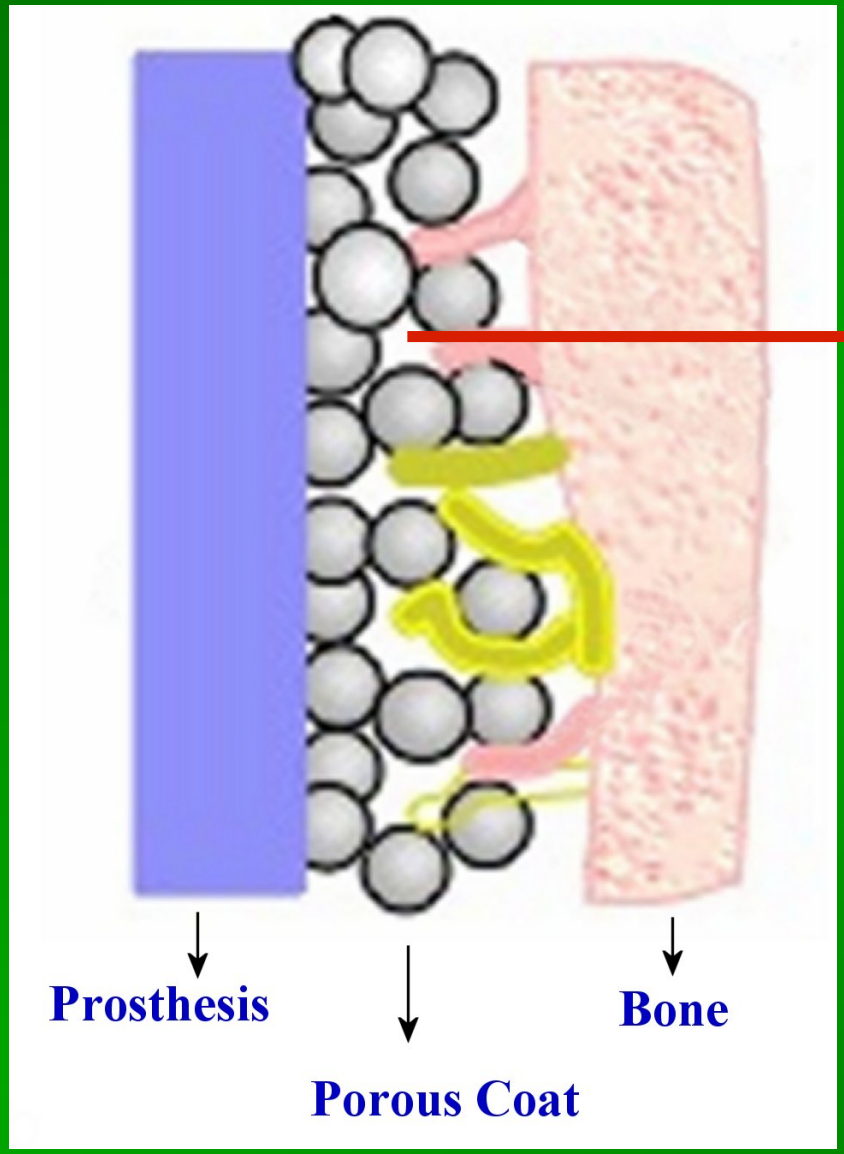
Other causes (neither infection nor loosening)

Cemented Prosthesis



- Cement (Polymethylmethacrylate)
- Prosthesis-cement interface
- Bone-cement interface

Cementless Prosthesis

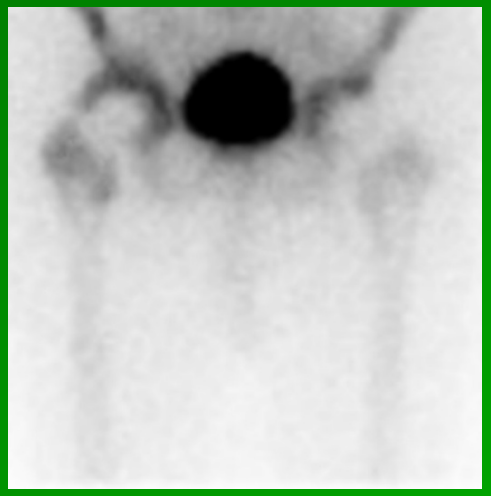


Bone-Prosthesis Interface

15 False (-) Bone Scans

- 14 prosthetic hips
  - 6 cementless femoral components
    - All fixed
  - 8 cemented femoral components
    - 6 fixed
    - 2 losening at cement-prosthesis interface
- 1 prosthetic knee
  - Cemented
    - Loosening at cement-prosthesis interface

Infected Prostheses



Fixed
Cementless
Lt. THR

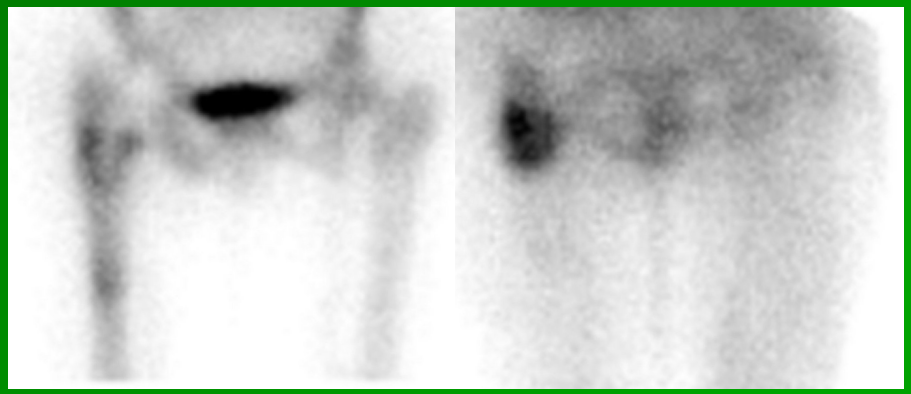
Fixed
Cemented
Rt. THR

Loose
Prosthesis-Cement
Rt. THR

Gallium Imaging

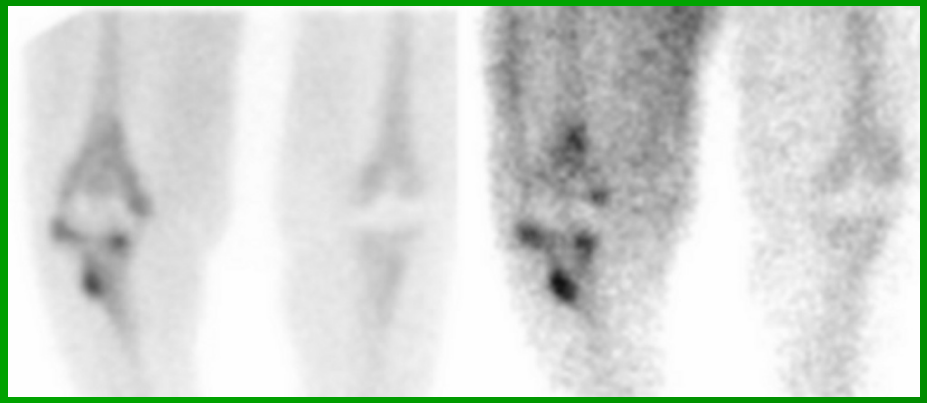
- Gallium-67 citrate
  - Uptake mechanisms
    - Transferrin delivery to inflammation
    - Lactoferrin binding at inflammation
    - Siderophore binding at inflammation
      - Direct bacterial uptake
      - Macrophage uptake
      - Leukocyte delivery to inflammation
  - Interpreted in conjunction with bone scan

Positive Bone/Gallium Scintigraphy



Bone Gallium

Spatially incongruent distribution of the 2 tracers



Spatially congruent distribution of the 2 tracers & intensity of Ga > MDP

Bone/Gallium Scintigraphy in Joint Replacement Infection

Group	n=	Sens%	Spec%	Acc%
Merkel *(The Hip 1984)*	14	61	71	67
Merkel *(JBJS 1985)*	31	48	86	83
Merkel *(JNM 1986)*	154	66	81	77
Gomez-Luzuriaga *(Intl Orthop 1988)*	40	75	90	80
Love *(SNM 2008)*	150	75	59	66

Aseptic Loosening vs. Infection

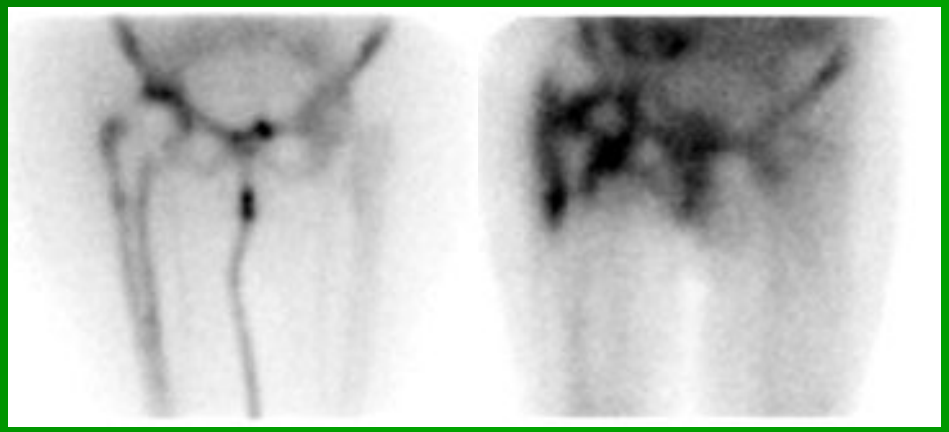
Aseptic Loosening	Infection
Histiocytes	Histiocytes
Giant cells	Giant cells
Lymphocytes	Lymphocytes
Plasma cells	Plasma cells
	Neutrophils

Bone/Gallium Scintigraphy in Joint Replacement Infection*

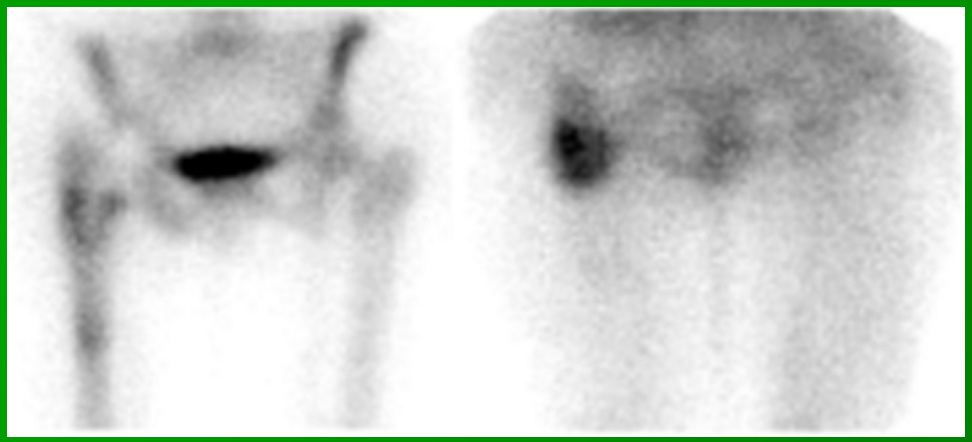
	Prosthesis	Sensitivity	Specificity	Accuracy
Bone	**All (150)**	**52/67 (.78)**	**31/83 (.37)**	**83/150 (.55)**
	THR (94)	20/34 (.59)	30/60 (.50)	50/94 (.53)
	TKR (56)	32/33 (.97)	1/23 (.04)	33/56 (.59)
Bo/Ga	**ALL (150)**	**51/67 (.76)**	**49/83 (.59)**	**100/150 (.67)**
	THR (94)	21/34 (.62)	42/60 (.70)	63/94 (.67)
	TKR (56)	30/33 (.91)	7/23 (.30)	37/56 (.66)

*Love et al., SNM 2008

Bone/Gallium Scintigraphy



Infected Rt. THR



Aseptically Loosened Rt. THR

Labeled Leukocyte Imaging

- In-vitro labeling
  - ^{111}In-oxine
  - ^{99m}Tc-exametazime
- Uptake mechanisms
  - Intact chemotaxis
  - Number of cells labeled ($\geq$ 2000/mL)
  - Cell types labeled (neutrophils)
  - Cellular inflammatory response (neutrophilic)
- Performed in conjunction with bone marrow imaging (^{99m}Tc sulfur colloid)

Leukocytes Accumulate in the Bone Marrow

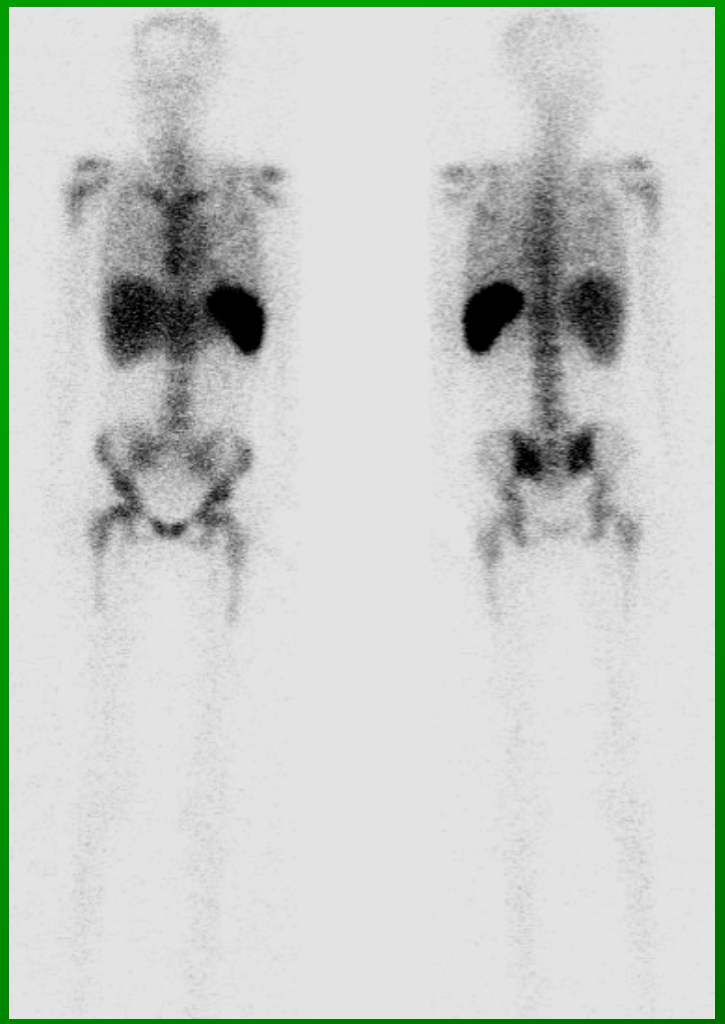
Adult: axial skeleton, proximal humeri and femora

Dynamic organ system

- Marrow hyperplasia
  - Generalized
  - Localized

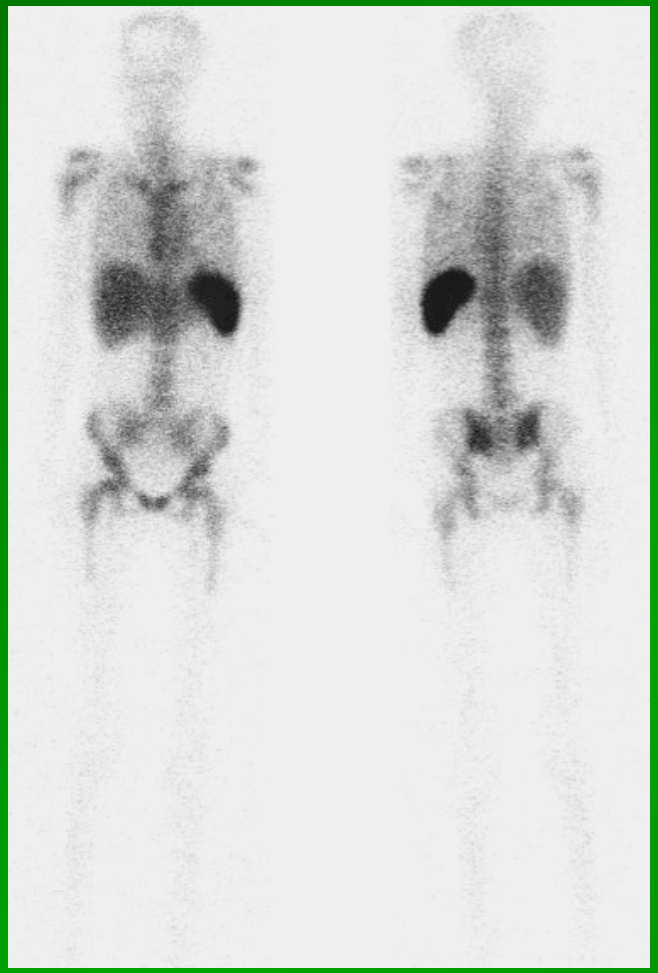
Normal distribution variable

- Altered labeled leukocyte accumulation

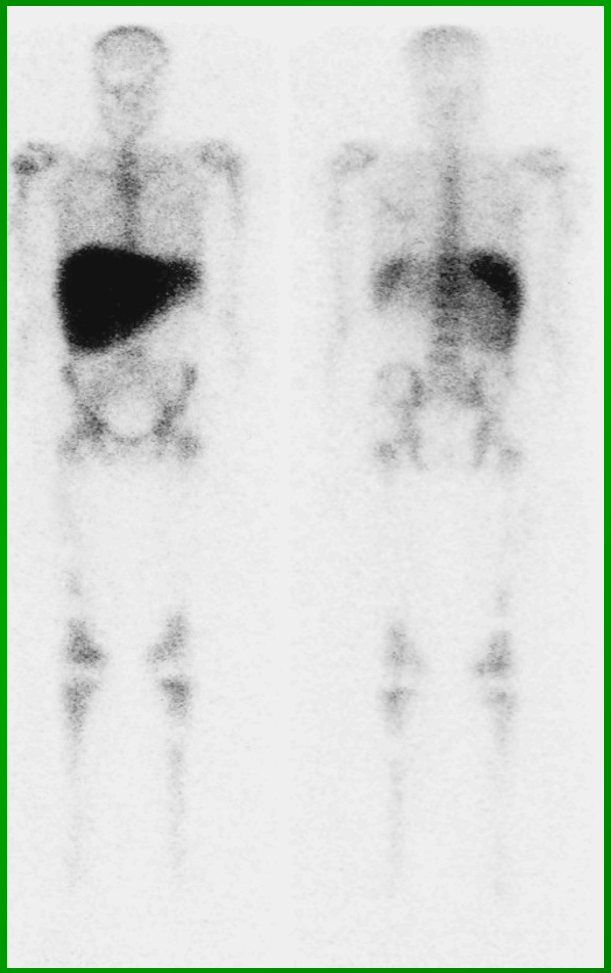


Ant Post

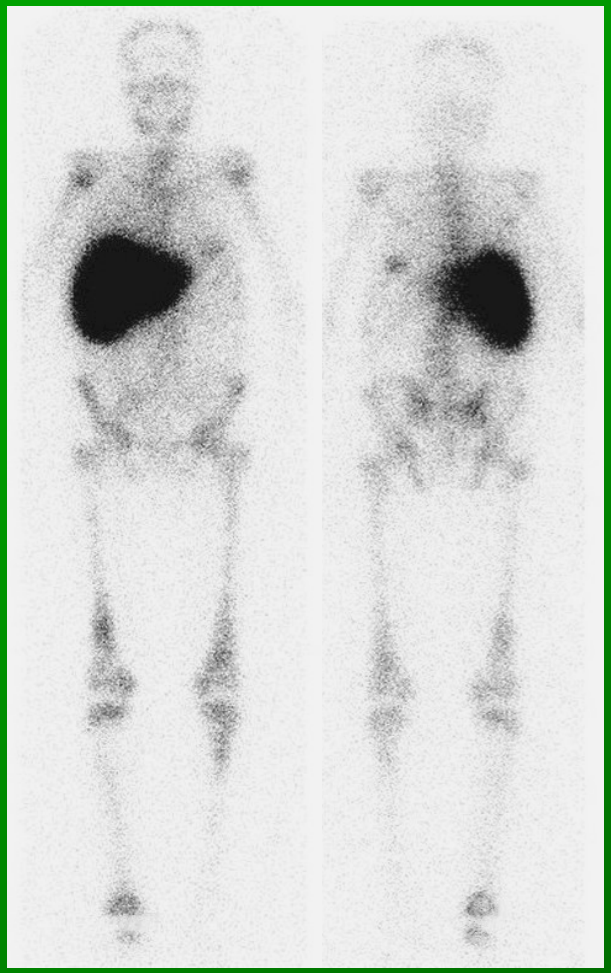
Generalized Marrow Expansion



Normal Adult



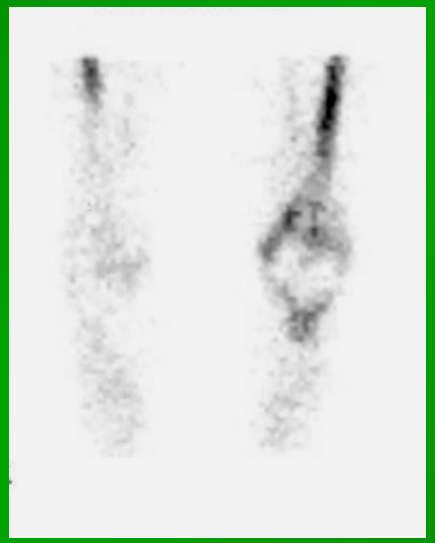
Sickle cell disease



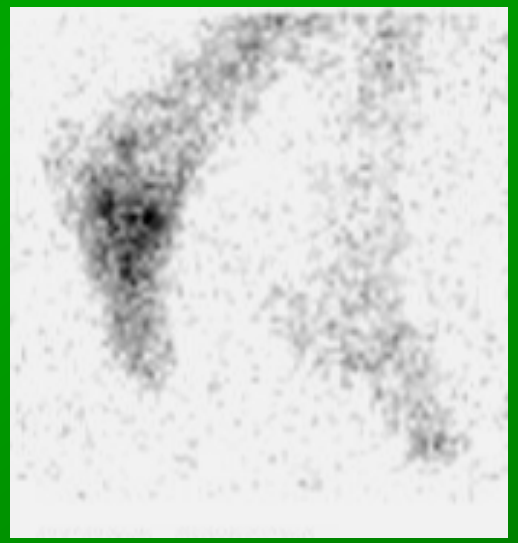
Gaucher’s disease

Localized Marrow Expansion

Bilateral THR



Lt. TKR



Neuropathic joint

Marrow Expansion

- Alters distribution of tracers that accumulate in the marrow
- Creates difficulties in labeled leukocyte image interpretation

Principle of Leukocyte/Marrow Imaging

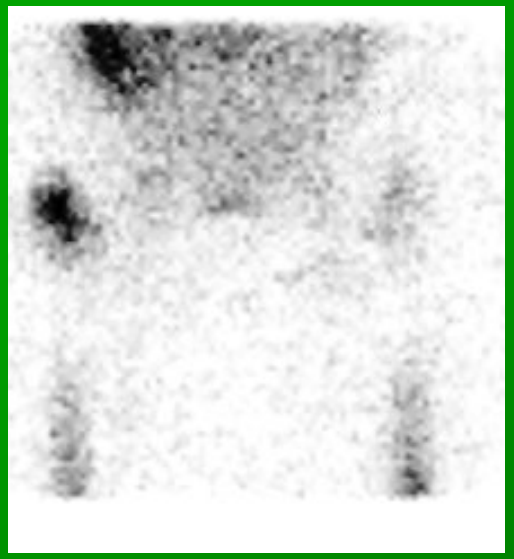
- Leukocytes and sulfur colloid both accumulate in marrow
- Infection
  - ↑ Leukocyte uptake
  - ↓ Sulfur colloid uptake
- Image interpretation
  - Activity on labeled leukocyte image without corresponding activity on marrow image = osteomyelitis

Which THR is Infected?

Lt. THR

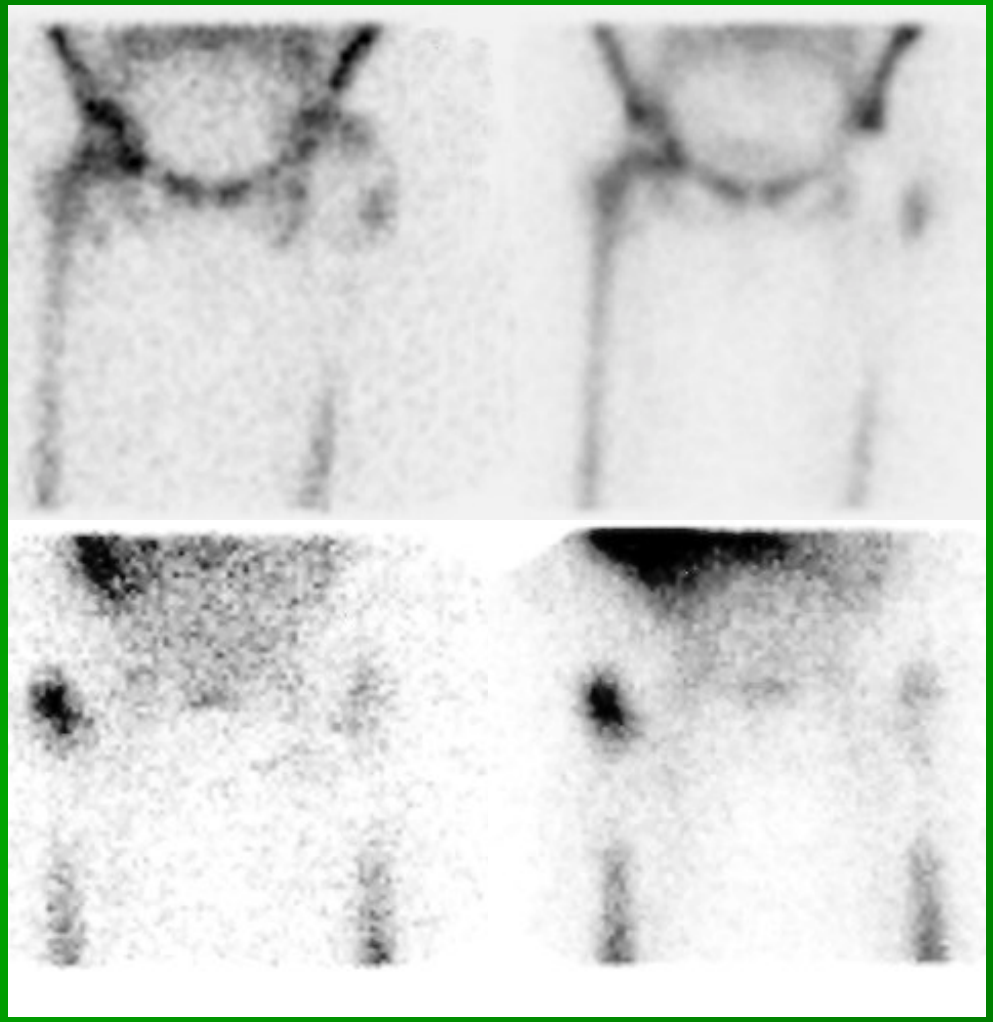
1

Rt. THR



2

Which THR is Infected?



Lt. THR

Rt. THR

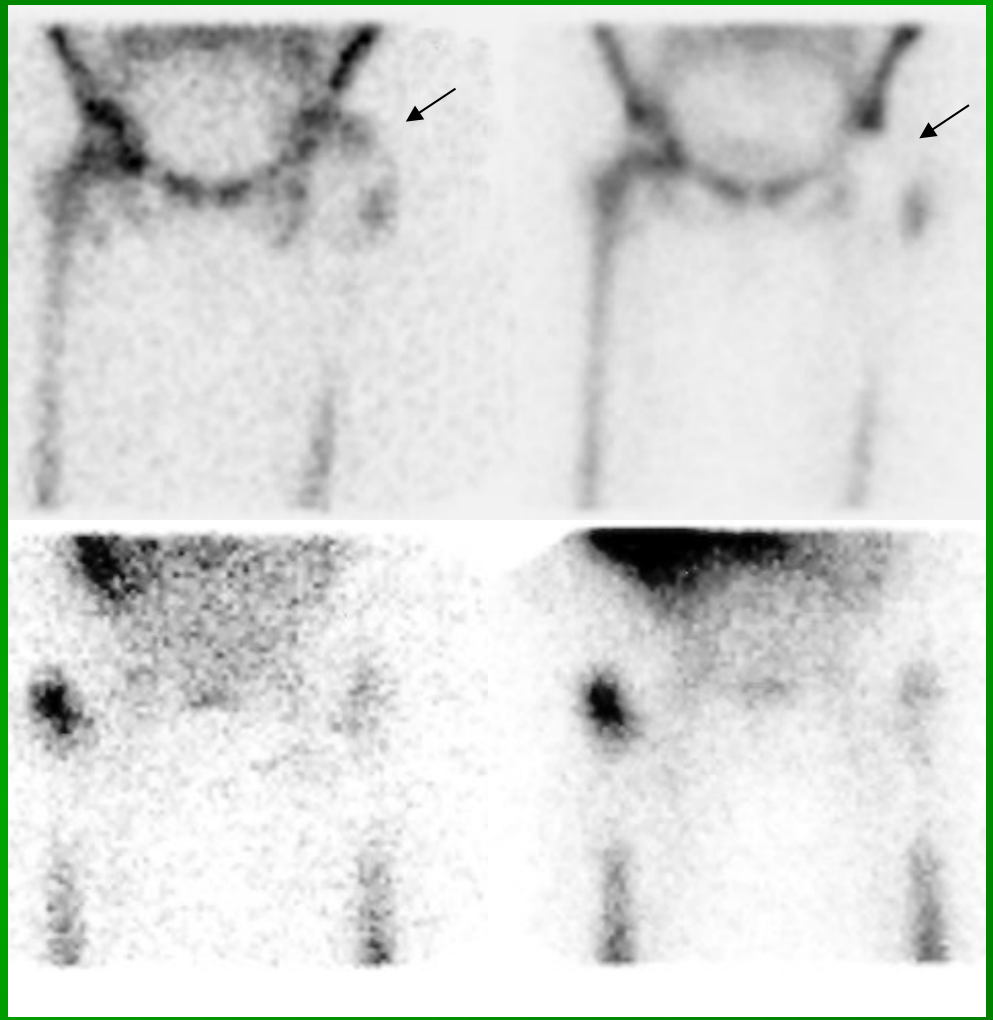
1

2

^{111}In-WBC

^{99m}Tc-SC

1 is Infected



Lt. THR

Rt. THR

1

2

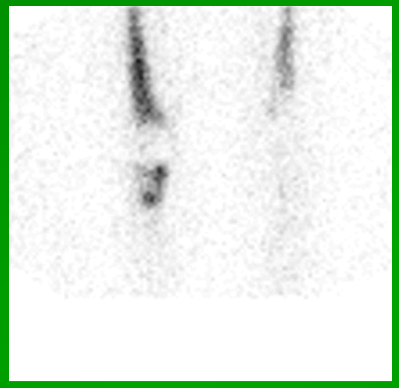
^{111}In-WBC

^{99m}Tc-SC

Which TKR's are Infected?

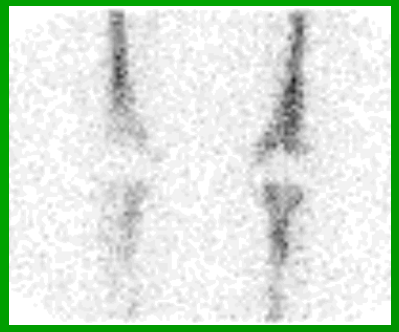
^{111}InWBC

Rt. TKR



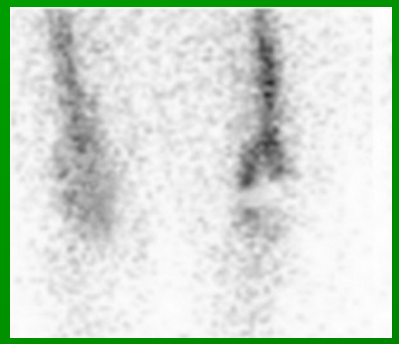
1

Lt. TKR



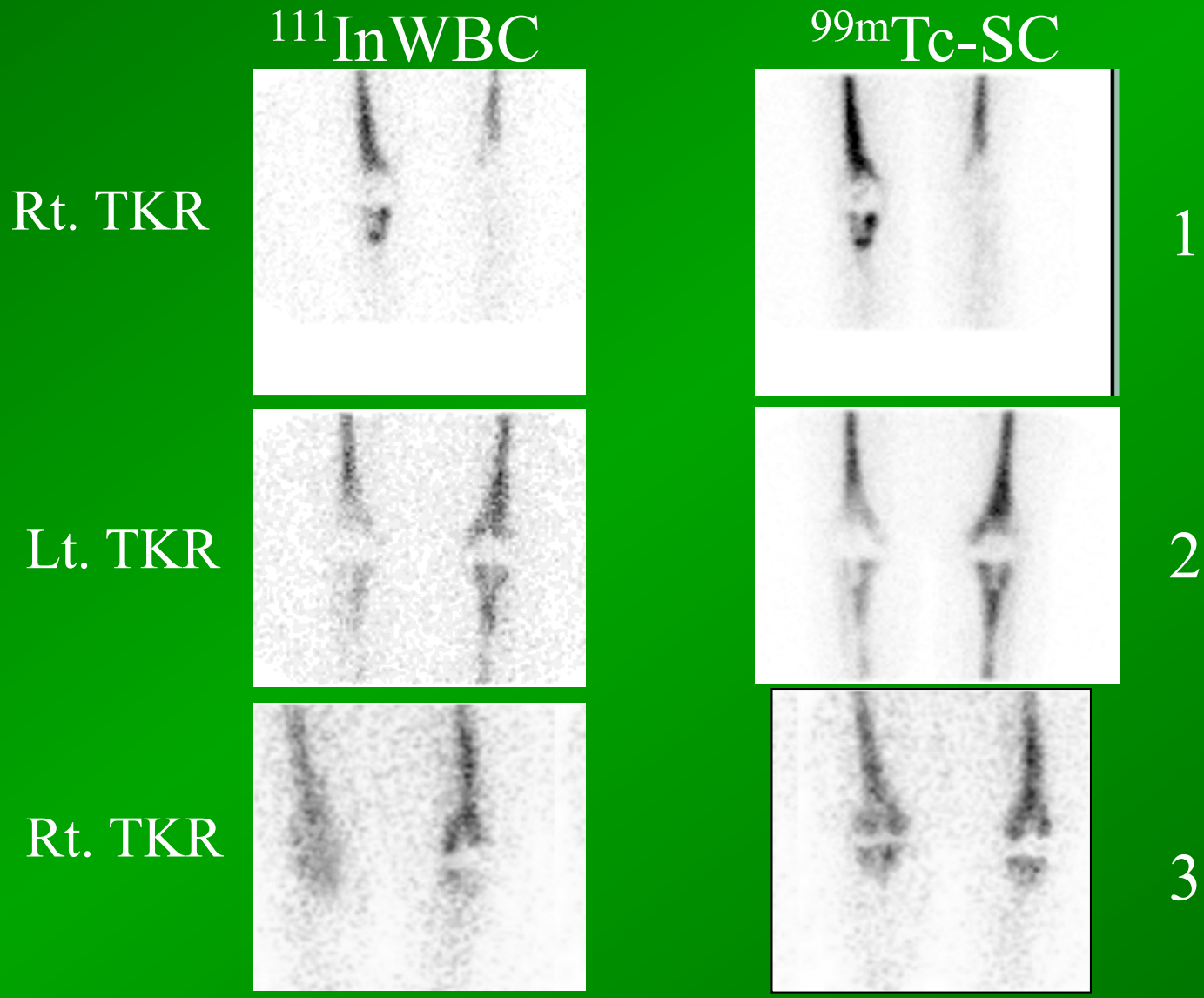
2

Rt. TKR

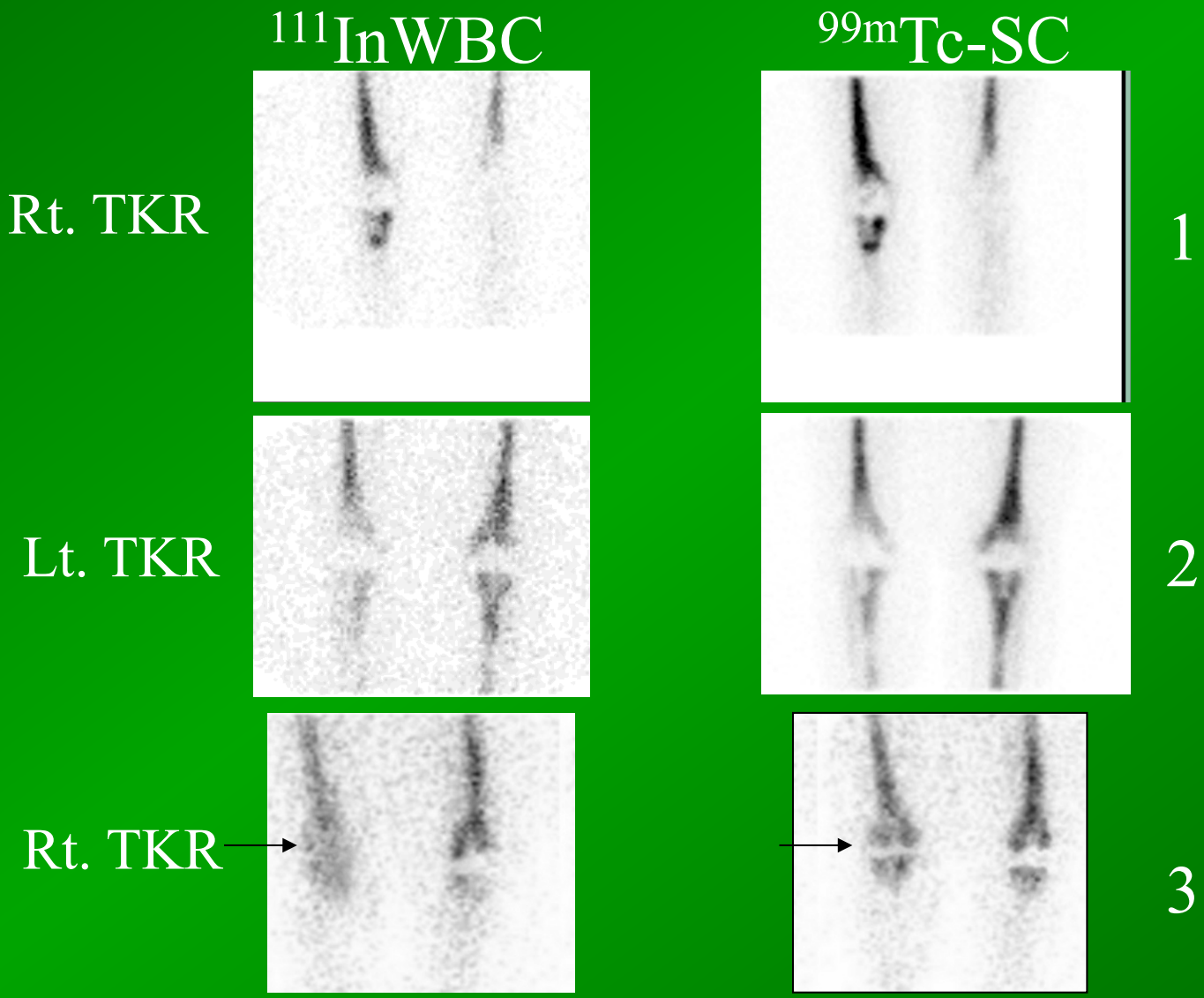


3

Which TKR's are Infected?



Only #3 is Infected



Leukocyte/Marrow Imaging

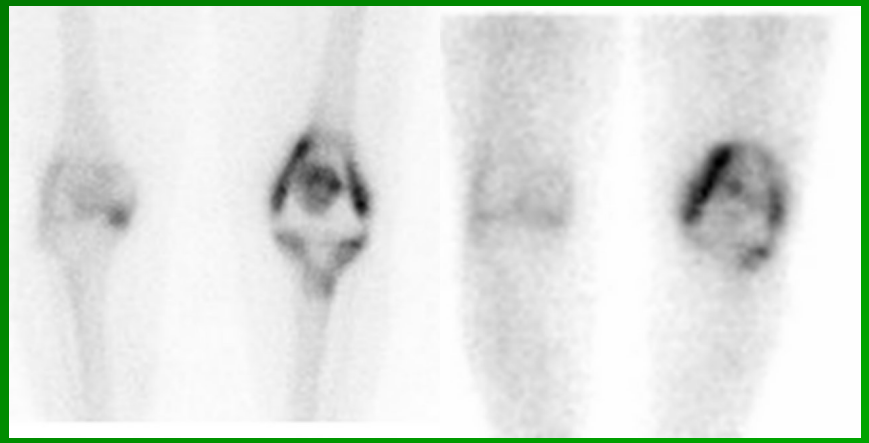
Group	n	Sens	Spec	Acc
Mulamba *(Acta Orthop Scan 1983)*	30	92%	100%	97%
Fink-Bennett *(SNM, 1988)*	54	100%	93%	96%
Palestro *(JNM, 1990)*	50	100%	97%	98%
Palestro *(Radiology, 1991)*	19	86%	100%	95%
Joseph *(J Arthroplasty, 2001)*	58	46%	100%	88%
Love *(JNM, 2004)*	59	100%	91%	95%
Pill *(J Arthroplasty 2006)*	51	50%	95%	86%
Love *(SNM 2008)*	150	96%	87%	91%

Leukocyte/Marrow Scintigraphy in Joint Replacement Infection*

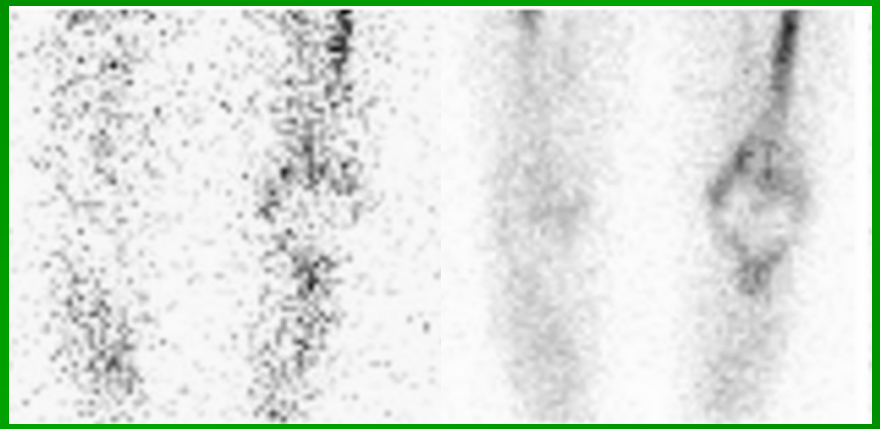
	Prosthesis	Sensitivity	Specificity	Accuracy
Bone	**All (150)**	**52/67 (.78)**	**31/83 (.37)**	**83/150 (.55)**
	THR (94)	20/34 (.59)	30/60 (.50)	50/94 (.53)
	TKR (56)	32/33 (.97)	1/23 (.04)	33/56 (.59)
Bo/Ga	**All (150)**	**51/67 (.76)**	**49/83 (.59)**	**100/150 (.67)**
	THR (94)	21/34 (.62)	42/60 (.70)	63/94 (.67)
	TKR (56)	30/33 (.91)	7/23 (.30)	37/56 (.66)
WBC/Ma	**All (150)**	**64/67 (.95)**	**72/83 (.87)**	**136/150 (.91)**
	THR (94)	32/34 (.94)	53/60 (.88)	85/94 (.90)
	TKR (56)	32/33 (.97)	19/23 (.83)	51/56 (.91)

Love et al, SNM 2008

Aseptic Loosening Lt. TKR



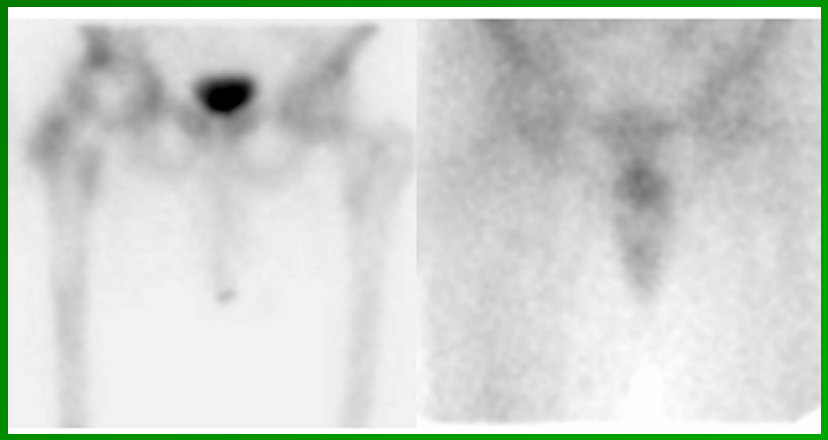
Bone Gallium



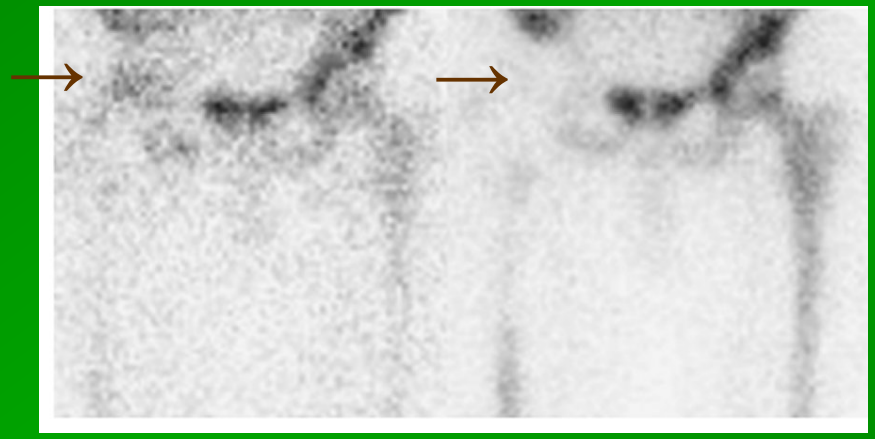
WBC Marrow

- Bone (+)
- Bo/Ga (+)
- WBC/Ma (-)

Infected Rt. THR



Bone Gallium



WBC Marrow

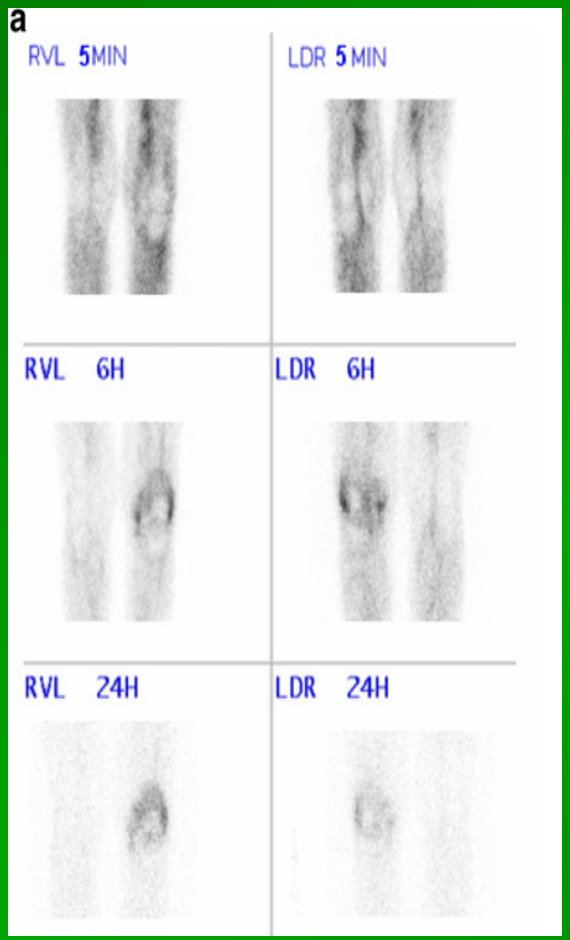
- Bone (-)
- Bo/Ga (-)
- WBC/Ma (+)

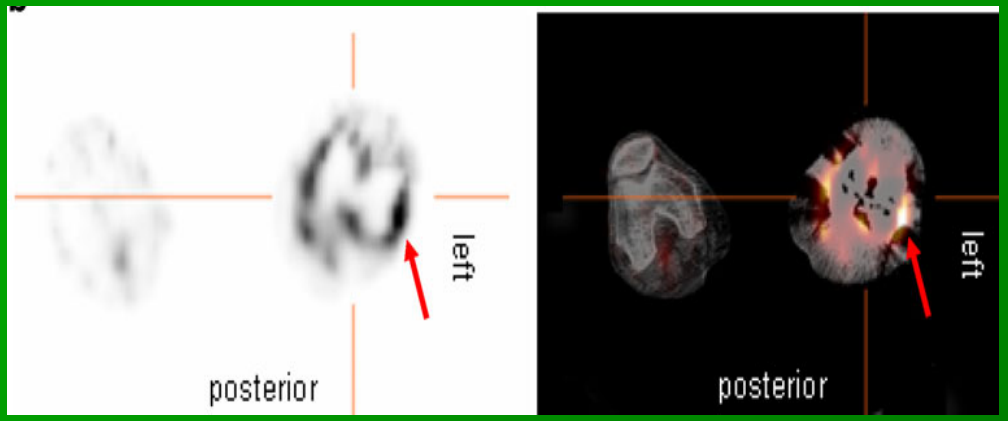
SPECT/CT

	Planar	SPECT	SPECT/CT
Sensitivity	67% (6/9)	89% (8/9)	89% (8/9)
Specificity	59% (13/22)	45% (10/22)	73% (16/22)
Accuracy	61% (19/31)	58% (18/31)	77% (24/31)
Positive PV	40% (6/15)	40% (8/20)	57% (8/14)
Negative PV	81% (13/16)	91% (10/11)	94% (16/17)

*Graute V, et al. Eur J Nucl Med Mol Imaging. 2010;37:1751-9.

Infected Lt. TKR*





* Adapted from Figure 2 Graute V, et al. Eur J Nucl Med Mol Imaging. 2010;37:1751-9.

SPECT/CT & Prosthetic Joints

- **Think out of the Box!**

  Extent of Infection

  Other causes of pain

  Loosening

  Fracture
  Particle disease
  Etc.
  CT guided joint aspiration

WBC/Marrow Imaging

- Factors affecting intensity of WBC uptake in prosthetic joint infection: unknown
- Monitoring response to therapy: unknown
- Effects of antibiotic/steroid therapy: unknown
- Alternatives to WBC/marrow imaging

Alternatives to WBC/Marrow Imaging

- In-vivo leukocyte labeling agents
- Radiolabeled antibiotics
- FDG-PET

^{18}FDG-PET

^{18}F-fluorodeoxyglucose

Cellular uptake

Cellular metabolic rate & number of glucose transporters

↑ in inflammation/infection

Advantages

- High-resolution cross-sectional images
- No *in-vitro* labeling
- Rapidly completed
- Relatively economical
- Available

FDG & Painful Joint Replacements

Author	N=	Sens	Spec	Acc
Zhuang (JNM, 2001)	74	19/21	43/53	62/74 (84%)
Van Acker (EJNM, 2001)	21	6/6	12/15	18/21 (86%)
Chacko (NMC, 2002)	41	11/12	28/29	39/41 (95%)
Manthey (NMC, 2002)	28	4/4	24/24	24/28 (86%)
Vanquickenbourne (EJNM, 2003)	17	7/8	7/9	14/17 (82%)
Stumpe (Radiology, 2004)	35	3/9	21/26	24/35 (69%)
Love (JNM, 2004)	59	9/25	33/34	42/59 (71%)
Pill (J Arthroplasty, 2006)	92	20/21	66/71	86/92 (93%)

FDG-PET vs WBC/Marrow (59 Joint Prostheses)

	Sensitivity	Specificity	Accuracy	PPV	NPV
PPA	1.00 (25/25)	.09 (3/34)	.47 (28/59)	.45 (25/56)	1.00 (3/3)
FDG/Ma	.96 (24/25)	.35 (12/34)	.61 (36/59)	.52 (24/46)	.92 (12/13)
BPI	.52 (13/25)	.44 (15/34)	.47 (28/59)	.40 (13/32)	.56 (15/27)
T/B	.36 (9/25)	.97 (33/34)	.71 (42/59)	.90 (9/10)	.67 (33/49)
WBC/Ma	1.0 (25/25)	.91 (31/34)	.95 (56/59)	.89 (25/28)	1.00 (31/31)

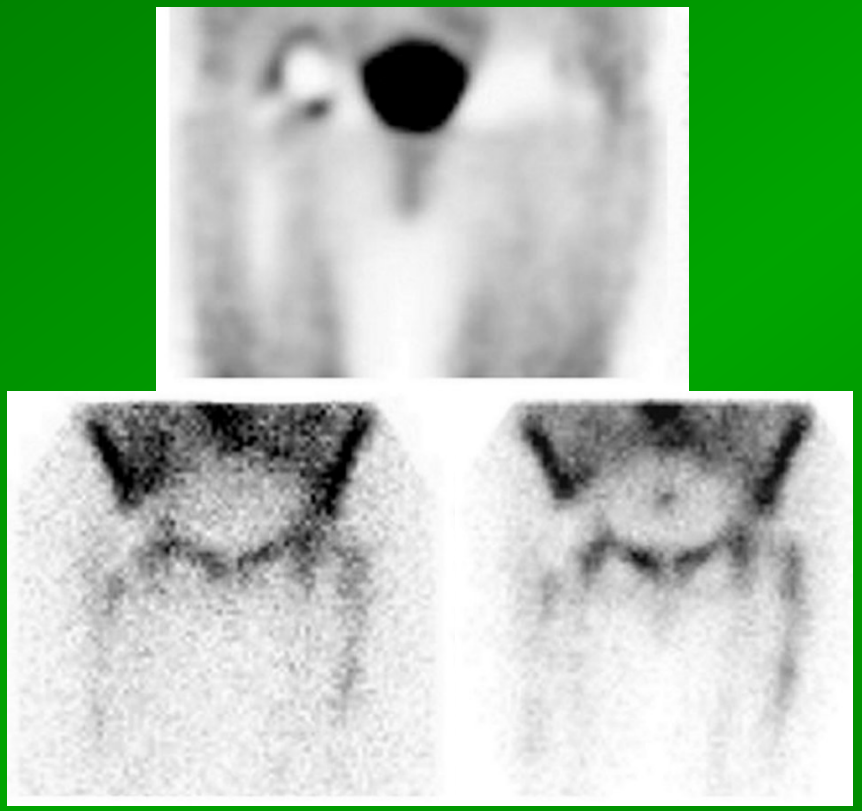
Fixed Femoral Components

Aseptically Loosened

Infected

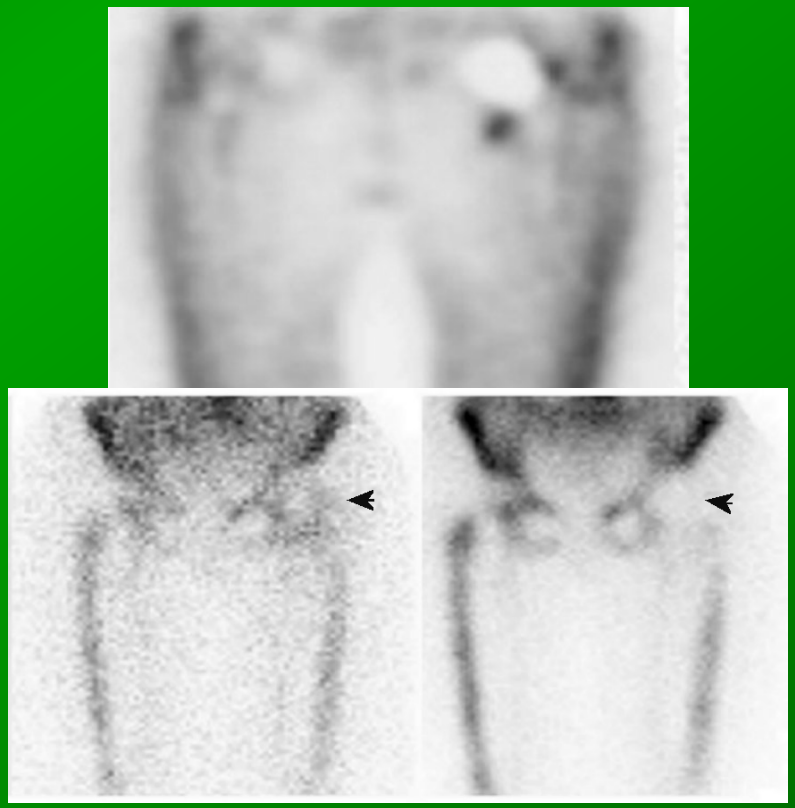
Fixed Femoral Components

Aseptically loosened right acetabular component



^{111}In-WBC Marrow

Infected left hemiarthroplasty



^{111}In-WBC Marrow

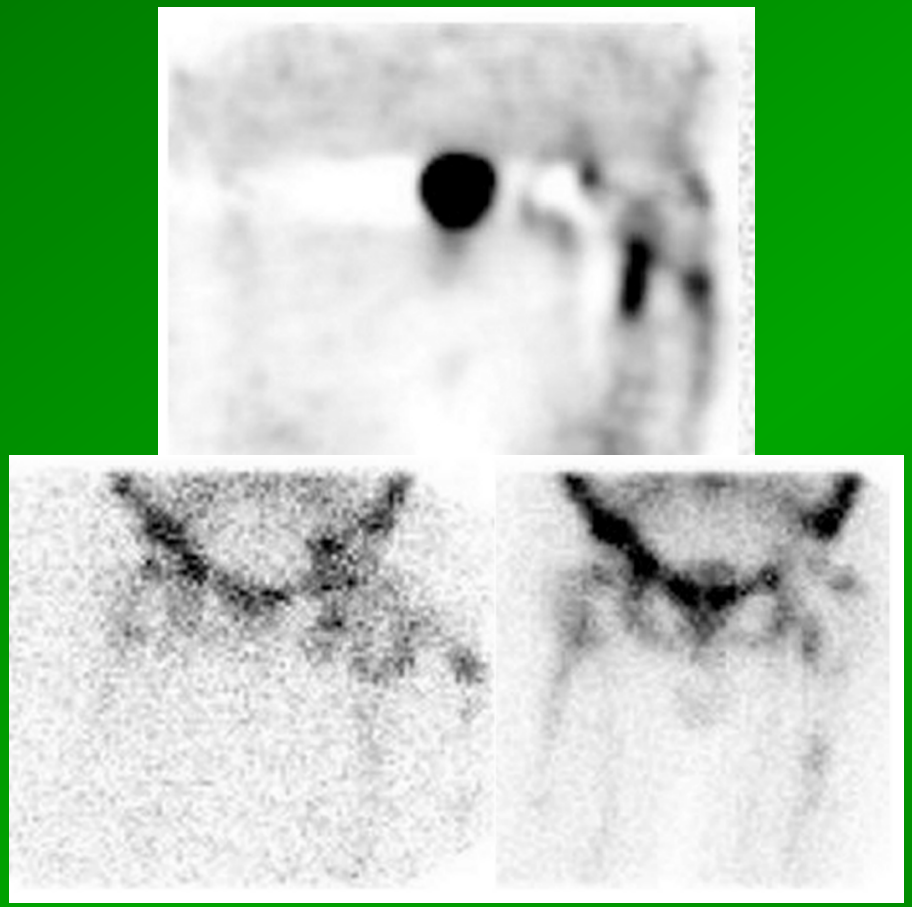
Loose Femoral Components

Infected

Aseptically loosened

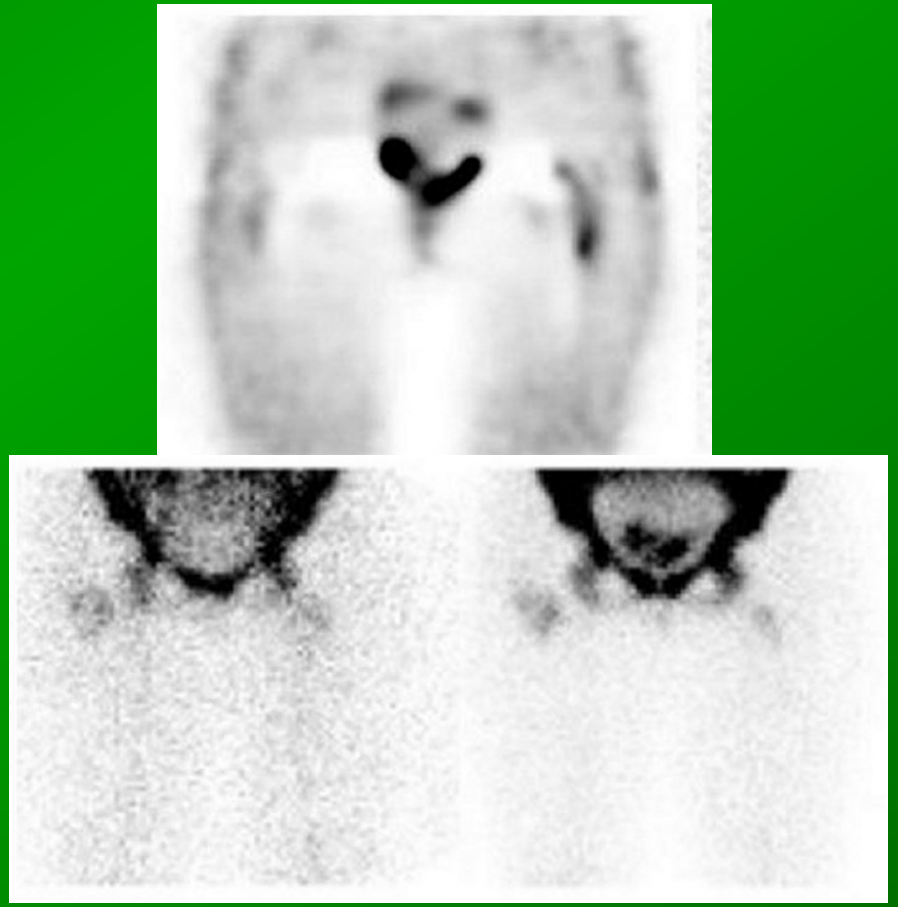
Loose Femoral Components

Infected



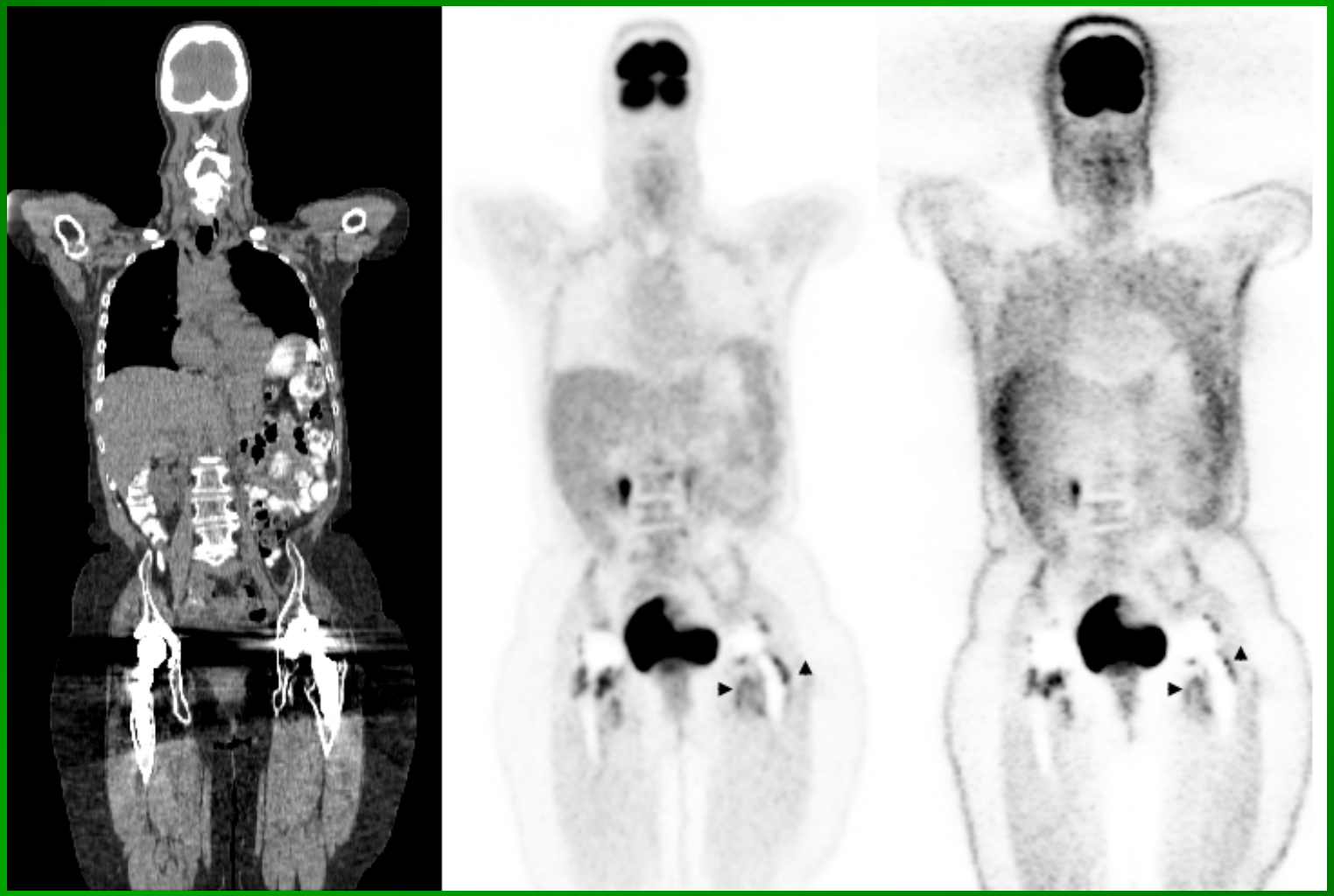
^{111}In-WBC Marrow

Aseptically loosened



^{111}In-WBC Marrow

Asymptomatic THR's



SUVmax: Rt: 7.6; Lt: 5.1

Summary

- Primary role of Nuclear Medicine
  - Identify the infected prosthetic joint
  - Radionuclide gold standard
    - Labeled leukocyte/marrow imaging
- Time to
  - Stop using gallium
  - Reevaluate role of ^{99m}Tc-MDP bone scan
  - Investigate ^{18}F-fluoride bone scan (screening test)
- Future R & D
  - Develop imaging tests that are sensitive *and* specific for infection, either in general or for particular components (bacteria, cells, etc.)