High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

National Cancer Center Hospital
Diagnostic Radiology Division
Ukihide Tateishi, MD., PhD.
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

**Definition: Solitary Pulmonary Nodule**

- A well-circumscribed round or oval lesion
- < 3 cm in diameter
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• A well-circumscribed round or oval lesion
  < 3 cm in diameter

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High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

CT characteristics

• Size
• Growth
• Density
• Margins
• Enhancement
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Size

- Only 3-6% of lesions >3cm are benign
- Likelihood ratio of malignancy for SPN>3cm=5.2
- NO lower size limit for malignancy

ELCAP study (LANCET 1999)- 12/19 (63%) cancers<11mm
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Growth

• Absence of growth over a 2-year period = benign
• Doubling time (25% increase in diameter)
  • < 30 days and > 465 days = benign
  • Between 30-465 days = intermediate
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Volumetric assessment of growth

- 1 mm helical acquisition
- Computer-aided segmentation & volumetry
- Accuracy within 3% (in vitro)
- Estimated doubling time (in vivo)
  - malignant SPNs < 177 days vs benign SPNs > 396 days

Yankelevitz et al. Radiology 217:251,2000

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Density

• The cutoff point for benign nodules = 264 Hounsfield units
• Only one of 66 nodules is malignant (n = 384)

High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Margins

<table>
<thead>
<tr>
<th>Margin</th>
<th>Likelihood ratio for malignancy</th>
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</thead>
<tbody>
<tr>
<td>Smooth</td>
<td>0.30</td>
</tr>
<tr>
<td>Lobulated</td>
<td>0.74</td>
</tr>
<tr>
<td>Spiculated</td>
<td>5.54</td>
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</tbody>
</table>
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Margins

• Spiculation or ‘corona radiata sign’
• Fine linear strands extending outward from the nodule
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Enhancement

• Dynamic contrast-enhanced incremental CT
• Calculation of enhancement value

  Maximum attenuation value minus baseline

• > 20 HU = malignant (Sensitivity=95-100 %)

High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Enhancement

- Pre- and postcontrast thin-section CT
- Can be performed as part of routine chest CT
- Calculation of enhancement value

\[ \text{Maximum attenuation value minus baseline} \]

- \(< 15 \text{ HU} = \text{benign (Sensitivity=98 \%)} \]

High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

CT nodule enhancement: Pitfalls

- Applicable for only “solid” SPNs: false-negative
- Inflammatory lesions: false-positive
- Awaiting further validation
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**Cavitation**

<table>
<thead>
<tr>
<th>Maximum wall thickness</th>
<th>Incidence of malignancy</th>
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</thead>
<tbody>
<tr>
<td>&lt; 5 mm</td>
<td>5%</td>
</tr>
<tr>
<td>5-15 mm</td>
<td>73%</td>
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<tr>
<td>&gt; 15 mm</td>
<td>84%</td>
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Adenocarcinoma
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Air bronchogram & Bubble-like lucencies
- Highly suggestive of malignancy
- Seen in 25-30% of malignant vs. 10% of benign SPNs
- Bronchioloalveolar carcinoma (BAC)
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#### Probability of malignancy in SPNs

*Retrospective cohort study*

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<tr>
<th>Feature</th>
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<td>Spiculation</td>
<td>2.8</td>
<td>1.5-5.4</td>
<td>0.002</td>
<td>3.2</td>
<td>1.3-7.8</td>
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<td>Diameter</td>
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<td>1.1-1.2</td>
<td>&lt;0.001</td>
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*Swensen SJ et al. Arch Intern Med 157;849:1997*
58 y.o. male, silicotic nodule

53 y.o. female, Ad (invasive)

NCCH, Diagnostic Radiology Div.
Detection of malignancy in SPNs

meta-analysis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>HRCT</td>
<td>51-93%</td>
<td>47-90%</td>
</tr>
<tr>
<td>Contrast-enhanced CT</td>
<td>95-100%</td>
<td>70-93%</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>97%</td>
<td>78%</td>
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False-negative findings for primary lung tumors on FDG-PET

• A retrospective description of 3,912 patients underwent FDG-PET
• 20 cases with false negative primary lung tumors
  Adenocarcinoma 65%, Squamous cell carcinoma 10%
• Eighteen (90%) patients underwent curative resection
• No patient is known to have recurrent tumor
  Cheran SK et al. AJR 182:1129, 2004

False-negatives=“early-stage disease”, “non-invasive tumors”
Minimal invasive adenocarcinoma

High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Possible false negatives on FDG-PET

Advanced solid lung cancer
  • Well- to Moderately-differentiated adenocarcinoma (indolent)

Non solid lung cancer
  • Well-differentiated adenocarcinoma
  • BAC (type A+B: non-invasive subtype)
  • Goblet cell-type adenocarcinoma
  • Squamous cell ca. in situ (Sq-CIS)

Precancerous lesion
  • AAH
  • Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIP-NECH)
  • Squamous cell dysplasia (SD)
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Small Adenocarcinoma of the Lung: Non-invasive vs. Invasive tumors on HRCT

Objectives

To clarify whether we can correctly differentiate invasive tumors from “non-invasive or in situ tumors”
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Small Adenocarcinoma of the Lung: Non-invasive vs. Invasive tumors on HRCT

Subjects

• Small peripheral adenocarcinoma ≤20mm
• Based on pathologic diagnosis by resected specimens
• A derivation of retrospective cohort (n=178)
• A validation of prospective cohort (n=104)
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## Univariate analysis of potential predictors of invasive tumors: Derivation set (n=178)

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<tr>
<th>Variable</th>
<th>OR</th>
<th>95%CI</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>1.84</td>
<td>1.01-3.34</td>
<td>0.05</td>
</tr>
<tr>
<td>Cavitation</td>
<td>6.03</td>
<td>0.88-41.1</td>
<td>0.08</td>
</tr>
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<td>Air bronchogram</td>
<td>20.2</td>
<td>8.32-48.9</td>
<td>&lt;0.0001</td>
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<tr>
<td>Smooth margin</td>
<td>0.23</td>
<td>0.09-0.59</td>
<td>0.002</td>
</tr>
<tr>
<td>Spiculation</td>
<td>18.4</td>
<td>8.00-42.5</td>
<td>&lt;0.0001</td>
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<td>Lobulation</td>
<td>3.53</td>
<td>0.41-30.2</td>
<td>0.25</td>
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<tr>
<td>Indentation</td>
<td>10.4</td>
<td>5.41-20.0</td>
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</tr>
<tr>
<td>GGA 100%</td>
<td>0.006</td>
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<td>GGA&gt;75%</td>
<td>0.025</td>
<td>0.012-0.053</td>
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<td>Bubble-like lucencies</td>
<td>1.15</td>
<td>0.07-18.6</td>
<td>0.92</td>
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<tr>
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Multivariate analysis of significant predictors of invasive tumors: Derivation set (n=178)

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<td>4.61</td>
<td>1.58-13.4</td>
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<td>0.02-0.83</td>
<td>0.07</td>
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<tr>
<td>Spiculation</td>
<td>37.8</td>
<td>13.0-109.7</td>
<td>&lt;0.0001</td>
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<td>Lobulation</td>
<td>NA</td>
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<td>GGA&gt;75%</td>
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<tr>
<td>Spiculation</td>
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<td>4.45-104.7</td>
<td>&lt;0.001</td>
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<tr>
<td>GGA&gt;75%</td>
<td>0.04</td>
<td>0.008-0.201</td>
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**Results 1**

- No significant predictors of invasive tumors are found both in derivation and validation analysis (n=282).

- Air bronchogram, indentation, and spiculation remain to be potential predictors because of reproducibility.
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Results 2

• The GGA content (100%~75%) is strong predictor of non-invasive tumor.

• The $A_z$ value of ROC analysis $=0.906\pm0.019$. 
## Small Adenocarcinoma of the Lung: Non-invasive vs. Invasive tumors on HRCT

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<th>Specificity</th>
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<th>NPV</th>
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<tr>
<td>0-24%</td>
<td>0.398</td>
<td>0.937</td>
<td>0.846</td>
<td>0.640</td>
<td>9.79</td>
</tr>
<tr>
<td>25-49%</td>
<td>0.650</td>
<td>0.905</td>
<td>0.857</td>
<td>0.748</td>
<td>17.79</td>
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<tr>
<td>50-74%</td>
<td>0.711</td>
<td>0.905</td>
<td>0.868</td>
<td>0.782</td>
<td>23.49</td>
</tr>
<tr>
<td>75-99%</td>
<td>0.807</td>
<td>0.905</td>
<td>0.882</td>
<td>0.843</td>
<td>40.01</td>
</tr>
<tr>
<td>100%</td>
<td>0.988</td>
<td>0.674</td>
<td>0.726</td>
<td>0.985</td>
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Histologic typing of small adenocarcinoma (<2cm)

Non-invasive tumors
• Type A  Localized Bronchioloalveolar cell carcinoma (LBAC)
• Type B  LBAC with alveolar collapse

Invasive tumors
• Type C  LBAC with active fibroblasts
• Type D  Poorly differentiated adenocarcinoma
• Type E  Tubular adenocarcinoma
• Type F  Papillary adenocarcinoma

Noguchi M, et al. CANCER 75:2844;1995
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<th>5-year survival</th>
<th>Nodal stage (n=0)</th>
<th>Stage I</th>
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<td>Type A</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Type B</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Type C</td>
<td>75%</td>
<td>72%</td>
<td>68%</td>
</tr>
<tr>
<td>Type D</td>
<td>52%</td>
<td>52%</td>
<td>48%</td>
</tr>
</tbody>
</table>

*Noguchi M, et al. CANCER 75:2844;1995*
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Histologic typing of small adenocarcinoma (<2cm)

<table>
<thead>
<tr>
<th>Type</th>
<th>5-year survival</th>
<th>Nodal stage (n=0)</th>
<th>Stage I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>100%</td>
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High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Histologic typing and HRCT Correlation

Type A lung adenocarcinoma: n=67

• Non-invasive
• Well-defined nodule
• Homogeneous (95%) vs. Heterogeneous (5%)
• 100% GGA, GGA+hyperattenuation
• Often multiple nodules
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Histologic typing and HRCT Correlation

Type B lung adenocarcinoma: n=55

- Non-invasive
- Well-defined nodule
- Heterogeneous (80%)
- 75-100%GGA+hyperattenuation
- Associated with ‘indentation’
or ‘air bronchogram’
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Histologic typing and HRCT Correlation

Type C  lung adenocarcinoma: n=173

• Invasive
• Ill-defined nodule
• Most frequent subtype
• Heterogeneous (100%)
• Solid nodule+GGA components
• Associated with ‘indentation’ or ‘air bronchogram’
• Similar to “Adenocarcinoma with BAC features”

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High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Histologic typing and HRCT Correlation

Type D,E,F lung adenocarcinoma: n=15

• Ill-defined nodule
• Rare subtype
• Solid nodule
• GGA0%
• Associated with ‘indentation’ or ‘air bronchogram’
• DDx: metastatic lung tumor

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Clinical implications of GGA component content

GGA Component Content
\[ \frac{D_{GGA} - D}{D_{GGA}} \times 100\% \]

1: Lymph node metastasis
2: Vascular invasion
3: Prognosis

53 y.o. female, Ad (type C)


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High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

GGA detection: Pitfalls
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Conventional Strategy

Intermediate SPN

Baseline HRCT
- Size
- Margin

Probability of malignancy

FDG-PET/CT

History
- Smoking
- Age
- Hemoptyisis

Surgical risk

Comorbidities

FDG-PET/CT positive
- VATS

FDG-PET/CT negative
- Careful observation
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

New Strategy

Intermediate SPN

Baseline HRCT
• Size
• Margin
• GGA%
  “detect non-invasive tumors”

Probability of malignancy

FDG-PET/CT

positive

VATS

down arrow

Surgical risk Comorbidities

History
• Smoking
• Age
• Hemoptysis

down arrow

down arrow

NCCH, Diagnostic Radiology Div.
High Resolution CT Diagnosis of the Solitary Pulmonary Nodule

Conclusions

• HRCT plays an important role in identifying SPN
• HRCT findings are nonspecific for detecting malignant SPNs
• The GGA content is strong predictor of non-invasive small peripheral adenocarcinoma of the lung
• HRCT can exclude non-invasive tumors in clinical setting and will reduce false negatives on FDG-PET
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