MOLECULAR IMAGING IN SARCOIDOSIS

Willy Mboyo Vangu
MD, MMed, MSc, PhD

Nuclear Medicine and Molecular Imaging
University of the Witwatersrand, South Africa
Objectives

Background on Sarcoidosis

Uptake mechanism of tracers

Describing imaging patterns

A word on current imaging sensitivity & specificity

Role for $^{18}\text{F-}\text{FDG}$ on therapy monitoring?
Sarcoidosis Pathogenesis?

Multiorgan granulomatous of unknown etiology

Macrophages + factors activation

Non-caseating granulomas (lung & nodes)

TNF-α = disease activity

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 (NOTCH4 in African American and 12q13.3 to 12q14.1 in European population)

Diagnosis

Histology: non-caseating epithelioid cell granuloma

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

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

Scadding JG. BMJ. 1961; 4:1165-1172
Place of molecular imaging?
67Ga Citrate

Non specific tracer: uses increased vascularity

Binds to circulating transferrin

67Ga citrate- transferrin: extravasates at the inflammation site

FDG in inflammatory site

Maisey, Wahl & Barrington, Atlas of Clinical PET, 1999
Love et al. Radiographics. 2005; 25:1357-1368
Other tracers?

$^{201}$TI, $^{99m}$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
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)
Musculoskeletal

Up to 1/3 of patients with bone lesions

Extremities >> axial skeleton

May be lytic or osteoblastic

Meaningful in presence of mediastinal lymphadenopathy
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

18F-FDG Vs 67Ga 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 67Ga citrate

# Sensitivity per biopsy proven granulomatous disease

<table>
<thead>
<tr>
<th>Location</th>
<th>(^{18}\text{FDG PET/CT})</th>
<th>(^{67}\text{Ga scan})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N0 of examined patient</td>
<td>N0 of biopsied sites</td>
</tr>
<tr>
<td>Thoracic</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Sinonasal</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pharyngo-laryngeal</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Thoracic + Extra Thoracic</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Thoracic + Extra thoracic (Comparative analysis: FDG Vs Ga)</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>

(Comparative analysis: FDG Vs Ga)
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

<table>
<thead>
<tr>
<th>Location</th>
<th>N0</th>
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</thead>
<tbody>
<tr>
<td>Mediastinum</td>
<td>54</td>
</tr>
<tr>
<td>Extrathoracic nodes</td>
<td>30</td>
</tr>
<tr>
<td>Lung</td>
<td>24</td>
</tr>
<tr>
<td>Spleen</td>
<td>9</td>
</tr>
<tr>
<td>Muscle</td>
<td>7</td>
</tr>
<tr>
<td>Lacrimal/parotid</td>
<td>6</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
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</table>
Correlation of 24 Lung Parenchyma Positive and 49 Lung Negative FDG PET Scans with Chest Radiographic Patterns

<table>
<thead>
<tr>
<th>PET Scan</th>
<th>Scadding Radiographic stages</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Positive findings (n=24)</td>
<td>1</td>
</tr>
<tr>
<td>Negative findings (n=49)</td>
<td>10</td>
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</tbody>
</table>

Chest. 2007;132:1949-1943
**18F-FDG PET in cardiac sarcoidosis**


**Present preparation for cardiac FDG PET**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Fasting period</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamagishi et al.</td>
<td>&gt; 5 h</td>
<td>Not specified</td>
</tr>
<tr>
<td>Okumura et al.</td>
<td>&gt; 12 h</td>
<td>Not specified</td>
</tr>
<tr>
<td>Ishimaru et al.</td>
<td>&gt; 12 h</td>
<td>Not specified</td>
</tr>
<tr>
<td>Ohira et al.</td>
<td>&gt; 12 h</td>
<td>Not specified</td>
</tr>
<tr>
<td>Mehta et al.</td>
<td>Not available</td>
<td>Not specified</td>
</tr>
<tr>
<td>Langah et al.</td>
<td>&gt; 18 h</td>
<td>Not specified</td>
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</table>
## Diet recommendation to suppress cardiac FDG PET uptake

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

15 h fasting Vs diet modification
Sensitivity & specificity of FDG PET for diagnosis of cardiac sarcoidosis

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

Comparison of imaging modalities in the diagnosis of cardiac sarcoidosis

<table>
<thead>
<tr>
<th>Modalities</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹⁸F-FDG PET</td>
<td>82-100</td>
<td>39-91</td>
</tr>
<tr>
<td>MRI</td>
<td>75-100</td>
<td>75-78</td>
</tr>
<tr>
<td>²⁰Tl and ⁹⁹mTc-sestamibi MPI</td>
<td>40-65</td>
<td>93-100</td>
</tr>
<tr>
<td>⁶⁷Ga scintigraphy</td>
<td>0-36</td>
<td>100</td>
</tr>
</tbody>
</table>


### 18F-FDG PET to monitor treatment?

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

<table>
<thead>
<tr>
<th>Localisation</th>
<th>Patient 1 (2 months)</th>
<th>Patient 2 (6 months)</th>
<th>Patient 3 (21 months)</th>
<th>Patient 4 (19 months)</th>
<th>Patient 5 (16 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinonasal</td>
<td>mSUV</td>
<td>mSUV</td>
<td>mSUV</td>
<td>mSUV</td>
<td>mSUV</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>9 nd</td>
<td>19 nd</td>
<td>5 5</td>
<td>11 9</td>
<td>- -</td>
</tr>
<tr>
<td>Axillary</td>
<td>8 nd</td>
<td>- nd</td>
<td>3 nd</td>
<td>6 nd</td>
<td>17 19</td>
</tr>
<tr>
<td>Infra-Diaphragmatic</td>
<td>9 nd</td>
<td>13 nd</td>
<td>14 12</td>
<td>16 nd</td>
<td>7 18</td>
</tr>
</tbody>
</table>

*nd: no detectable abnormality*

Adapted from Braun et al. (2008)
A negative FDG PET= cure?

74% relapse in induced remission patients?


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
Future directions in therapy monitoring

Current use of $^{18}\text{F}}$-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


Prospective studies to validate FDG use in therapy needed
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