Value of FDG-PET-CT in Lung Cancer

Sigrid Stroobants, MD, PhD
Department of Nuclear Medicine
University Hospital Antwerp, Belgium
Outline

• Diagnosis (characterization of nodules)
• Initial Staging
  ➢ Tumor
  ➢ Nodes
  ➢ Metastasis
• Restaging after neoadjuvant treatment
• PET in radiation treatment planning
PET in Lung Cancer - Diagnosis

• FDG-PET useful to distinguish benign vs malignant nodules
  – many well documented prospective series
  – Meta-analysis Gould et al; JAMA, 2001
    • sensitivity 96% - specificity 78% - accuracy 91%

• Limits
  – sensitivity: subcentimetric nodules – carcinoids- BAC- GGO
    Nomori et al; Lung Cancer 2004
    • 136 non-calcified nodules <3cm
    • 20 nodules <1 cm: 0/8 cancers true +
    • 101 solid nodules 1-3 cm: 57/63 cancers true +
    • 15 GGO nodules 1-3 cm: 1/10 cancers true +

  – specificity: inflammatory/granulomatous lesions
    • Use of threshold values (e.g. SUV >2.5) not superior
    • Dual time point imaging
Fluoro-deoxy-glucose positron emission tomography for evaluation of indeterminate lung nodules: assigning a probability of malignancy may be preferable to binary readings


Table 1 Final tissue diagnosis for benign lesions and malignant lesions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign (n = 55)</td>
<td></td>
</tr>
<tr>
<td>Inflammation/infection</td>
<td>17 (30.9)</td>
</tr>
<tr>
<td>Granuloma</td>
<td>17 (30.9)</td>
</tr>
<tr>
<td>Focal fibrosis</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>15 (27.2)</td>
</tr>
<tr>
<td>Malignant (n = 103)</td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Non-small-cell carcinoma (NSCLC) (n = 83)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>21 (20.4)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>39 (37.9)</td>
</tr>
<tr>
<td>Bronchioloalveolar adenocarcinoma</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Unspecified or mixed NSCLC*</td>
<td>12 (11.7)</td>
</tr>
<tr>
<td>Metastases</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Unspecified, poorly differentiated non-small-cell carcinoma, or adeno-squamous cell carcinoma

Table 2 The sensitivity and specificity of fluorine-18 fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) with the cutoff SUV_{raw} of 2.5 for differentiating benign from malignant pulmonary nodules less than 2 cm and 2 cm or greater in diameter

<table>
<thead>
<tr>
<th></th>
<th>Lesion &lt; 2 cm (n = 42)</th>
<th>Lesion ≥ 2 cm (n = 89)</th>
<th>All (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>75.0</td>
<td>91.9</td>
<td>89.3</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>72.2</td>
<td>40.7</td>
<td>50.9</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>73.8</td>
<td>76.4</td>
<td>75.9</td>
</tr>
</tbody>
</table>

SUV = Standardized Uptake Value

POC = Positive Predictive Value
Characterization of SPN

Accidental finding of a SPN in RLL adjacent to the oesophagus. Bronchoscopy normal; Sputum cytology normal

EUS + FNAC: fibroblasts, epithelial cells, benign aspect

PET

Thoracotomie: Hamartoma
PET in Lung Cancer - Diagnosis

• For lesions > 1 cm without GGO aspect
  – overall good NPV: correct exclusion of malignancy in the vast majority of nodules seen in daily practice
  – surgical procedure can be avoided, repeat XR or CT after 3, 6, 12 and 24 months to confirm absence of growth

• For lesions < 1 cm
  – Negative PET does not exclude malignancy
  – high PPV

• PPV can be disappointing in region with endemic granolomatous disease
Outline

• Diagnosis (characterization of nodules)
• Initial Staging
  ➢ Tumor
  ➢ Nodes
  ➢ Metastasis
• Restaging after neoadjuvant treatment
• PET in radiation treatment planning
PET for T-staging

- T-stage depending on size and local extension
  - Limited value of PET due to poor anatomical resolution
  - DD T4 in Lung Ca based on 2 lesions or atelectasis

T4 (2 lesions)

T1 + fibrotic mass
FDG uptake as prognostic marker

J Vansteenkiste et JCO 1999; 17: 3201-3206

Can PET guide adjuvant therapy?
- Prospective studies needed
- Threshold = center dependent
- Standardization and cross calibration
PET for N-staging

- Diagnosis of metastatic involvement based on increased metabolism
  - Detection of M+ in small LN
  - Exclusion of M+ in inflammatory enlarged LN
# PET for N-staging

**Meta analysis Gould et al. Annals of Internal Medicine 2003**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Sensitivity (IQR)</th>
<th>Median Specificity (IQR)</th>
<th>Maximum Joint Sensitivity and Specificity (95% CI)†</th>
<th>Sensitivity at Point on Summary ROC Curve Corresponding to Median Specificity (95% CI)</th>
<th>Specificity at Point on Summary ROC Curve Corresponding to Median Sensitivity (95% CI)</th>
<th>Likelihood Ratio for Positive Test‡</th>
<th>Likelihood Ratio for Negative Test‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies (1119 patients in 23 studies)</td>
<td>61 (50–71)</td>
<td>79 (66–89)</td>
<td>70 (67–73)</td>
<td>59 (52–66)</td>
<td>78 (72–83)</td>
<td>2.8</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>PET</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies (1959 patients in 32 studies)</td>
<td>85 (67–91)</td>
<td>90 (82–96)</td>
<td>86 (84–88)</td>
<td>81 (74–86)</td>
<td>86 (81–90)</td>
<td>8.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Patients with enlarged lymph nodes on CT (214 patients in 12 studies)</td>
<td>100 (90–100)</td>
<td>78 (68–100)</td>
<td>85 (79–90)</td>
<td>91 (79–96)</td>
<td>NC</td>
<td>4.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Patients without enlarged lymph nodes on CT (479 patients in 14 studies)</td>
<td>82 (65–100)</td>
<td>93 (92–100)</td>
<td>87 (84–89)</td>
<td>75 (59–87)</td>
<td>90 (82–95)</td>
<td>10.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* CT = computed tomography; IQR = interquartile range; NC = not able to calculate; PET = positron emission tomography; ROC = receiver-operating characteristic.
† The maximum joint sensitivity and specificity is the point on the summary ROC curve at which sensitivity and specificity are equal; it is a global measure of test performance, similar to the area under the curve, and does not necessarily represent the optimal operating point or the one applied in everyday clinical practice.
‡ To calculate likelihood ratios, we used the point on the summary ROC curve that corresponded to the median specificity.
PET for N-staging

pT1N0

pT1N2
DD malignant vs benign LN

pT2N0

pT1N0

pT2N3
PET for N-staging

• Pitfalls
  – Minimal disease ➞ false negative
  – Inflammatory disease ➞ false positives
  – Limited spatial resolution ➞ N1 vs N2, central T
Impact of size of metastatic foci

Nomori et al, J. Thorac cardiovasc Surg 2004

### TABLE 5. Diagnostic results of PET and CT scanning

<table>
<thead>
<tr>
<th>Variable</th>
<th>PET</th>
<th>CT</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.78</td>
<td>0.53</td>
<td>( P = .026 )</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.98</td>
<td>0.98</td>
<td>( P = .63 )</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.97</td>
<td>0.96</td>
<td>( P = .28 )</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.74</td>
<td>0.70</td>
<td>0.77</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.98</td>
<td>0.97</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*PET, Positron emission tomography; CT, computed tomography.*

**Figure 2.** The distribution of sizes of metastatic foci in false-negative and true-positive lymph nodes with PET scan.
Definition of PET+LN

Hellwig et al, JNM 2007
Retrospective analysis of 95 patients with suspected NSCLC and underwent mediastinoscopy and had PET prior to surgery
Comparison of visual analysis (> mediastinal BG) and SUV max LN

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>2.4 ± 1.7</td>
</tr>
<tr>
<td>True Negative</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>False Negative</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>False Positive</td>
<td>4.8 ± 2.5</td>
</tr>
<tr>
<td>True Positive</td>
<td>7.2 ± 4.4</td>
</tr>
<tr>
<td>Malignant</td>
<td>6.8 ± 4.4</td>
</tr>
</tbody>
</table>
Include “pattern” and CT features in LN characterisation

Lee et al. (Korea), PET/CT in TB endemic region

Fig. 4 Typical benign lymph node distribution pattern in a 65-year-old man with right upper lobe squamous cell cancer. a Projection image shows multiple bilateral hilar and interlobar lymph nodes with increased FDG uptake. Pathology showed reactive hyperplasia in every lymph node selected. b Axial PET image shows bilateral hilar hypermetabolism. c Noncontrast CT image shows calcification of bilateral lymph nodes.
Staging of Non–Small-Cell Lung Cancer with Integrated Positron-Emission Tomography and Computed Tomography

Didier Lardinois, M.D., Walter Weder, M.D., Thomas F. Hanx, M.D., Ehab M. Kamel, M.D., Stephan Korom, M.D., Burkhard Seifert, Ph.D., Gustav K. von Schulthess, M.D., Ph.D., and Hans C. Steinert, M.D.

<p>| Table 3. Diagnostic Accuracy of the Imaging Methods with Respect to Node Stage in 37 Patients. |
|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Imaging Method</th>
<th>Classification (Score of 3)</th>
<th>Classification Correct (Score of 2)</th>
<th>Classification Incorrect (Score of 0 or 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT alone</td>
<td>22 (59)</td>
<td>2 (5)</td>
<td>13 (35)</td>
</tr>
<tr>
<td>PET alone</td>
<td>18 (49)</td>
<td>14 (38)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Visual correlation of PET and CT</td>
<td>22 (59)</td>
<td>4 (11)</td>
<td>11 (30)</td>
</tr>
<tr>
<td>Integrated PET–CT</td>
<td>30 (81)</td>
<td>1 (3)</td>
<td>6 (16)</td>
</tr>
</tbody>
</table>
PET for N-staging
Impact of integrated PET-CT

pT2N1
PET for N-staging

Impact of integrated PET-CT

Lee et al. (Journal of Thoracic and cardioovascular surgery 2007)

Comparison of PET (n=210) and intergrated PET-CT (n=126) with ISS
Definition of PET+ = visual (> mediastinal BG)

---

**TABLE 4. Efficacy of mediastinal staging by PET versus PET/CT**

<table>
<thead>
<tr>
<th></th>
<th>Standard PET (n = 210)</th>
<th>Integrated PET/CT (n = 126)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%, 95% CI)</td>
<td>61.1 (43.5-76.9)</td>
<td>85.7 (67.3-96.0)</td>
<td>.0299</td>
</tr>
<tr>
<td>Specificity (%, 95% CI)</td>
<td>94.3 (89.7-97.2)</td>
<td>80.6 (71.4-87.9)</td>
<td>.0005</td>
</tr>
<tr>
<td>Positive predictive value (%, 95% CI)</td>
<td>68.8 (50.0-83.9)</td>
<td>55.8 (39.9-70.9)</td>
<td>.2552</td>
</tr>
<tr>
<td>Negative predictive value (%, 95% CI)</td>
<td>92.1 (87.2-95.6)</td>
<td>95.2 (88.1-98.7)</td>
<td>.3658</td>
</tr>
<tr>
<td>Accuracy (%, 95% CI)</td>
<td>88.6 (87.2-95.6)</td>
<td>81.7 (88.1-98.7)</td>
<td>.0808</td>
</tr>
</tbody>
</table>

---

**TABLE 5. Analysis of operations performed**

<table>
<thead>
<tr>
<th></th>
<th>Standard PET (n = 210)</th>
<th>Integrated PET/CT (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinoscopy or mediastinotomy (No., %)</td>
<td>33 (16)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>Mediastinoscopy followed by thoracotomy (No. %)</td>
<td>51 (24)</td>
<td>44 (35)</td>
</tr>
<tr>
<td>Thoracotomy (No. %)</td>
<td>126 (60)</td>
<td>57 (45)</td>
</tr>
</tbody>
</table>

PET, Positron emission tomography; CT, computed tomography. P value for $\chi^2$ test = .029.
Fig. 2. Pooled values of metastatic involvement of CT-based lymph node size categories (error bars represent 95% CIs).
PET for N-staging

Langen et al, Eur J Cardio Thor Surgery 2006

Table 2
Predicted positive and negative values of FDG-PET in patients with enlarged lymph nodes of different size categories, assuming FDG-PET sensitivity of 91% and specificity of 78% for enlarged nodes [4]

<table>
<thead>
<tr>
<th>Lymph node size category</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT 10–15 mm</td>
<td>95</td>
<td>62</td>
</tr>
<tr>
<td>CT 16–20 mm</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>CT &gt;20 mm, with outlier</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>CT &gt;20 mm, without outlier</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

NPV: negative predictive value; PPV: positive predictive value.
PET for N-staging
Predictors of false negative PET

Al-Sarraf et al. (Eur J of cardiothoracic Surgery, 2008)

Retrospective analysis in patients who underwent direct thoracotomy after a negative mediastinal PET-CT and were found to have occult N2 disease
PET+ if SUV max >2.5
N= 153; occult N2 in 25 (16%) especially ATS 7 and 4R

**Univariate analyse**
- Central tumour  p=0.049
- RUL  p=0.040
- Enlarged LN on CT  p=0.048
- PET N1  p=0.006

Histology, T stage, differentiation, SUV max primary  p=NS

**Multivariate analysis**
- Central T, RUL and PET N1
PET for N- staging

Conclusions

• High NPV of PET-CT in LN staging
  -> omit invasive tests

• BUT “side conditions”
  – adequate FDG-uptake of primary tumour
  – caution with central tumours and hilar N1 disease
  – Large nodes on CT

• Always confirm PET+ nodes histologically
  – PET and EBUS/EUS are complementary
PET or PET-CT

- Negative (N0)
  - Surgical treatment

- Positive (N2-N3)
  - Tissue confirmation
    - a: In central tumors, tumors with low FDG uptake, tumors with LN ≥ 1.6 cm and/or PET N1 disease, invasive staging remains indicated
    - b: Endoscopic techniques are minimally invasive and can be the first choice
    - c: Due to its higher NPV mediastinoscopy remains indicated

  - EBUS/EEUS (FNA)
    - Negative
    - Positive

  - Mediastinoscopy
    - Negative
    - Positive
    - Multimodality treatment
PET for M-Staging

• PET improves conventional staging (CS) ¹
  – detection of lesions missed on CS (5 - 20%)
  – differentiation of lesions equivocal on CS (7 – 19%)
    • caution if lesion < 1 cm!
  – change in overall stage in 27 - 62% (up > down)

• PET impacts on choice of treatment in 25-41% ²

• Never alter treatment based on PET+ only
  – Up to 50% of single lesions are not M+!!! ³

³ Lardinois et al, J Clin Oncol. 23:6846-6853, 2005
PET for M-Staging


Fig. 2. Comparison of overall survival.
PET for M-Staging

pTx N2 M1
PET for M-Staging
Preoperative Staging of Lung Cancer with Combined PET–CT

Barbara Fischer, Ph.D., Ulrik Lassen, Ph.D., Jann Mortensen

1. Reduction number of thoracotomies
   20/91 (22%) \(\Rightarrow\) 38/98 (39%)

2. Reduction number of futile thoracotomies
   21/60 (35%) \(\Rightarrow\) 38/73 (52%)

Table 3. Distribution of Futile Thoracotomies.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PET–CT</th>
<th>Conventional Staging number (percent)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Futile thoracotomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>39 (65)</td>
<td>35 (48)</td>
<td>74 (56)</td>
</tr>
<tr>
<td>Yes†</td>
<td>21 (35)</td>
<td>38 (52)</td>
<td>59 (44)</td>
</tr>
<tr>
<td>Total</td>
<td>60 (100)</td>
<td>73 (100)</td>
<td>133 (100)</td>
</tr>
</tbody>
</table>

Reason that thoracotomy was considered futile

<table>
<thead>
<tr>
<th>Reason</th>
<th>PET–CT</th>
<th>Conventional Staging number (percent)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploratory thoracotomy</td>
<td>5 (24)</td>
<td>4 (11)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Benign lung lesion</td>
<td>0</td>
<td>3 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>3 (14)</td>
<td>0</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Stage IIIB disease</td>
<td>4 (19)</td>
<td>8 (21)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Stage IIIA (N2) disease</td>
<td>5 (24)</td>
<td>6 (16)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Recurrence within 12 mo</td>
<td>3 (14)</td>
<td>13 (34)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Death within 12 mo</td>
<td>1 (5)</td>
<td>4 (11)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Total</td>
<td>21 (100)</td>
<td>38 (100)</td>
<td>59 (100)</td>
</tr>
</tbody>
</table>
Outline

• Diagnosis (characterization of nodules)
• Initial Staging
  ➢ Tumor
  ➢ Nodes
  ➢ Metastasis
• Restaging after neoadjuvant treatment
• PET in radiation treatment planning
Rx

↓ Cellular Proliferation or ↑ Cell Death

↓ Viable Cell Number

↓ Tumor size

Biochemical and Molecular Imaging by PET

Anatomic Imaging, e.g., CT
Stage III-N2 NSCLC

- Important prognostic factors
  - Tumour clearance of mediastinal LNs (so-called LN downstaging)
  - Pathologic response of primary tumour
- These factors can only be assessed post-surgery

III-A-N2 induction treatment
CT PET re-med EUS

CT surgery

PET good

EUS bad

PET non-radical
PET after IC Residual N2 disease

Corneline Hoekstra et al, Journal of Clinical Oncology 2005

Inclusions N = 79
- First PET scan (n = 79)

Exclusions
- Confirmed upstaging (n = 12)
- Technical/logistical problems (n = 9)
- Patient refusal (n = 2)

Second PET scan (n = 56)

Exclusions
- Technical problems (n = 4)
- Stop IC: toxicity (n = 2), PD (n = 1), death cardiac problems (n = 1)
- Patient refusal (n = 1)

Third PET scan (n = 47)

Pathology in 25 patients
- Sensitivity 50%
- Specificity 71%
- PPV 66%
- NPV 67%

PET: $P = 0.035$

Fig 2. Flow chart exclusions. PET, positron emission tomography; IC, induction chemotherapy; PD, progressive disease.
## PET for N-restaging

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Stage</th>
<th>CTRT</th>
<th>Imaging</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vansteenkiste et al.</td>
<td>2001</td>
<td>31</td>
<td>IIIA-N2</td>
<td>0%</td>
<td>PET + CT (visual corr.)</td>
<td>71%</td>
<td>88%</td>
</tr>
<tr>
<td>Akhurst et al.</td>
<td>2002</td>
<td>56</td>
<td>I-III</td>
<td>29%</td>
<td>PET + CT (visual corr.)</td>
<td>67%</td>
<td>61%</td>
</tr>
<tr>
<td>Ryu et al.</td>
<td>2002</td>
<td>26</td>
<td>III</td>
<td>100%</td>
<td>PET + CT (visual corr.)</td>
<td>58%</td>
<td>93%</td>
</tr>
<tr>
<td>Cerfolio et al.</td>
<td>2003</td>
<td>34</td>
<td>IB-IIIA</td>
<td>21%</td>
<td>PET + CT (visual corr.)</td>
<td>50%</td>
<td>99%</td>
</tr>
<tr>
<td>Hellwig et al.</td>
<td>2004</td>
<td>37</td>
<td>III</td>
<td>70%</td>
<td>PET + CT (visual corr.)</td>
<td>50%</td>
<td>88%</td>
</tr>
<tr>
<td>Port et al.</td>
<td>2004</td>
<td>25</td>
<td>I-IIIA</td>
<td>0%</td>
<td>PET + CT (visual corr.)</td>
<td>20%</td>
<td>71%</td>
</tr>
<tr>
<td>Hoekstra et al.</td>
<td>2005</td>
<td>25</td>
<td>IIIA-N2</td>
<td>0%</td>
<td>PET + CT (visual corr.)</td>
<td>50%</td>
<td>71%</td>
</tr>
<tr>
<td>Cerfolio et al.</td>
<td>2006</td>
<td>93</td>
<td>IIIA-N2</td>
<td>100%</td>
<td>Integrated PET-CT</td>
<td>62%</td>
<td>88%</td>
</tr>
<tr>
<td>Pottgen et al.</td>
<td>2006</td>
<td>37</td>
<td>IIIA/B</td>
<td>100%</td>
<td>Integrated PET-CT</td>
<td>73%</td>
<td>89%</td>
</tr>
<tr>
<td>De Leyn et al.</td>
<td>2006</td>
<td>30</td>
<td>IIIA-N2</td>
<td>0%</td>
<td>Integrated PET-CT</td>
<td>77%</td>
<td>92%</td>
</tr>
</tbody>
</table>
Mediastinal downstaging after IC

- De Leyn et al, JCO 2006
  - Prospective study
  - 30 patients stage IIIA-N2 NSCLC
  - Cisplatinum based IC
  - PET-CT after IC prior to surgery
  - Re – mediastinoscopy
  - Lymphadenectomy at surgery
Example PET-CT after IC

PET-N2 → PET-CT N0

PET-N2 = PET-CT N2
Example PET-CT after IC
Prospective Comparative Study of Integrated Positron Emission Tomography-Computed Tomography Scan Compared With Mediastinoscopy in the Assessment of Residual Mediastinal Lymph Node Disease After Induction Chemotherapy for Mediastinoscopy-Proven Stage IIIA-N2 Non–Small-Cell Lung Cancer: A Leuven Lung Cancer Group Study

Paul De Leyn, Sigrid Stroobants, Walter De Wever, Toni Lerut, Willy Coosemans, Georges Decker, Philippe Nafteux, Dirk Van Raemdonck, Luc Mortelmans, Kristiaan Nackaerts, and Johan Vansteenkiste

**Table 2.** Comparison of CT Alone, PET Alone, and PET-CT for Detection of Residual Mediastinal Nodal Disease After Induction Chemotherapy

<table>
<thead>
<tr>
<th>Test</th>
<th>CT Alone (%)</th>
<th>PET Alone (%)</th>
<th>PET-CT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>59</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>Specificity</td>
<td>62</td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>Accuracy</td>
<td>60</td>
<td>70</td>
<td>83</td>
</tr>
<tr>
<td>PPV</td>
<td>66</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>NPV</td>
<td>53</td>
<td>64</td>
<td>75</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; PET, positron emission tomography; PPV, positive predictive value; NPV, negative predictive value.
PET as a surrogate marker of OUTCOME

Hoekstra et al, Journal of Clinical Oncology 2005

- **ΔSUV <35%**
- **ΔSUV >35%**
- **ΔSUV <60%**
- **ΔSUV >60%**

Two-sided log-rank $P = 0.007$

After 1 cycle

After 3 cycle

Surgery / RT

CR/PR/SD

Chemo → Chemo → Chemo
PET and Response after IC

Corneline Hoekstra et al, Journal of Clinical Oncology 2005
PET for Restaging in NSCLC

- Lower accuracy for detection of mediastinal involvement compared to chemonaive patients
  - Use of other modalities
    - eg. PET-CT + EBUS/EUS upfront, re-mediastino after

- Promising results as an early prognostic marker
  - Validation in a multicenter setting
Outline

• Diagnosis (characterization of nodules)
• Initial Staging
  ➢ Tumor
  ➢ Nodes
  ➢ Metastasis
• Restaging after neoadjuvant treatment
• PET in radiation treatment planning
Use of FDG-PET in RTP

• Patient selection
  - Detection of “unknown” M+ in 10-20% of patients

• Follow-up during/after radiotherapy
  - Better discrimination between viable tissue vs necrosis/fibrosis/scar
  - But also uptake in inflammatory tissue!

• Target volume delineation
PET in Radiotherapy planning
Target volume delineation

• New RT techniques are able to accurately conform the dose to PTV
  – Steep dose gradients
    ➔ reduced dose to normal tissue
    allows dose escalation in some patients
  – Accurate delineation of gross tumor volume (GTV) is crucial

• Drawbacks of CT-based GTV
  – High inter-observer variability
  – Relatively low accuracy for nodal staging

Is PET-CT better?
Observer variation in target volume delineation of lung cancer related to radiation oncologist-computer interaction: A ‘Big Brother’ evaluation


The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; Academic Medical Center, Amsterdam, The Netherlands; Dr Bernard Verbeeten Institute, Tilburg, The Netherlands; Arnhem Radiotherapy Institute, Arnhem, The Netherlands; Radboud University Nijmegen, Nijmegen, The Netherlands; Erasmus Medical Center, Rotterdam, The Netherlands

Radiotherapy and Oncology 77 (2005) 182-190

11 RO delineate 22 NSCLC pts

mean GTV 36cm³ - 129 cm³

Difficulties

DD Tumor/atelectasis/inflamm identification of involved LN
PET in Radiotherapy planning
Target volume delineation

⇒ No FDG uptake in atelectasis

Courtesy of Prof Baum, Bad Berka, Germany
PET in Radiotherapy planning
Target volume delineation

Van Baardwijk et al, Cancer treatment reviews, 2006

### Table 3
Impact of PET on target volume in radiation treatment planning

<table>
<thead>
<tr>
<th>Tumour site (author, year of publication)</th>
<th>No. of patients</th>
<th>Conventional imaging based target volume</th>
<th>Influence of PET on target volume</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Vanuytsel 2000(^{111})</td>
<td></td>
<td>PTV(_{CT}) 579 ml</td>
<td>PTV(_{PET}) 402 ml</td>
<td>PTV(_{PET}) was significant smaller than PTV based on CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTV(_{CT}) 444.4 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciernik 2003(^{35})</td>
<td>6</td>
<td>GTV(_{CT}) 36.1 ml</td>
<td>GTV(_{PET}) 27.8 ml</td>
<td>Mean change in PTV of 26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTV(_{CT}) 399.7 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley 2004(^{106})</td>
<td>24</td>
<td>GTV(_{CT}) 111.3 ml</td>
<td>GTV(_{PET}) 99.8 ml</td>
<td>No difference in GTV(<em>{CT}) and GTV(</em>{PET}) in the total group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Wel 2005(^{119})</td>
<td>21</td>
<td>Lymph nodes</td>
<td>GTV(_{CT-PET}) 9.9 ml</td>
<td>Adding PET data decreased GTV in mediastinal nodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GTV(_{CT}) 13.7 ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Alterations in GTV by adding PET data in 25-50% of patients
- Decrease in GTV (atelectasis, PET- enlarged LN);
  sometimes increase in GTV (PET+ non-enlarged LN)
- Reduced inter-observer variability
What are the pitfalls?
Display window setting affects lesion size.
PET in Radiotherapy planning
Target volume delineation

Nestle et al. JNM 2005

TABLE 1
Results of GTV Delineation Following Different Philosophies for Contour Definition: All Patients

<table>
<thead>
<tr>
<th></th>
<th>SUV$_{max}$ (n=25)</th>
<th>GTV$_{vis}$ (n=25)</th>
<th>GTV$_{2.5}$ (n=24)</th>
<th>GTV$_{40}$ (n=25)</th>
<th>GTV$_{bg}$ (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume (mL)</td>
<td>Volume (mL)</td>
<td>Volume (mL)</td>
<td>Volume (mL)</td>
<td>Volume (mL)</td>
</tr>
<tr>
<td></td>
<td>Radius* (cm)</td>
<td>Radius* (cm)</td>
<td>Radius* (cm)</td>
<td>Radius* (cm)</td>
<td>Radius* (cm)</td>
</tr>
<tr>
<td>Mean</td>
<td>17.1</td>
<td>157.7</td>
<td>164.6</td>
<td>53.6</td>
<td>94.7</td>
</tr>
<tr>
<td></td>
<td>3.03</td>
<td>3.05</td>
<td>2.18</td>
<td>2.52</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>17.2</td>
<td>107.8</td>
<td>108.3</td>
<td>41.4</td>
<td>62.2</td>
</tr>
<tr>
<td></td>
<td>2.95</td>
<td>2.96</td>
<td>2.15</td>
<td>2.45</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>38.8</td>
<td>666.2</td>
<td>655.7</td>
<td>168.3</td>
<td>318.0</td>
</tr>
<tr>
<td></td>
<td>5.42</td>
<td>5.39</td>
<td>3.42</td>
<td>4.23</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>1.7</td>
<td>9.3</td>
<td>8.1</td>
<td>5.7</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>1.30</td>
<td>1.24</td>
<td>1.11</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>
PET in Radiotherapy planning
Target volume delineation

• What is the best method?
  – lack of “gold” standard (pathology)
  – comparison with phantom data/CT volumes
  – Best results currently SBR
    Center dependent!!!!!!

• Control of patient set up and organ motion
  – hybrid PET-CT in treatment position
  – respiratory gating
PET in Radiotherapy planning
Target volume delineation
PET in NSCLC

- **T staging**
  - Limited additional value
  - SUV max as prognostic factor?

- **N-staging**
  - Important additional value for INITIAL staging
  - High NPV omit invasive procedures
    - Cave! Central tumors, large LN
  - Always confirm PET+ nodes
  - Restaging and use of RTP still experimental

- **M-staging**
  - Most important additional value
  - Confirm PET + lesions alter treatment