Role of FDG PET and PET/CT Imaging in Indeterminate Pulmonary Nodules and Lung Cancer

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Outline

- PET/CT protocols
- Indeterminate lung nodules
- Lung cancer
  - Staging
  - Monitoring therapy
  - Restaging
  - Mesothelioma
  - Small cell carcinoma
  - Impact on radiation therapy planning
Integrated PET/CT Imaging System

Benefit of the combined technique:
1) Attenuation correction with CT
2) Anatomical localization
Integrated PET/CT Systems: Protocols

- Field of view: base of skull to mid-thigh
  - When clinical relevant
    - Include extremities and/or brain
    - Limited field of view for SPN

- Patient positioning:
  - Arms-up

- Optimal CT protocols:
  - mAs?
  - IV contrast?
  - Breathing pattern?
Optimal CT protocol is still debated

- **CT for attenuation correction:**
  - High quality maps because of high photon flux
  - Low current (10 mAs): satisfactory attenuation maps.

- **CT for anatomical localization:**
  - Reduced mA (~80 mAs) =
    - compromise for limited radiation dose

- **Optimized diagnostic CT:**
  - CT protocol optimized for indication
  - IV contrast: Problems of overcorrection
    - Great vessels

Semin Ultrasound CT MR 2008; Aug 29(4).
Issues regarding Phase of Respiration for CT

- **Diagnostic CT:** Breath-hold at inspiration
- **PET:** Respiratory motion → misregistration in region of diaphragm
  - Curvilinear artifacts along diaphragm
  - Inaccurate localization of lesion in the region of diaphragm (dome of liver versus lung bases) in 2% of patients
- **Recommendation for transmission CT:**
  - Breath-holding at end tidal volume
  - Respiratory gating

Lung Cancer

- Global epidemic
  - estimated 3 million deaths annually associated with tobacco use
- Leading cause of cancer deaths in western world
- 215,020 new cases and 161,840 deaths in the U.S. annually (2008 data)

Histological types:
- Non-small cell: ~80%
  - Squamous cell
  - Adenocarcinoma (including bronchioalveolar
  - Large cell
- Small cell: ~20%

Evaluation of Lung Nodules

- Accounts for ≈ 20% of newly diagnosed lung cancer*
- In the US: 150,000 new SPN/year
  - 30-50% are malignant
- **CXR and CT: not accurate** to differentiate benign from malignant non-calcified pulmonary nodules that are between 1-3 cm in diameter
- **Morphologic stability over 2 years: reliable sign of benignity:**
  - Doubling time of malignant nodules: 30-400 days
  - Doubling in volume results in 26% increase in diameter

Bayesian analysis can be used to stratify risk (based on clinical information and imaging characteristics) and guide management:

- **Probability of cancer < 5%:** monitoring
- **Probability of cancer between 5%-60%:** biopsy
- **Probability of cancer >60%:** resection

PIOPILN Study
Prospective investigation of PET in lung nodules

- 90 patients from 5 centers with indeterminate nodules (CT)
  - Size range: 0.7 to 4 cm
  - All nodules had histology: 67% were malignant

- PIOPLIN and other studies: SUV > 2.5 = visual
  - Sensitivity: 90-100%
  - Specificity: 69-95%
  - False positive: Active granuloma
  - False negative: Bronchioalveolar, mucinous carcinoma, carcinoid
    Hyperglycemia (decreases uptake by up to 50%).

Middle-aged woman with a 1.5 cm lung nodule
What should be done next?

- A. Follow-up
- B. Biopsy
- C. Chemotherapy
- D. Antibiotics
Question

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- A. Biopsy
- B. Reassure the patient that the nodule is benign
- C. Follow-up with CT at 3-6 months interval for 2 years
- D. Follow-up with chest X-ray in 6 months
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Middle-aged woman with an infiltrative lung nodule
What is in the differential diagnosis?

- A. Neuroendocrine tumor
- B. Bronchioalveolar carcinoma
- C. Infection
- D. All of the above
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Middle-aged woman with an infiltrative lung nodule

Biopsy: Bronchioalveolar carcinoma
(Sensitivity FDG PET ~ 50% for bronchioalveolar and carcinoid)

Recurrent lung carcinoid

48 year-old female with a remote history of early stage melanoma presented with a pulmonary mass.
49 year-old male presented for evaluation of known sarcoidosis

Active sarcoidosis: lung, vertebral bodies

45-year-old with an apical SPN and pulmonary fibrosis

Diagnosis:
1) SPN was negative
2) Patchy FDG uptake in pulmonary fibrosis

Meta-Analysis of Accuracy of FDG PET for Evaluation of Pulmonary Nodules

Includes 40 studies (dedicated and gamma-camera based PET) and 1,474 focal pulmonary lesions:

- Maximum joint sensitivity and specificity of ROC curve: 91%
- Practically to decrease F-, FDG PET operates at sensitivity of 96% and specificity 78%

Optimal visual criterion:

- Greater that mediastinal uptake for nodules > 1 cm
- Any uptake worrisome for smaller nodules

Diagnostic Accuracy of FDG PET and CT for the Characterization of Lung Nodule

- 344 patients for which definite diagnosis was obtained
- Prevalence of malignancy: 53%
- Average size: 16 mm

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<thead>
<tr>
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<th>PET</th>
<th>CT</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>91.7%</td>
<td>95.6%</td>
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<tr>
<td>Specificity</td>
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<td>40.6%</td>
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<tr>
<td>ROC</td>
<td>0.93</td>
<td>0.82</td>
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</table>

## Meta-Analysis of Accuracy of Cross-sectional Imaging for Evaluation of Pulmonary Nodules

- **40 studies between Jan 1990 and Dec 2005**

<table>
<thead>
<tr>
<th></th>
<th>Dynamic CT</th>
<th>Dynamic MRI</th>
<th>FDG PET</th>
<th>99mTc-depreotide</th>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>93%</td>
<td>94%</td>
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<tr>
<td><strong>Specificity</strong></td>
<td>76%</td>
<td>79%</td>
<td>82%</td>
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<tr>
<td><strong>PPV</strong></td>
<td>80%</td>
<td>86%</td>
<td>91%</td>
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<tr>
<td><strong>NPV</strong></td>
<td>95%</td>
<td>93%</td>
<td>90%</td>
<td>91%</td>
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<tr>
<td><strong>Odds ratio</strong></td>
<td>39.91</td>
<td>60.59</td>
<td>97.31</td>
<td>84.50</td>
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<tr>
<td><strong>ROC</strong></td>
<td>.93</td>
<td>0.94</td>
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</table>

How about small nodules?

66 year-old female referred for evaluation of a 8 mm SPN
Small Pulmonary nodules

- Early Lung Cancer Action Project (ELCAP) CT screening study:
  - Non-calcified nodules < 5 mm are rarely malignant
  - Annual repeat screening is recommended
- Phantom-study: detection of nodules < 7 mm is unreliable
- Screening CT study on 911 patients
  - 14% had non-calcified nodules > 5 mm
  - 3.6% had non-calcified nodules > 10 mm
  - Follow-up: 11 NSCLC (all stage I), 1 SCLC
  - FDG PET accuracy = 76% (19/25, size range 8-20 mm)
  - FDG sensitivity = 69%, specificity = 91%, PPV = 90%, NPV = 71%
    - Nodules > 10 mm: 95%

PET recommended: Probability of cancer low to moderate (5%-60%) and an indeterminate nodule measures at least 8-10 mm.

PET NOT recommended: SPN that has a high probability of malignancy (>60%) or nodule < 8-10 mm
Staging NSCLC

- **T staging**: tumor size
  - T1 < 3 cm
  - T2 > 3 cm
  - T3 > 3 cm with chest wall, pleural, or pericardial extension
  - T4 with invasion of adjacent organs

- **N staging**: nodal metastases
  - N0: no nodes
  - N1: ipsilateral hilar nodes
  - N2: ipsilateral mediastinal or subcarinal nodes
  - N3: contralateral nodes or scalene/supraclavicular nodes

- **M Staging**: distant metastases
  - M0: no distant metastases
  - M1: distant metastases present
Regional Lymph Node Classification for Lung Cancer Staging*

Clifton F. Mountain, MD, FCCP; and Carolyn M. Dresler, MD, FCCP

Recommendations for classifying regional lymph node stations for lung cancer staging have been adopted by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer. (*CHEST 1997; 111:1718-23*)
Staging NSCLC

- **Stage I: no nodes or mets**
  - T1 or T2; N0; M0
  - 40% 5-year survival

- **Stage II: regional nodes**
  - T1 N1 or T2 N1; M0
  - 20% 5-year survival

- **Stage IIIa: extrapulmonary extension**
  - T3 N0 or N1; T1-3 N2
  - 15% 5-year survival

- **Stage IIIb: more extensive mediastinal involvement**
  - T4 any N; any T N3, malignant pleural effusion
  - 5% 5-year survival; 40% 1-year survival
FDG PET for Staging

◊ **T staging:**
  - CT and MRI: best to demonstrate the extension of the tumor, relationship to adjacent organs & vessels.
  - FDG PET: limited for T staging due to poor anatomic resolution, lack of anatomical landmark.

◊ **N staging:**
  - CT and MRI: limited by size criteria.
  - FDG PET: best to detect tumor in normal size lymph nodes.

◊ **M Staging:**
  - FDG PET: detect metastases > ~7 mm when CT and MRI are normal or equivocal.
  - Whole body technique: unsuspected metastases.
Staging NSCLC: N-staging critical

- Early stage NSCLC including ipsilateral nodal involvement:
  - Surgical resection is the treatment of choice
- Accurate staging is essential for management.
- Study of 235 patients: If CT negative:
  - ~20% have positive mediastinoscopy
- Invasive diagnostic methods remain necessary

Staging NSCLC: Invasive Methods

- Accurate assessment of malignancy has traditionally required invasive diagnostic methods
  - **Needle biopsy**
    - 10% sampling error; 15% pneumothorax
  - **Bronchoscopy**
    - low sensitivity; occasional pneumothorax
  - **Mediastinoscopy**
    - Surgical procedure; limited to anterior mediastinum
    - Study of 859 patients: If mediastinoscopy negative:
      - ~15% have N2 disease at thoracotomy
  - **Thoracotomy**
    - open surgery; 1-3% mortality

N-Staging NSCLC: FDG PET

Meta-analysis for FDG PET and CT:
Includes 14 studies (514 patients) for FDG PET and 29 studies (2,226 patients) for CT:
- Sensitivity of FDG PET = 79%, CT = 60%
- Specificity of FDG PET = 91%, CT = 77%

Prospective study of 102 patients:
- Sensitivity of FDG PET = 91%, CT = 75%
- Specificity of FDG PET = 86%, CT = 77%
- FDG PET detected distant metastases in 10% patients
- FDG PET changed the stage in 60% patients

Cost effectiveness of FDG PET has been demonstrated*

Dwamena BA et al. Radiology 1999;213:530-536
ACCP Evidenced-Based Practice Guidelines
FDG PET compared to CT for mediastinal Staging

Stage IA being treated with curative intend
Stage IB-IIIB treated with curative intend
If PET is abnormal, biopsy is recommended

66 year-old with right hilar mass

Primary lung ca with atelectasis

AP window LN
66 year-old with right hilar mass
Common metastases to adrenals, skeleton, liver, brain.

FDG PET is superior to conventional imaging:
- Detect unsuspected distant metastases: ~13% of patients
  - Stage I: 7.5%
  - Stage II: 18%
  - Stage III: 24%
- Change management: 18% of these

Staging NSCLC: FDG PET

Stage IV: Indeterminate Adrenal Masses

- Patients with malignancy: ~30% are malignant.
- Patients without known malignancy: rarely malignant.
- Contrast-CT with delayed washout images and MRI with T2-weighted images: accurate but requires additional imaging
- FDG PET: high accuracy
  - Study of 27 patients with NSCLC:
    - Sensitivity = 100%, specificity = 80%

63-year-old male with newly diagnosed lung cancer and mediastinal metastasis.

Left adrenal metastasis

Left vocal cord paralysis

Urine diversion in ileal loop

From Delbeke D. Diagnostic Imaging 2003
Staging NSCLC: FDG PET
Stage IV: Detection of Skeletal Metastases

- 110 patients comparing bone scintigraphy and FDG PET
- 43 patients with metastases, 21 of which with bone metastases proven with other imaging studies or biopsy

<table>
<thead>
<tr>
<th>Modality</th>
<th>PPV</th>
<th>NPV</th>
<th>Acc</th>
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<tbody>
<tr>
<td>BS</td>
<td>90%</td>
<td>61%</td>
<td>66%</td>
</tr>
<tr>
<td>FDG PET</td>
<td>90%</td>
<td>98%</td>
<td>96%</td>
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</table>

- Specificity PET (95%) > BS (61%)
- FDG PET better for lytic metastases
- Bone scintigraphy better for blastic metastases

50 year-old female with lung cancer

- Pleural metastasis
- Rib metastasis
- Sacral metastasis
Cerebral cortex uses only glucose as substrate → high background uptake in cortex

Metastases can hyper-, iso- or hypometabolic compared to cortex: ~ 60% are easily detectable on FDG PET images

MRI is the standard of care for evaluation of brain metastases

Study of 1,026 oncology patients:
Abnormal findings: 3.9 %
Unsuspected metastases: 0.4%

Staging Lung Cancer: PET/CT versus PET or CT

- Prospective analysis of 49 consecutive patients with NSCLC
- Conventional staging vs PET + CT vs integrated PET-CT
- Surgery in 40/49 (82%)

Integrated PET-CT provided additional info in 20/49 (41%)

- Location of LN’s in 9 patients
- Accurate determination of chest wall infiltration in 3
- Accurate determination of mediastinal invasion in 3
- Differentiation of tumor vs atelectasis/inflammation in 7
- Location of distant metastases in 2

FDG PET in The Preoperative Assessment of NSCLC: The PLUS Multicenter Randomized Trial

- 188 patients from 9 hospitals were randomized to
  - Conventional work-up (CWU)
  - CWU + PET
- End point: futile (unnecessary) thoracotomy
- Results
  - CWU: 41% futile thoracotomy
  - CWU + PET: 21% futile thoracotomy
  - Decrease of unnecessary surgery by 50%
  - Decrease cost of healthcare!

Detection of Unknown Primary

FDG PET

In a study of 44 patients presenting with cervical metastasis FDG PET detected the primary tumor in 34% (15/44) of patients, 7 (47%) of which were in the lung.

Carcinoma of unknown primary metastatic to the liver

NSCLC mistaken for esophagus on CT

Mesothelioma: FDG PET

- FDG-avid
- Change in clinical stage (15 patients)
  - Upstage: 13%
  - Downstage: 27%
  - Change in management: 20%
- Study of 29 patient
  - Major impact on M-staging
- Prognosis
  - SUV > 4: 3 times higher risk of death

Small Cell Lung Carcinoma

- Neuroendocrine aggressive tumor
- VA Lung Cancer Study Group: Two stage classification:
  - Limited: tumor confined to unilateral chest
    - Treatment: Chemoradiation
  - Extensive: Contralateral or distant disease
    - Treatment: Chemotherapy alone
- Change of management due to FDG PET: 8-29%

70 year-old male referred for initial staging of SCLC
Impact of PET/CT on Radiation Therapy

- 39 patients with various solid tumors
- Comparison Gross Target Volume (GTV) delineated on CT, then with PET overlay
- PET changed GTV in 56% of patients
  - GTV increased by 25% or more because of PET
  - GTV was reduced by 25% or more because of PET
- GTV variability between 2 independent oncologists decreased from a mean volume difference of 25 cm³ to 9 cm³.
- PET/CT change treatment from curative to palliative because of distant metastases in 16% of patients

PTV Changes for Lung Radiation Therapy

PET overlay over CT:
1) Decreased ROI over atelectasis mistaken for tumor on CT
2) Increased ROI over metastatic mediastinal LN missed on CT

Courtesy of Dr Caggiano, Holy Name Hospital
FDG PET for Lung Carcinoma: Conclusions

Indeterminate Pulmonary Nodule:
- High NPV: FDG- → monitoring
- F+ granulomatous disease: FDG+ → biopsy
- False – bronchioalveolar and mucinous adenocarcinoma, carcinoid, small lesions

Staging NSCLC:
- Stage I, II and III: Mediastinoscopy recommended when FDG PET is positive
  - FDG help guide mediastinal biopsy
  - FDG help select other invasive procedures
- Detection of unsuspected distant metastases: ~ 15%
- Impact on therapy: ~40%
FDG PET for Lung Carcinoma: Conclusions

- Monitoring therapy
  - Early prediction of response
  - Late after completion: Good predictor of prognosis

- Planning radiation therapy

- Potential new tracers:
  - Hypoxia: $^{18}$F-MISO, Cu-ATSM
  - Cell proliferation: $^{18}$F-FLT

- Potential role:
  - SCLC
  - Mesothelioma
ACCP Evidenced-Based Clinical Practice Guidelines: Recommendations for FDG PET

- Stage IA being treated with curative intent
- Stage IB-IIIB treated with curative intent
- If PET is abnormal, biopsy is recommended
- Stage IIIA-IIIB: routine imaging for extrathoracic disease with most appropriate study (see below)

- Patients with abnormal clinical evaluation: Site specific symptoms warrant evaluation with most appropriate study.
  - Head CT/MRI
  - Whole body PET
  - Bone scintigraphy
  - Abdominal CT

Breast cancer
Colorectal cancer
Lung cancer
Lymphoma


www.nccn.org
PET/CT in NCCN Practice Guidelines
Summary of Recommendations: NSCLC

**Recommended:**
- Diagnosis of in patients with one or two pulmonary nodules
- Initial staging except if multiple distant metastases
- Restaging stage III and IV after 2 to 3 months after treatment or before surgery
- Restaging in patients with symptoms suggestive of recurrence
- Radiation therapy
Thank YOU!