PET/CT Characterization of Malignant and Benign Lung Lesions

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• The accurate characterization as benign or malignant of a lung lesion found on routine chest imaging is a “diagnostic dilemma”.

• This dilemma is becoming more pronounced today as the volume of diagnostic imaging performed continues to increase.
Metabolic characterization $\Rightarrow$ FDG uptake
Cancer cells preferably utilize anaerobic glycolysis for energy and rely on both increased glucose transport across the cell membrane and enhanced hexokinase activity to meet higher glucose demand.

Increased glycolysis is also a function of many inflammatory conditions.

Idiopathic Pulmonary Fibrosis and Diffuse Parenchymal Lung Disease: Implications from Initial Experience with $^{18}$F-FDG

Noninvasive Pulmonary $[^{18}\text{F}]-2$-Fluoro-Deoxy-d-Glucose Positron Emission Tomography Correlates with Bactericidal Activity of Tuberculosis Drug Treatment

Usefulness of $^{18}$F-fluorodeoxyglucose positron emission tomography for diagnosing disease activity and monitoring therapeutic response in patients with pulmonary mycobacteriosis

Positron emission tomography in interstitial lung disease

Impact of FDG PET on the management of TBC treatment

A pilot study

M. Sathekge\textsuperscript{1}; A. Maes\textsuperscript{2,3}; M. Kgomo\textsuperscript{4}; A. Stoltz\textsuperscript{5}; H. Pottel\textsuperscript{6}; C. Van de Wiele\textsuperscript{7}
Differential diagnosis between inflammatory lung disease and malignancy is essential for:

- Metabolic characterisation of SPN or mass
- Evaluation of metastatic lung disease
CT has been shown to have poor specificity (58%) for characterization of the nodule.

- 70-75% of indeterminate nodules prove to be malignant.

• FDG-PET: A systematic review reported a pooled sensitivity and specificity of 94.2% and 83.3%.

• 450 patients with lung nodules in 13 small studies

• The component studies were limited by small sample size, incomplete masking, and biased patient selection.

• 18F-FDG PET should be used selectively when pretest probability and CT findings are discordant or in patients with intermediate pretest probability who are at high risk for surgical complications

PET/CT interpretation in lung lesions

- Patient Data
- CT Interpretation
  - Clinical
  - Imaging
  - Pathology
  - Distribution Pattern
  - Appearance Pattern
  - Uptake Pattern
  - Intensity
- PET Interpretation
- Previous findings (CT or PET/CT)
- Diagnostic CT findings
- Visuel
- SUV
What is the visual or standardized uptake value (SUV) cutoff for classifying a solitary pulmonary nodule as benign?
Nodules with an SUV less than 2.5 or whose activity appears visually to be less than or equal to that of the mediastinal blood pool can be considered benign with enough confidence to avoid an immediate biopsy; these nodules can safely be followed with CT.


Any visually perceptible uptake by a pulmonary nodule is associated with a significant chance of malignancy.


"For every complex problem, there is a solution that is simple, neat, and wrong."

Henry Louis Mencken
Pulmonary Carcinoid Tumours

- Carcinoid tumour accounts for 1–5% of malignant SPNs
- low malignancy (typical carcinoids),
- intermediate malignancy (atypical carcinoids)
- high malignancy (small cell and giant cell neuroendocrine carcinomas)
- The ratio of typical to atypical carcinoids is 9 : 1
- Typical carcinoids grow slowly, the 5-year survival rate is > 95%,
- Atypical carcinoids, the 5-year survival rate is approximately 60% even after successful surgical resection.
- Typical carcinoids can lead to false-negative results of PET imaging

Min JH et al. Lung Cancer. 2010 May 15. [Epub ahead of print]
• 31 SPNs (58%) purely non-solid lesions,
• 22 SPNs (42%) contained partly solid components.
• All patients underwent surgical resection
• 28 patients (53%) had adenocarcinomas (12 BAC, 16 mixed)
• 25 patients (47%) had benign lesions (16 subacute or organizing pneumonia, 7 non-specific inflammation, 2 simple eosinophilia).

<table>
<thead>
<tr>
<th>Maximal SUV</th>
<th>Benign SPN</th>
<th>Malignant SPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.7</td>
<td>0.8</td>
</tr>
<tr>
<td>SD</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Range</td>
<td>1.8-5.0</td>
<td>0.5-1.6</td>
</tr>
</tbody>
</table>
• When FDG-PET/CT reveals a **significant uptake** in SPNs with non-solid components, the lesion may have potentially **benign** characteristics and should be followed up with serial CT scans.

• When FDG **uptake is not observed** in SPNs with non-solid components, the findings are more suggestive of **malignant** lesions, which should be surgically resected.
The most common causes of benign SPN:
• %25 healed or nonspecific granulomas
• %15 active granulomatous infections
  – tuberculosis,
  – coccidioidomycosis,
  – histoplasmosis,
  – cryptococcosis,
  – aspergillosis
• %15 Hamartomas

Less common miscellaneous causes of benign nodules:
• nonspecific inflammation and fibrosis,
• lung abscesses,
• round pneumonia,
• round atelectasis,
• bronchogenic cysts,
• healed pulmonary infarcts,
• focal hemorrhage,
• hemangiomas,
• arteriovenous malformations

How can we improve the specificity of FDG-PET imaging?
Factors affecting SUV

- Plasma glucose level
- Lesion size
- Body habitus (the volume of distribution of the 18F-FDG for a given subject)
- Timing of imaging after FDG injection
- Motion-related distortion
- Method for determining counts within the lesion region of interest
• The prevalence of malignancy in nodules that measured 5 mm was exceedingly low (range, 0 to 1%).

• The risk for malignancy was higher in nodules that measured between 5 and 10 mm (range, 6 to 28%)

• It was very high in nodules that measured 2 cm in diameter (range, 64 to 82%)

Table 1. Sensitivity, specificity and the area under the ROC curve for different normalizations of SUV at cut-off values of 2.0 and 2.5

<table>
<thead>
<tr>
<th>SUV</th>
<th>Sensitivity (SUV &gt; 2.5)</th>
<th>Specificity (SUV &gt; 2.5)</th>
<th>Sensitivity (SUV &gt; 2)</th>
<th>Specificity (SUV &gt; 2)</th>
<th>Area under ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV_{BW}</td>
<td>93.6</td>
<td>75.8</td>
<td>96.8</td>
<td>60.6</td>
<td>0.915</td>
</tr>
<tr>
<td>SUV_{BW}+Glu</td>
<td>94.7</td>
<td>69.7</td>
<td>96.8</td>
<td>57.6</td>
<td>0.912</td>
</tr>
<tr>
<td>SUV_{LBW}</td>
<td>92.6</td>
<td>63.6</td>
<td>96.8</td>
<td>57.6</td>
<td>0.911</td>
</tr>
<tr>
<td>SUV_{LBW}+Glu</td>
<td>94.7</td>
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<td>96.8</td>
<td>57.6</td>
<td>0.912</td>
</tr>
<tr>
<td>SUV_{BSA}</td>
<td>92.6</td>
<td>66.7</td>
<td>96.8</td>
<td>60.6</td>
<td>0.916</td>
</tr>
<tr>
<td>SUV_{BSA}+Glu</td>
<td>92.6</td>
<td>63.6</td>
<td>96.8</td>
<td>57.6</td>
<td>0.909</td>
</tr>
<tr>
<td>SUV_{BW}+Tsize</td>
<td>93.6</td>
<td>66.7</td>
<td>96.8</td>
<td>48.5</td>
<td>0.864</td>
</tr>
</tbody>
</table>

BW, body weight; Glu, glucose; LBW, lean body weight; BSA, body surface area; Tsize, tumor size


Table 6. Corresponding sensitivity, accuracy and cutoff value for various SUVs tested at a specificity of 80%

<table>
<thead>
<tr>
<th>SUV</th>
<th>Max</th>
<th>Mean</th>
<th>Vol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff value</td>
<td>Sensitivity (%)</td>
<td>Accuracy (%)</td>
</tr>
<tr>
<td>SUV_{BSA}</td>
<td>5.2</td>
<td>81</td>
<td>71</td>
</tr>
<tr>
<td>SUV_{LBW}</td>
<td>1.5</td>
<td>73</td>
<td>78</td>
</tr>
<tr>
<td>SUV_{GLC}</td>
<td>2.3</td>
<td>62</td>
<td>70</td>
</tr>
<tr>
<td>SUV_{BSA-GLC}</td>
<td>5.9</td>
<td>65</td>
<td>72</td>
</tr>
<tr>
<td>SUV_{LBW-GLC}</td>
<td>1.4</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>SUV_{PVC}</td>
<td>2.9</td>
<td>73</td>
<td>76</td>
</tr>
<tr>
<td>SUV_{PVC-BSA}</td>
<td>6.9</td>
<td>73</td>
<td>76</td>
</tr>
<tr>
<td>SUV_{PVC-LBW}</td>
<td>2.0</td>
<td>73</td>
<td>76</td>
</tr>
<tr>
<td>SUV_{PVC-GLC}</td>
<td>3.0</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>SUV_{PVC-BSA-GLC}</td>
<td>7.0</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>SUV_{PVC-LBW-GLC}</td>
<td>2.2</td>
<td>69</td>
<td>74</td>
</tr>
</tbody>
</table>

BSA, body surface area; GLC, blood glucose; LBW, lean body weight; PVC, partial-volume correction; SUV, standardized uptake value.

Could the uptake kinetics differentiate inflammation and tumor?
Dual point acquisition

- Dual phase acquisition may be utilized to differentiate malignant and benign conditions
- Increasing calculated SUVs between two time points suggests the presence of malignancy
- Unchanged or decreased SUVs with dual phase technique infers benignity
- Based on intracellular concentrations of glucose 6 phosphatase
- Best reserved for cases where: the initial SUV is close to the threshold of 2.5 and likely has little value when SUV < 1.0

Dual point acquisition

- Delayed FDG PET is not useful for differentiating benign and malignant pulmonary nodules with an initial mean SUV less than 2.5 in geographic regions with epidemic granulomatous disease such as tuberculosis or in patients at high risk of granulomatous inflammation.

Jung Chen J et al. AJR 2008; 191:475–479
• 344 people with SPNs identified on chest radiography.
• The SPNs were 7-30 mm (average 16 mm)
• A masked panel of 3 PET and 3 CT experts rated the studies on a 5-point scale.
• SPN tissue diagnosis or 2 years follow-up
• The prevalence of malignancy was %53

VA SNAP Cooperative Studies Group
<table>
<thead>
<tr>
<th>Category</th>
<th>Relationship between SPN 18F-FDG uptake and likelihood of malignancy</th>
<th>Relationship between CT SPN characteristics and likelihood of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely benign</td>
<td>No increased uptake—uptake essentially the same as in reference lung tissue (generally corresponds to an SUV of 0.6–0.8)</td>
<td>Central laminated, diffuse or popcorn pattern of calcification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lesion with cavitations and wall thickness &lt; 1 mm</td>
</tr>
<tr>
<td>Probably benign</td>
<td>Uptake substantially less than in blood pool (general mediastinal activity) but greater than in reference lung tissue (SUV greater than 0.6–0.8 but less than 1.5–2.0)</td>
<td>Large (&gt;2 cm) dominant nodule with satellite lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solid nodule with polygonal shape or smooth and well-defined margin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diameter &lt; 10 mm; lobulated margin contours</td>
</tr>
<tr>
<td>LR</td>
<td>0.10</td>
<td>0.11</td>
</tr>
</tbody>
</table>

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<tr>
<td>Indeterminate</td>
<td>Uptake 2–3 times that in reference lung tissue but less than in blood pool (generally corresponds to SUV of 1.5–2.0 but less than 2.5)</td>
<td>All other characteristics not defined in other likelihood categories</td>
</tr>
</tbody>
</table>
| Probably malignant        | Uptake greater than in blood pool (blood pool generally corresponds to an SUV of 2.5)                                                                                                       | Diameter > 2 cm  
Ground-glass opacity with round shape  
Mixed ground-glass opacity with central zone of high attenuation                                                                                                                                  |
| Definitely malignant      | Uptake much greater than in blood pool—anything substantially greater than SUV of 2.5                                                                                                         | Densely spiculated margin, ragged margin  
Lesion with cavitations and wall thickness > 16 mm                                                                                                                                                    |
| LR                        | 5.18                                                                                                                             | 1.61                                                                                                                                 |

• PET correctly classified 58% of the benign nodules that had been incorrectly classified as malignant on CT.

• 25% of nodules were characterized as indeterminate by CT readers, whereas only 1% of nodules were classified as indeterminate by PET readers.

• Nodules that were classified as indeterminate on CT were correctly characterized on PET in over 80% of the cases (sensitivity, 83%; specificity, 89%).

Conclusion

• There is no single solution to differentiate benign and malignant lung lesions.

• The specificity of FDG PET/CT imaging can be highly enhanced by
  – Correct patient selection,
  – Correlate PET and CT images,
  – Being interested in the individual patient behind the images.