MOLECULAR IMAGING IN SARCOIDOSIS

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Objectives

Background on Sarcoidosis

Uptake mechanism of tracers

Describing imaging patterns

A word on current imaging sensitivity & specificity

Role for ^{18}F-FDG on therapy monitoring?

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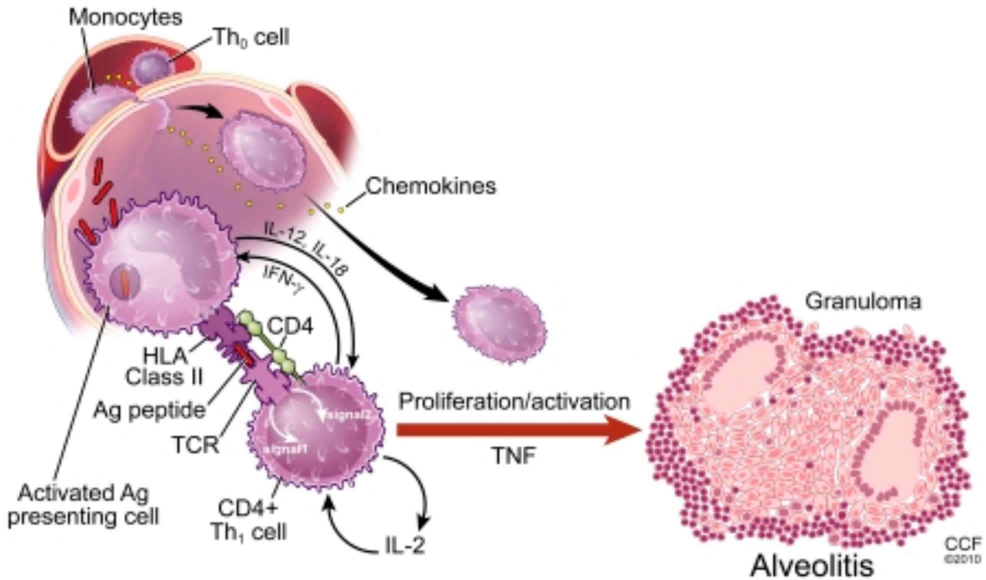
Sarcoidosis Pathogenesis?

Multiorgan granulomatous of unknown etiology

Macrophages + factors activation

Non-caseating granulomas (lung & nodes)

TNF-α= disease activity



Russel et al. Sem Arthr Rheum, 2013 (In press)
Van Moorsel & Christiani. Am J Respir Crit Care Med. 2012;106: 816-818
Morais et al. Respir Med. 2012;106:1771-1777
Baughman et al. Am J Respir Crit Care Med. 2011; 183:573-581

Pathogenesis…

Influence of environment & genetic factors

Family-based & case controlled studies: HLA association (DRB1)

DRB1: highly polymorphic & making sarcoidosis a heterogeneous condition ($NOTCH_4$ in African American and 12q13.3 to 12q14.1 in European population**)**

Van Moorsel & Christiani. Am J Respir Crit Care Med, 2012;106: 816-818

Morais et al. Respir Med. 2012;106:1771-1777

Diagnosis

Histology: non-caseating epithelioid cell granuloma

BALF: CD4/CD8 > 4.0 + 2 years clinical observation

Van Moorsel & Christiani. Am J Respir Crit Care Med, 2012;106: 816-818

Morais et al. Respir Med. 2012;106:1771-1777

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Diagnosis: Scadding criteria

Stage 0: no thoracic involvement

Stage I: adenopathies & no lung involvement

Stage II: adenopathies + lung involvement

Stage III: lung involvement alone

Stage IV: lung fibrosis

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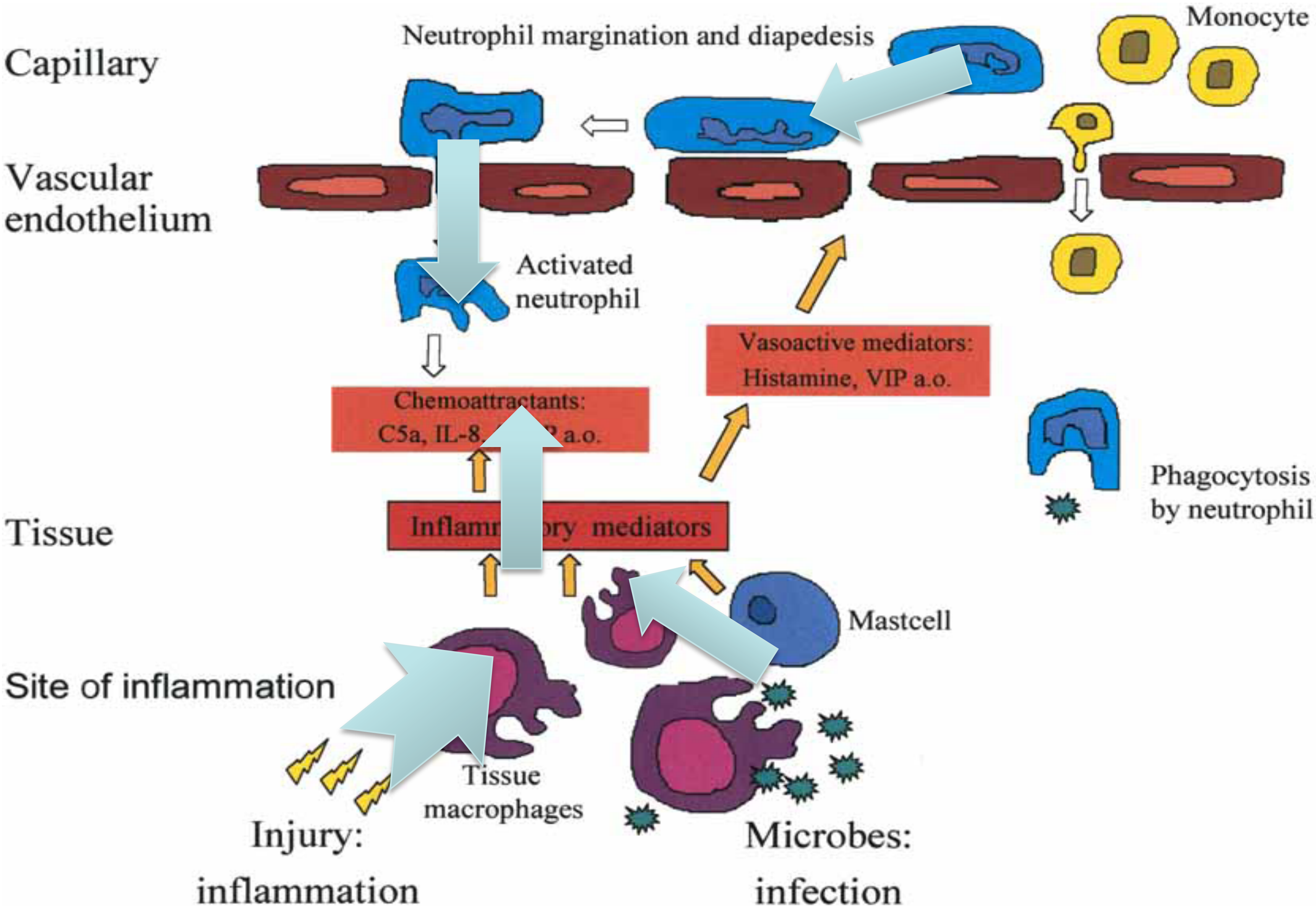
Scadding JG. BMJ. 1961; 4:1165-1172

ATS, ERS & WASOG. *Am J Respir Crit Care Med* 1999; 160:736–755

Place of molecular imaging?



Rennen et al. Curr Med Chem, 2002;1: 63-75

^{67}Ga Citrate

Non specific tracer: uses increased vascularity

Binds to circulating transferrin

^{67}Ga citrate- transferrin: extravasates at the inflammation site

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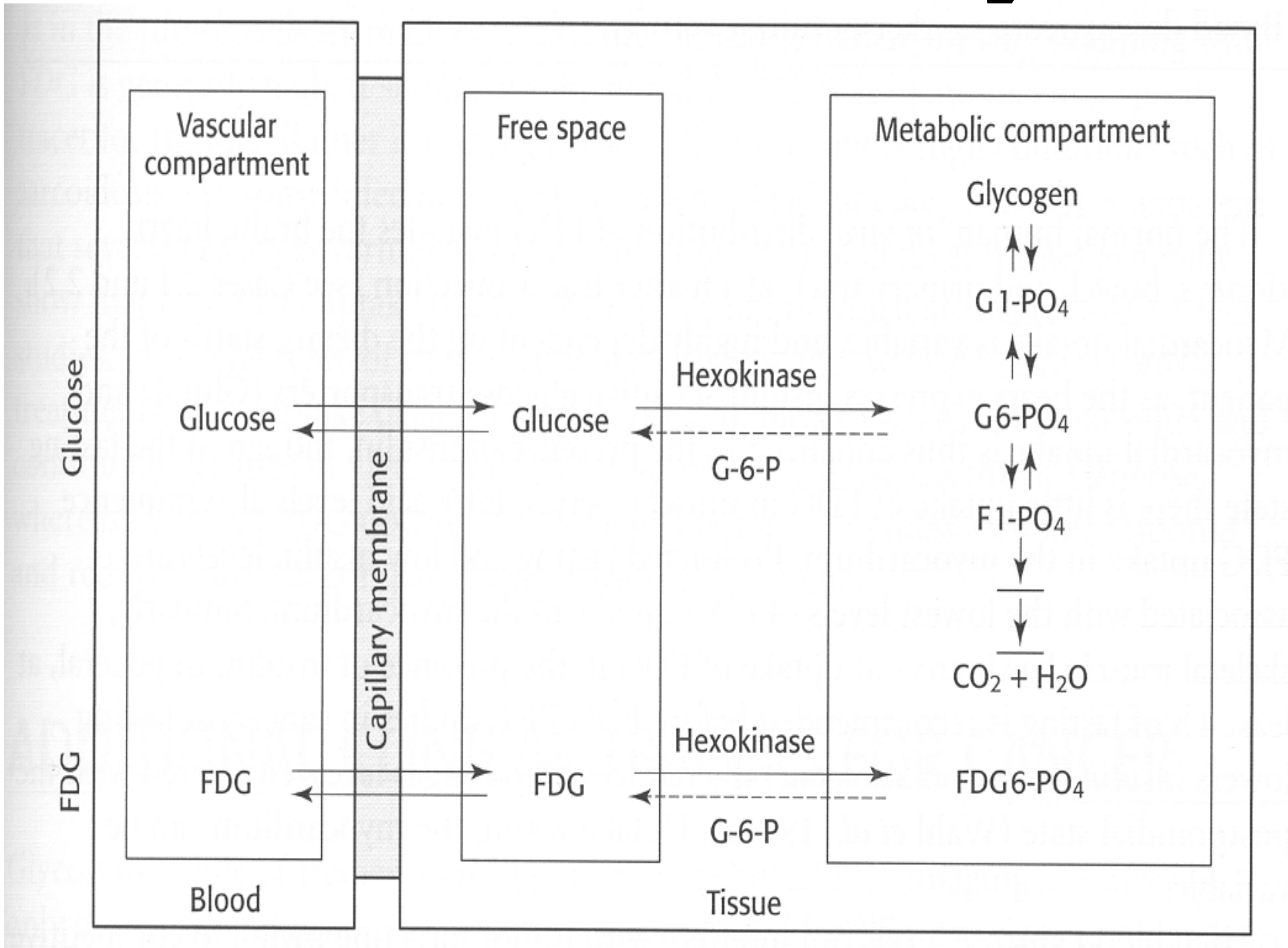
Vallbhajosula et al. Eur J Nucl Med, 1983; 8:354-357
Stevens and Allegra. South Med J, 1986; 79:1148-1151
Divgi. Proc Am Thorac Soc, 2009; 6:464-468

FDG in inflammatory site



Maisey, Wahl & Barrington, Atlas of Clinical PET, 1999
Brown et al. Nucl Med Biol. 2002; 29:443-453
El –Haddad et al. Sem Nucl Med. 2004; 34:313-329
Love et al. Radiographics. 2005; 25:1357-1368

Other tracers?

^{201}Tl, ^{99m}Tc-sestamibi & ^{123}I FFA: myocardial involvement

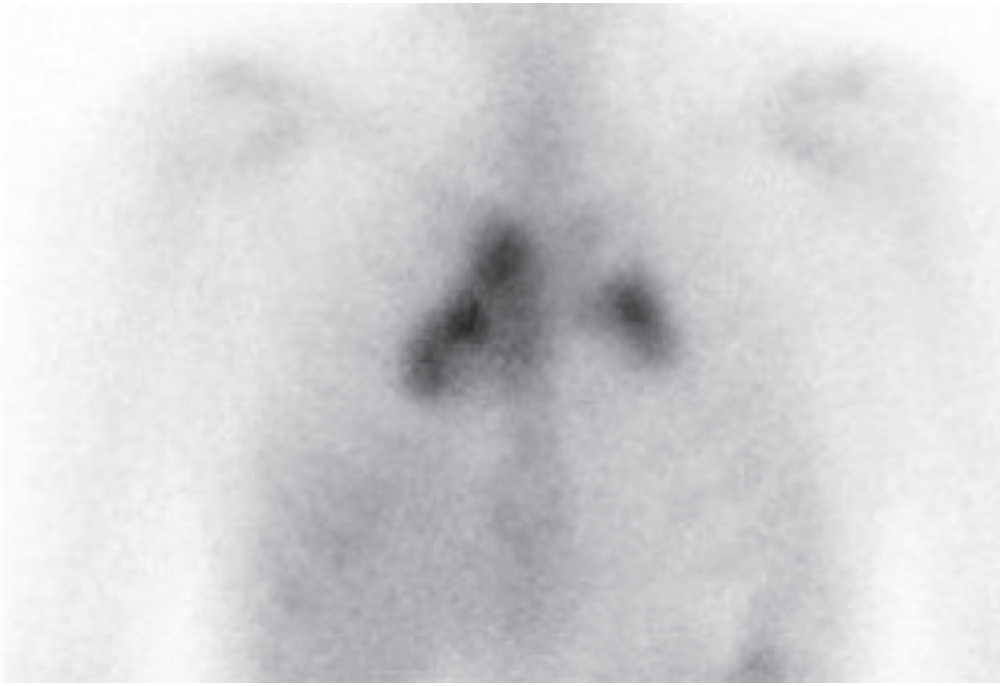
^{99m}Tc- Bone scan: >>> sensitive to bone lesions

^{111}In Octreotide: in extra thoracic disease

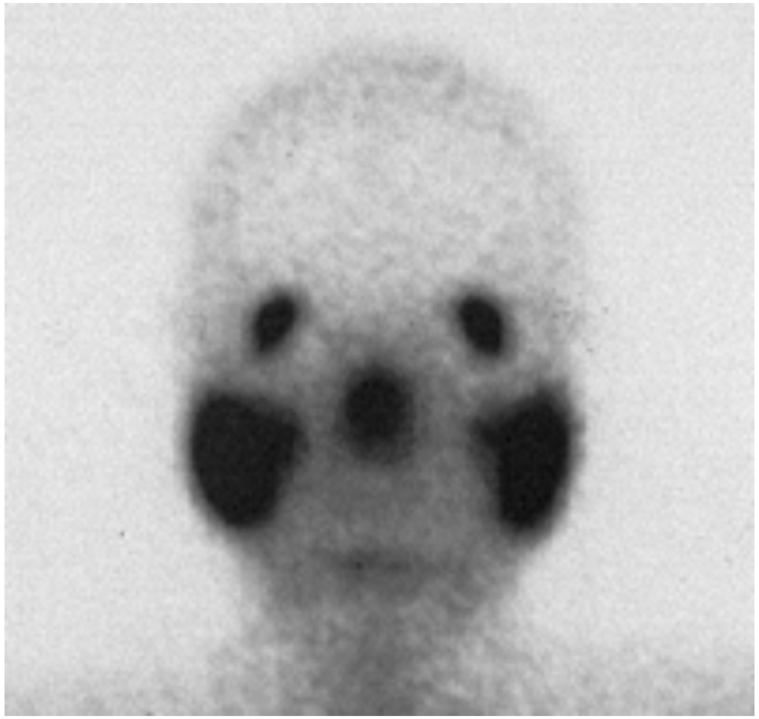
^{123}I MIBG: cardiac innervation

Typical appearance: ^{67}Ga-citrate

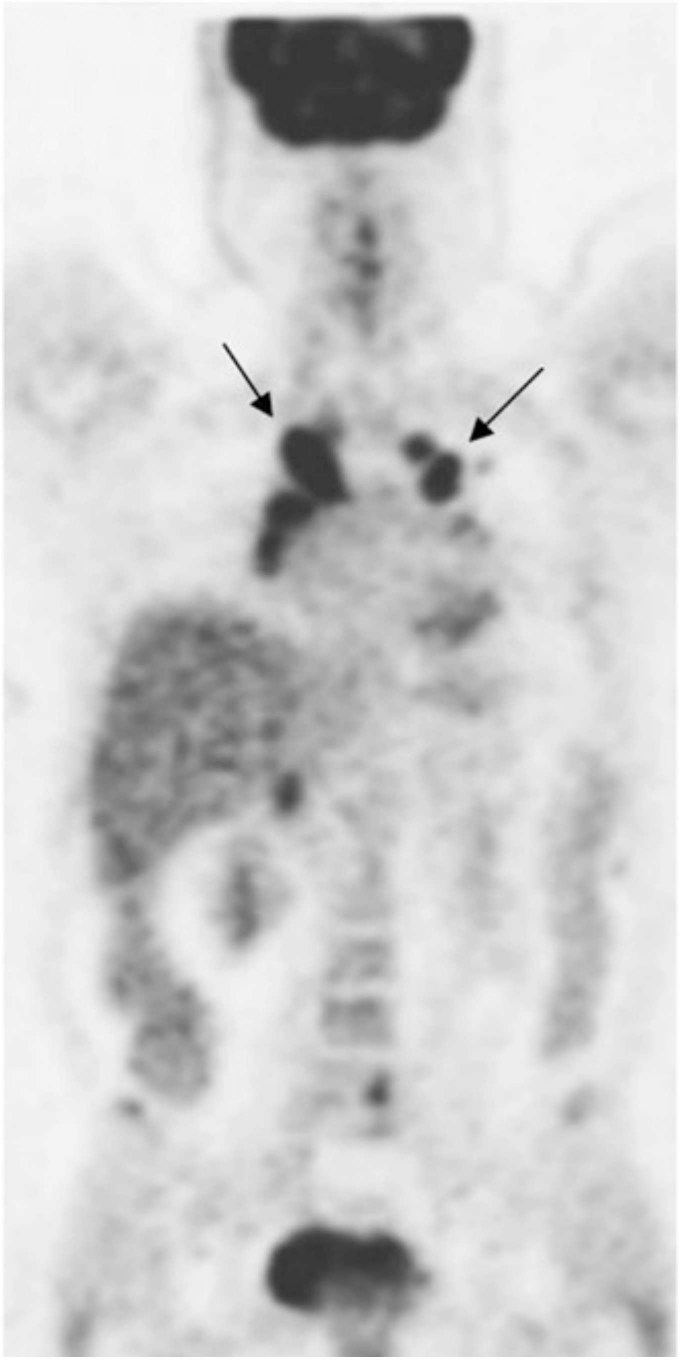
Lambda(λ)sign



Panda Face



^{18}F-FDG PET



Head & Neck

- Usually uptake in cervical lymph nodes

- Parotid glands uptake similar to ^{67}Ga-citrate

CHEST

>90% of patients have lung disease

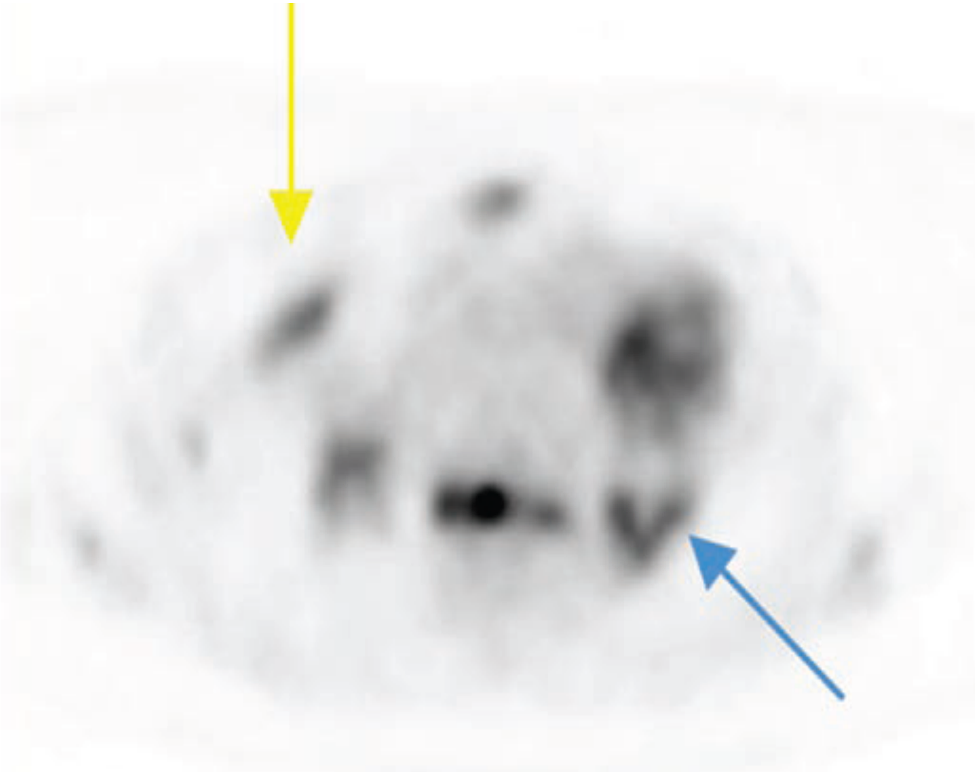
Avid mediastinal & hilar nodes on FDG PET

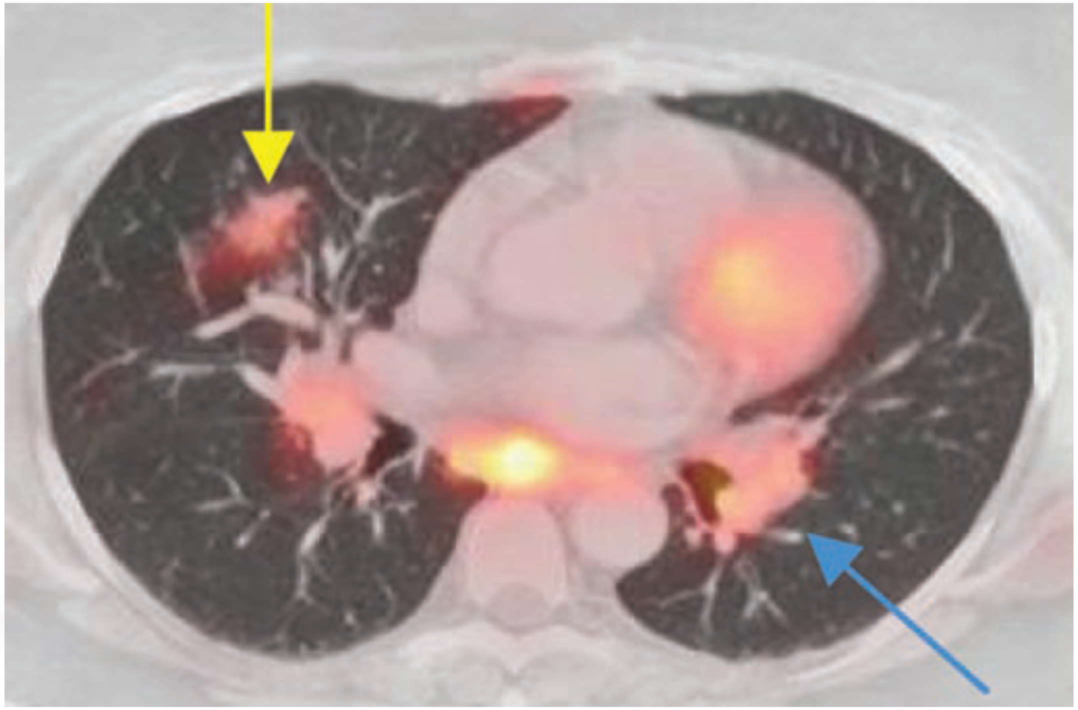
Lung involvement may show uptake

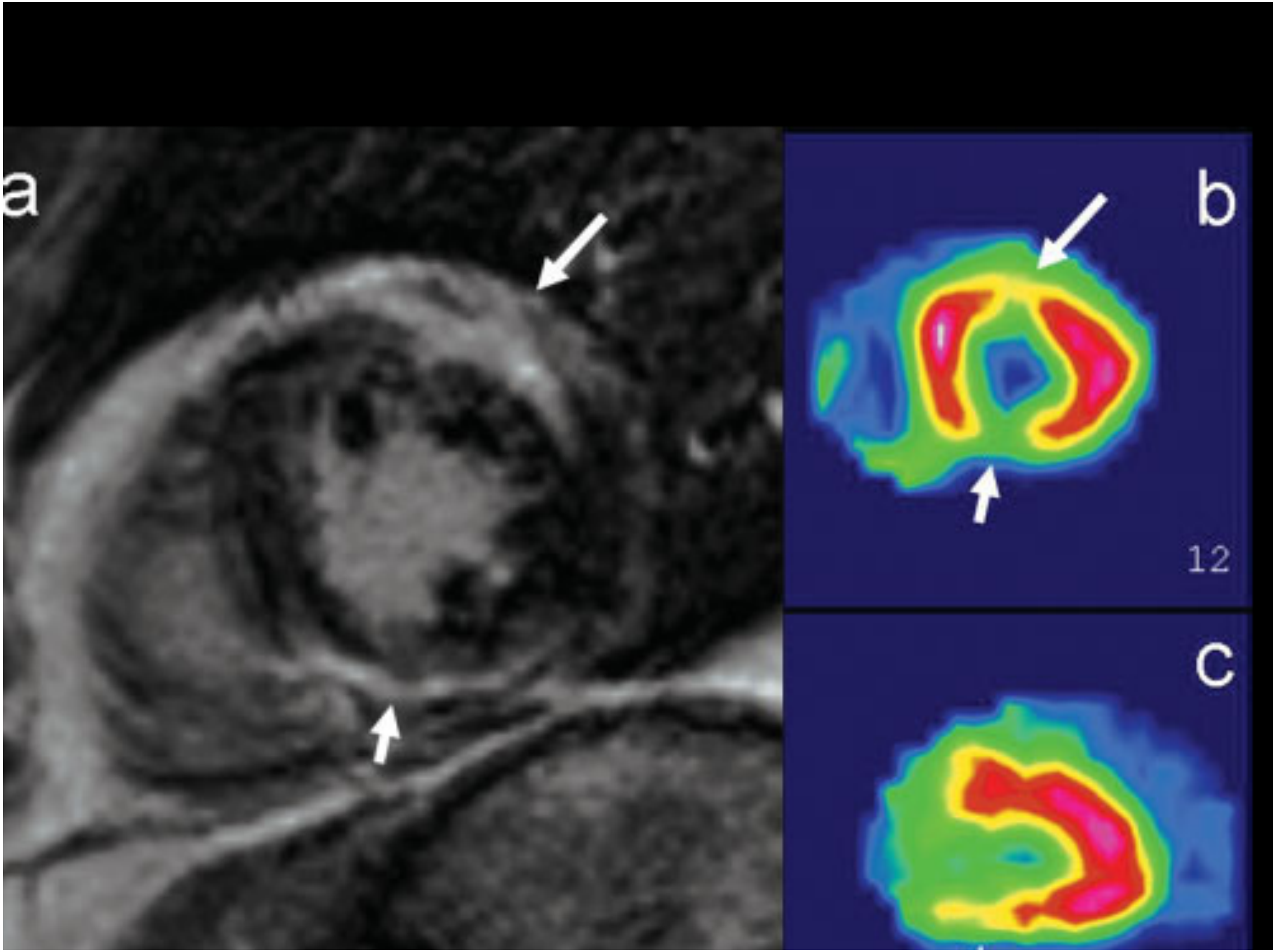
Note: ~2% of patients have cardiac involvement, a potentially fatal

Prevalence at autopsy= up to 25%

56 yrs old female with biopsy proven sarcoidosis



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Abdomen

Lympadenopathy in 30% of cases

FDG avid nodes

Parenchymal lesions (spleen in 75%): also FDG avid

Need to differentiation between sarcoid & lymphoma (Sarcoidosis-lymphoma syndrome)

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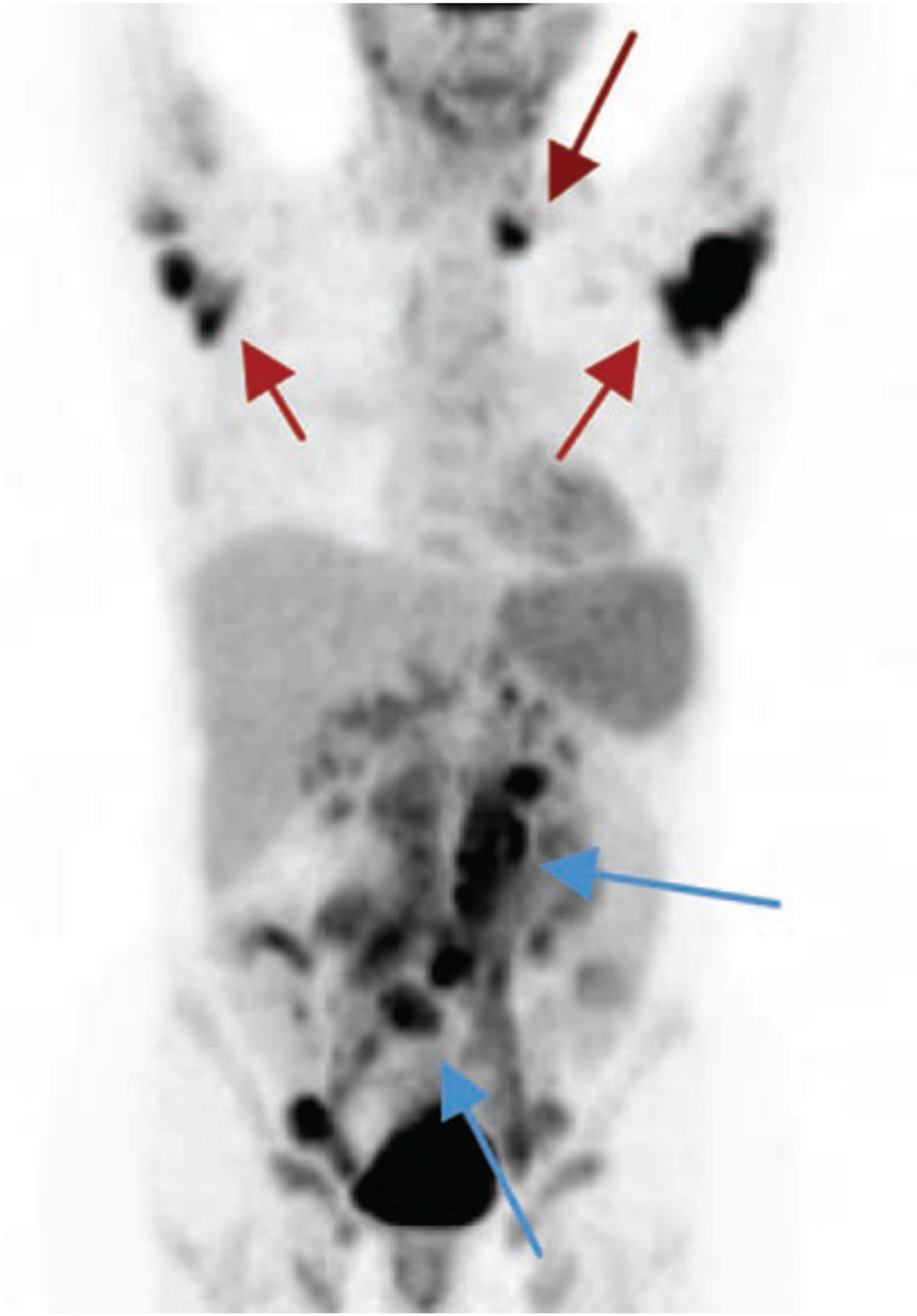


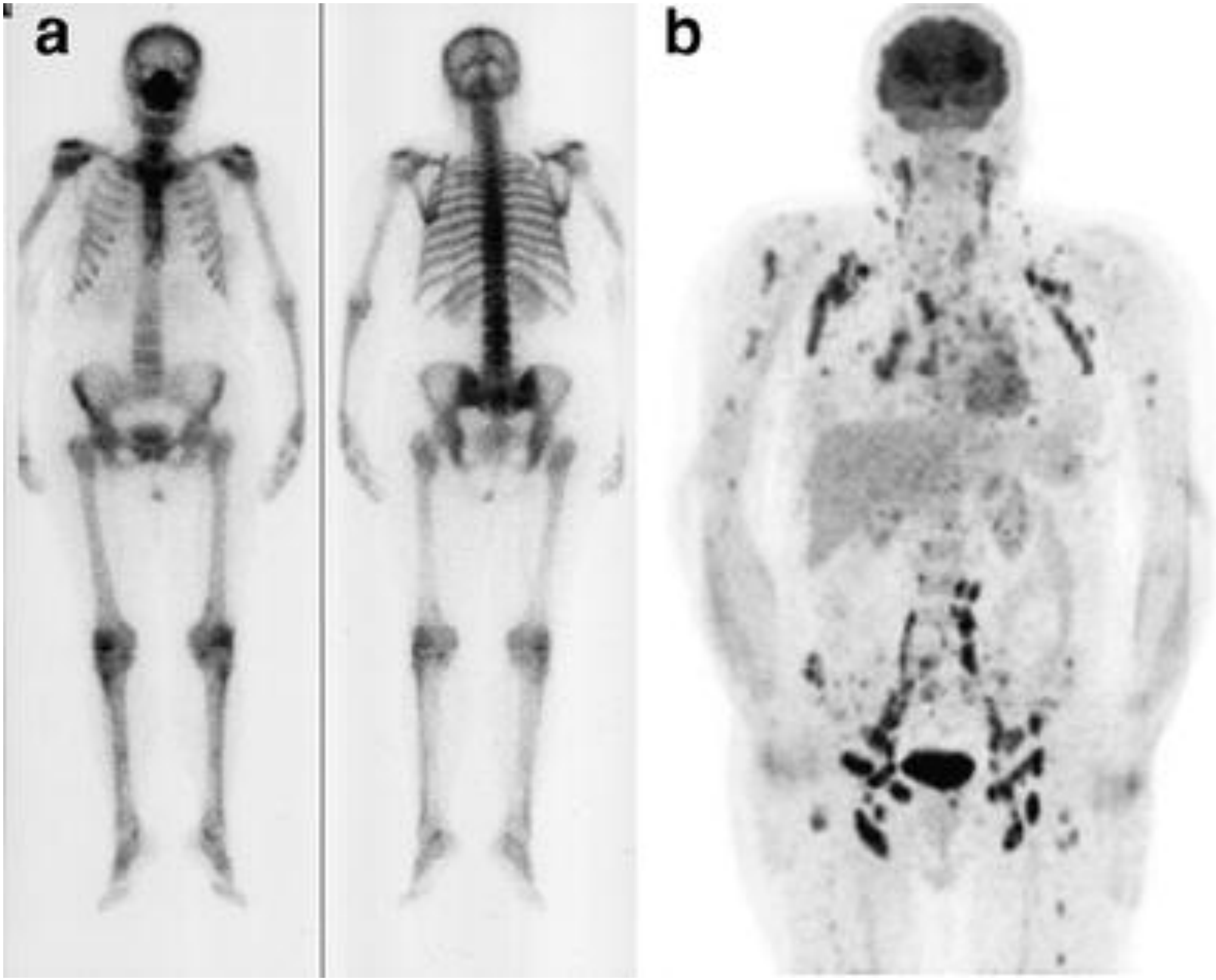
Musculoskeletal

Up to 1/3 of patients with bone lesions

Extremities >> axial skeleton

May be lytic or osteoblastic

Meaningful in presence of mediastinal lymphadenopathy



N.Ö. Küçük, E Özkan & G. Ozka. Eur J Nucl Med Mol Imaging, 2007;34: 2751

Sensitivity & specificity ?

Small scale studies in literature (< 10 patients)

Mostly cases reports or studies (1-3 patients)

Most of them lack correlation with histology

Pitfall: appearances may mimic malignant diseases

Lewis & Salama, J Nucl Med. 1994;35:1647-1649
Brudin et al. J Nucl Med. 1994; 21:297-305
Nguyen. Clin Nucl Med. 2007; 32:53-54
Kaira et al. Clin Nucl Med. 2007; 32:114-116

^{18}F-FDG Vs ^{67}Ga citrate in patients with Sarcoidosis

18 patients with disease proven by histology

Studies were done in median interval time of 6.6 days

Visual & quantitative analysis of pulmonary + extra pulmonary uptake (SUV & lesion/lumbar spine)

Findings compared to histology and follow up

Conclusion: FDG more accurate than ^{67}Ga citrate

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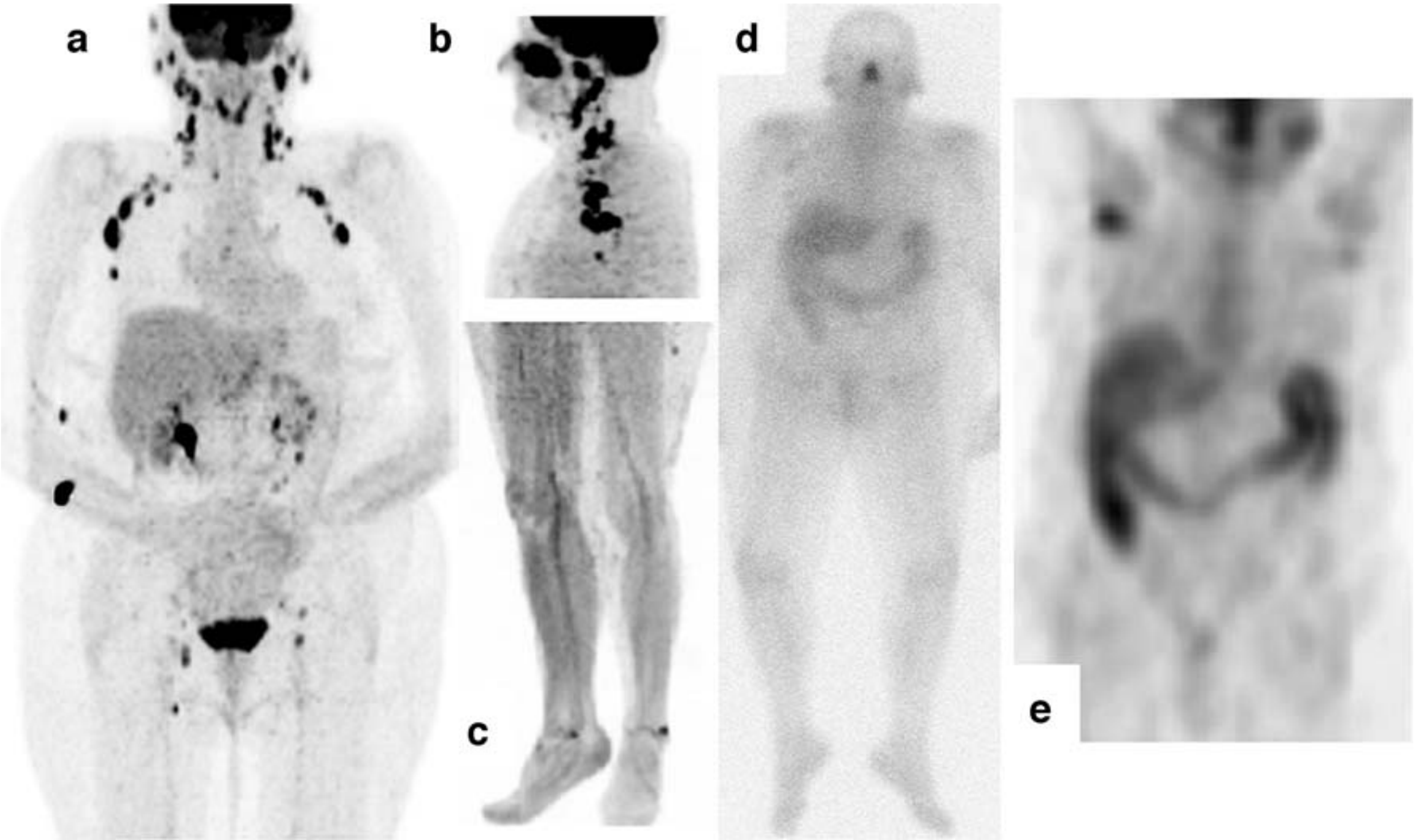
Yoshihiro et al. J Nucl Med. 2006; 47:1571-1576

^{18}F-FDG PET/CT in sarcoidosis management

Braun et al. Eur J Nucl Med Mol Imaging. 2008; 35:1537-1543

Sensitivity per biopsy proven granulomatous disease

Location	^{18}FDG PET/CT			^{67}Ga scan		
	N0 of examined patient	N0 of biopsied sites	sensitivity (%)	N0 of examined patient	N0 of biopsied sites	sensitivity (%)
Thoracic	13	13	100	7	7	71
Sinonasal	5	5	100	4	4	75
Pharyngo-laryngeal	5	5	80	3	3	67
Thoracic + Extra Thoracic	20	31	87	12	21	67
Thoracic + Exra thoracic (Comparative analysis: FDG Vs Ga)	12	21	86	12	21	67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Results of 188 Whole-Body Fluorodeoxyglucose Positron Emission Tomography Scans in 137 Patients With Sarcoidosis

Alvin S. Teirstein, Josef Machac, Orlandino Almeida, Ping Lu, Maria L. Padilla, and Michael C. Iannuzzi.

Chest. 2007; 132:1949-1953

Results of 139 Positive Whole-Body FDG PET Scans in 137 Sarcoidosis Patients

Location	N0
Mediastinum	54
Extrathoracic nodes	30
Lung	24
Spleen	9
Muscle	7
Lacrimal/parotid	6
Subcutaneous	3
Bone	3

Chest. 2007;132:1949-1943

Correlation of 24 Lung Parenchyma Positive and 49 Lung Negative FDG PET Scans with Chest Radiographic Patterns

PET Scan	Scadding Radiographic stages				
	0	**I**	**II**	**III**	**IV**
Positive findings (n=24)	**1**	**4**	**10**	**6**	**3**
Negative findings (n=49)	**10**	**14**	**5**	**1**	**19**

Chest. 2007;132:1949-1943

^{18}F-FDG PET in cardiac sarcoidosis

Ohira. Tsujino. Yoshinaga. Eur J Nucl Med Mol Imaging. 2011; 38:1773-1783

Present preparation for cardiac FDG PET

	Pretest preparation	
Authors	**Fasting period**	**Diet**
Yamagishi et al.	**> 5 h**	**Not specified**
Okumura et al.	**> 12 h**	**Not specified**
Ishimaru et al.	**> 12 h**	**Not specified**
Ohira et al.	**> 12 h**	**Not specified**
Mehta et al.	**Not available**	**Not specified**
Langah et al.	**> 18 h**	**Not specified**

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Diet recommendation to suppress cardiac FDG PET uptake

Authors	Types of meals	Time of last food intake	Carbohydrate
Lum et al.	Low-carbohydrate meal	The night prior to the scan	Not Defined
Williams and Kolodny	Very high-fat, low-carbohydrate protein-permitted meal	3-6 h before the scan	Not defined
Wykrzykowska et al.	Very high-fat, low-carbohydrate protein-permitted meal	The night prior to the scan	< 5 g
Cheng et al.	Low-carbohydrate meal	The night prior to the scan	< 5 g
Hokkaido University	Low-carbohydrate meal	The night prior 250-300 kcal to the scan	< 5 g

Ohira. Tsujino. Yoshinaga. Eur J Nucl Med Mol Imaging. 2011; 38:1773-1783


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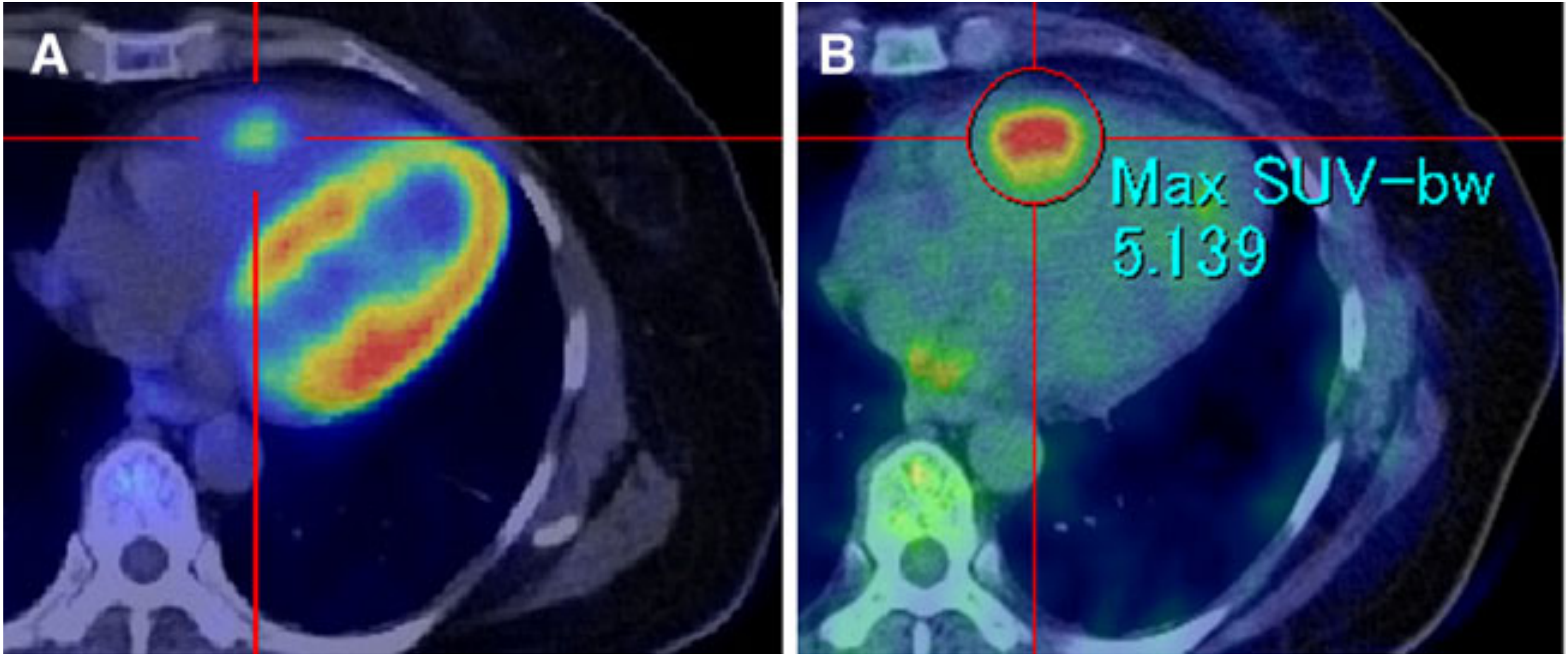
15 h fasting Vs diet modification



Sensitivity & specificity of FDG PET for diagnosis of cardiac sarcoidosis

Authors	Year	Number of patients	Sensitivity (%)	Specificity (%)
Yamagishi et al.	2003	17	82	NA
Okumura et al.	2004	22	100	91
Ishimura et al.	2005	32	100	82
Ohira et al.	2008	21	88	39
Langah et al.	2009	76	85	90
Weighted mean		168	89.9	81.4
Mean		168	91	75.5

Ohira. Tsujino. Yoshinaga. Eur J Nucl Med Mol Imaging. 2011; 38:1773-1783

Comparison of imaging modalities in the diagnosis of cardiac sarcoidosis

Modalities	Sensitivity (%)	Specificity (%)
^{18}F-FDG PET	82-100	39-91
MRI	75-100	75-78
^{20}Tl and ^{99m}Tc-sestamibi MPI	40-65	93-100
^{67}Ga scintigraphy	0-36	100

Ohira. Tsujino. Yoshinaga. Eur J Nucl Med Mol Imaging. 2011; 38:1773-1783

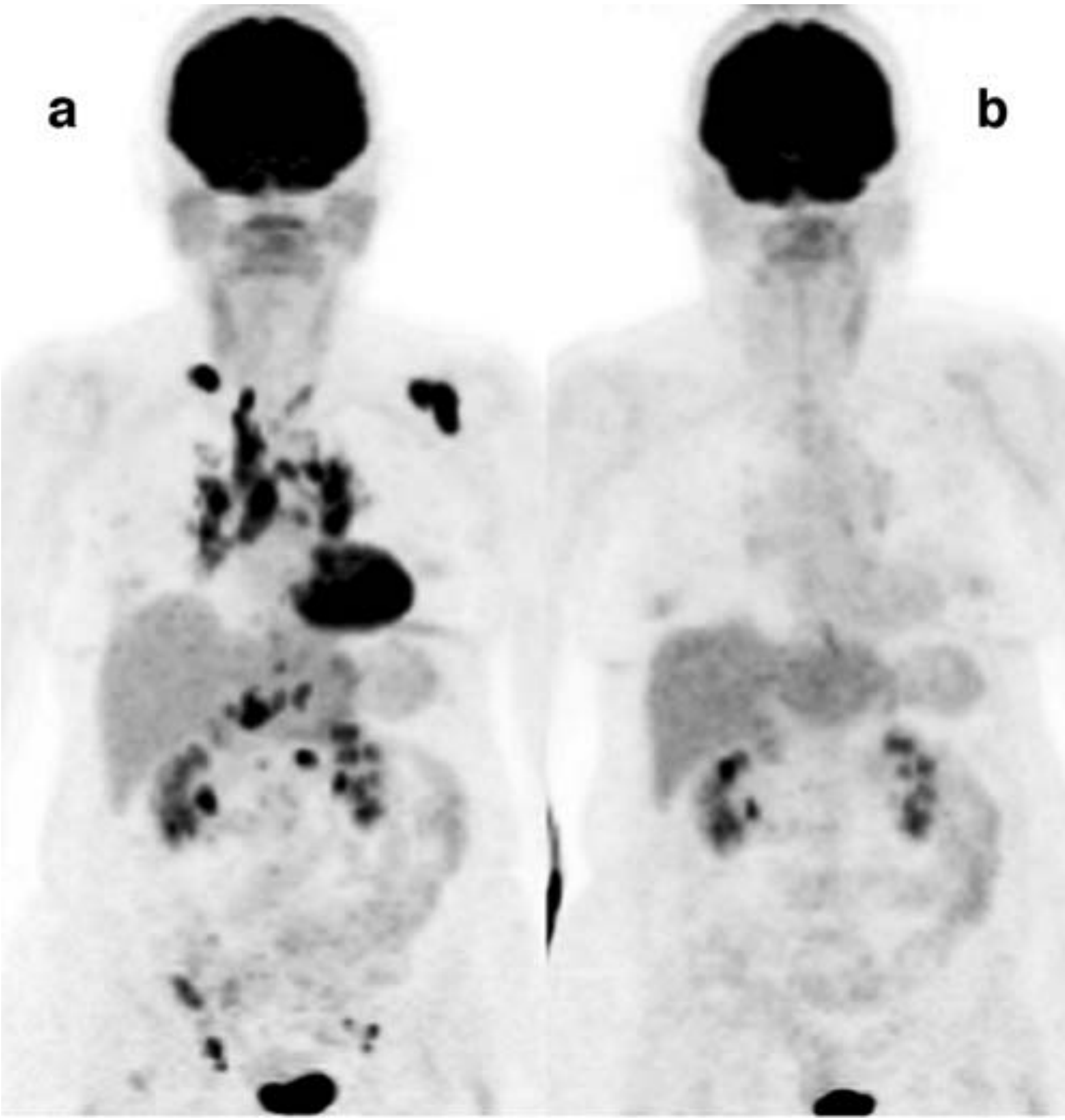
^{18}F-FDG PET to monitor treatment?

SUVs of FDG PET/CT in 5 patients before, during or after therapy

Localisation (time between 2 PET/CT)	mSUV									
	Patient1 (2 months)		Patient2 (6 months)		Patient3 (21 months)		Patient4 (19 months)		Patient 5 (16 months)	
	1st PET	2nd PET	1st PET	2nd PET	1st PET	2nd PET	1st PET	2nd PET	1st PET	2nd PET
Sinonasal	10	nd	-	-	3	2	14	12	16	20
Mediastinal	9	nd	19	nd	5	5	11	9	-	-
Axillary	8	nd	-	-	3	nd	6	nd	17	19
Infra-Diaphragmatic	9	nd	13	nd	14	12	16	nd	7	18

nd: no detectable abnormality

Adapted from Braun et al. (2008)



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A negative FDG PET= cure?

74% relapse in induced remission patients?

Gottieb et al. Chest. 1997; 111:623-631

Is the disease dormant during remission?

Can we detect pathologic TNF or STAT1?

STAT1: significantly associated to sarcoidosis

Crouser et al. Am J Respir Crit Care Med. 2009; 179:929-938
Rosenbaum et al. Clin Immunol. 2009; 132:174-183

Future directions in therapy monitoring

Current use of ^{18}F-FDG is based in experience in oncology

Today: No consensus on FDG PET response criteria

Use of different methodologies & have varying endpoints

Tumor response is not necessary = favorable outcome

Weber. J Nucl Med. 2009; 50:1s-10s

Eisenhauer et al. Eur J Cancer. 2009; 45:228-247

Prospective studies to validate FDG use in therapy needed

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SUMMARY

Sarcoidosis= multiorgan disease & may mimic malignancy

^{18}F-FDG PET: good sensitivity but specificity to be defined

^{67}Ga: acceptable alternative to FDG

Need: multicentric prospective studies needed for long term impact & outcomes on the use of FDG in sarcoidosis