Gordon Gamsu Memorial Lecture Pulmonary Nodule Characterization

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Learning Objectives

- To increase knowledge of
  - the significance and imaging findings of subsolid nodules (SSNs)
  - the role of noninvasive imaging techniques for nodule evaluation
  - Fleischner Society and ACCP guidelines for the management of nodules (solid and subsolid)

Selected Topics:
Pulmonary Nodule Characterization

- CT protocol
  - Characterization:
    - Attenuation (focusing on subsolid)
    - Morphology
    - Growth
  - Management of nodules

CT Protocol: Nodule Evaluation

- Attention to radiation dose:
  - Ref 40-80 mAs for nodule suspected or follow up
  - Tube current modulation: optimize tube current, maintain image quality
- Typically noncontrast
- Contiguous thin (1 mm) sections (nodule detection and characterization, particularly for ground-glass nodules)

Selected Topics:
Pulmonary Nodule

- CT protocol
  - Characterization:
    - Attenuation (subsolid)
    - Morphology
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Transient Subsolid Nodules

- 38-70% of SSN nodules
- Lee et al: 69.8% SSNs (screening CT)
- Oh et al: 37.6% GGN, 48.7% PSN, (majority screening, some nonscreening)
- Some investigations: Large solid portions and large size assoc. with transient nodules

Subsolid Nodules on Screening CT

- 44/233 (19%) pts with nodules
- Malignancy rate: subsolid > solid (p = 0.004)

<table>
<thead>
<tr>
<th>Type</th>
<th>Malignancy Rate</th>
</tr>
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<tbody>
<tr>
<td>Subsolid</td>
<td>34%</td>
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<tr>
<td>Part-solid</td>
<td>63%</td>
</tr>
<tr>
<td>Pure GG</td>
<td>18%</td>
</tr>
<tr>
<td>Solid</td>
<td>7%</td>
</tr>
</tbody>
</table>

AdCa Classification IASLC/ATS/ERS

- AdCa in situ (formerly Bronchoalveolar AdCa):
  - ≤ 3 cm purely lepidic tumor

- Minimally invasive AdCa:
  - (lepidic predominant tumor, invasive focus ≤ 5mm, overall size ≤ 3 cm)

- Invasive adenocarcinoma
  - Including Lepidic predominant AdCa

Atypical Adenomatous Hyperplasia (AAH)

- Lung cancer resection specimens (Kras, EGFR mutations)
- Mildly/ mod. atypical type II pneumocytes and/or Clara cells along alveolar walls, occ. resp. bronchioles
- Rounded, cuboidal, low columnar, or “peg” cells
- Round to oval nuclei
- Intranuclear inclusions, gaps among cells
- Usually < 0.5 cm
- Continuum with Ad in situ

AAH: Imaging

- Round
- Up to 10 mm
- Pure ground glass (faint)
- Difficult to differentiate AAH from Adenocarcinoma in situ by imaging

Adenocarcinoma in situ

- Formerly known as bronchioloalveolar (bronchoalveolar) cancer
- Pathology
  - Purely lepidic growth of type II pneumocytes and Clara cells
  - No stromal, vascular or pleural invasion
  - Nonmucinous >> rarely mucinous
  - ≤ 3 cm size
- 100% 5-yr survival

Malignancy rate: subsolid > solid (p = 0.004)
Adenocarcinoma *in situ*: CT
- Nonmucinous
  - Typically: pure ground glass nodule
  - Less commonly part solid or solid
  - Bubble like lucencies occasionally
- Mucinous: solid

Minimally Invasive AdenoCa (MIA)
- Pathology
  - Predominantly lepidic
  - Invasive focus \( \leq \) 5mm
  - \( \leq \) 3 cm overall size
- CT
  - Nonmucinous: variable
    - (Part solid or pure ground glass nodule)
  - Mucinous: solid or part solid
- Close to 100% 5 yr survival

Lepidic Predominant Adenocarcinoma
- Predominantly lepidic
- At least one focus > 5 mm of invasion in largest dim.
  + myofibroblastic stroma
- Nonmucinous
- Necrosis
- Invasion vessels, lymphatics, pleura
- 90% 5-year survival

Lepidic Predominant Invasive AdCa: CT
- Mixed ground glass and solid attenuation

Other Invasive Adenocarcinomas
- Acinar-predominant
- Papillary-predominant
- Solid-predominant
- Micropapillary-predominant
- Air bronchograms and bubble like lucencies are well-differentiated tumors

Differential Diagnosis: Persistent Pure Ground Glass Nodule
- BAC or AdCa 75% (13+/- 6.9 mm)
- AAH 6 % (8 +/- 3.8 mm)
- Organizing pneumonia or nonspecific fibrosis (focal interstitial fibrosis) 19% (12+/6.7 mm)

**Focal Interstitial Fibrosis**

Park CM et al. Eur Radiol 2007;17:2325

- Focal nonspecific response to injury (including infection, radiation, drugs, trauma)
- Interstitial septal thickening + fibroblast proliferation (preservation of the alveoli)
- Solitary nodular GGO
- 77.8% upper lobe, oval 55.6%, smooth margins 55.6%
- Pleural retraction, vascular convergence 22.2%
- 4.8-22.5 mm

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**Selected Topics: Pulmonary Nodule**

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**GGO Nodules: Morphology**

- Morphology did not discriminate between malignant and benign
  - Polygonal shape
  - Pleural tags
  - Spiculation
  - Lobulation
  - Progression helpful

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**GGOs: Morphology**

Lee et al. Eur Radiol 2009;19:552-6

- 80 GGNs (47 malignant, 33 benign)
- Evaluated: Air-bronchogram, bubble-like lucencies, cavity, fine spiculated margin, lobulated border
- Predictive of malignancy:
  - >8 mm
  - Lobulated border for pure and mixed GGNs

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**Differentiate Preinvasive from Invasive**


- 272 GGNs: 64 pure GGNs, 208 Part solid
- Preinvasive: 21 AAH; 72 AIS
- Ratio = max dimensions solid / entire nodule
- Pure GGNs: Preinvasive lesions:
  - nonlobulated (P<0.05);
  - <10 mm (53.3% sens; 100% spec)
- Part solid: Preinvasive lesions:
  - smaller lesion size and solid proportion, non lobulated, non spiculation differentiators (P<0.05)

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- CT protocol
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- Management of nodules
Growth Rates: Small Lung Cancers
Hasegawa M, Br. J. Radiology 2000;73:1252

- Screening population 1996 -1998
- 61 cancers: VDT 52-1733 days
  Ground glass = 813 days
  Ground glass/ solid= 457 days
  Solid =149 days

Decreasing GGOs
Kakinuma et al. JCAT 2004;28;17

- 8 cases
- 3 types of progression of pure GGOs
  1. Increasing size (BAC n=5)
  2. Decreasing size with appearance of solid component: Rapidly (adenoca mixed subtype n=1) and slowly (BAC n=1)
  3. Increasing density (BAC n=1)

Solid Nodule Growth: Quantitative Evaluation

- Linear measures susceptible to interobserver variation
- Computer-assisted quantitative techniques: late 1990s
- Increasing availability of CT thin sections given PACS archive capabilities
- Primarily directed towards solid nodules:
  ▪ To identify growth indicating malignant nodules
  ▪ To evaluate treatment response of known malignancy

Automated Nodule Volume Assessment

- Investigated mainly for solid nodules
- Volume change > 20 to 30% indicator of growth for some algorithms
  ▪ Used for management in NELSON trial
  ▪ Variability among software packages
- Integration into PACS a major need

Subsolid Nodule Measurement and Growth

- Amorphous shape, irregular margins, mixed attenuation difficult to qualitatively assess and express consistently
- Slow growth

Quantitative Assessment

- Currently, measurement primarily manual
- Tumor disappearance rate (vanishing ratio)
  = (Area on lung window-Area on mediastinal window)/ Area on lung window X 100%
- Size of solid component only?
- Nodule texture?
Subsolid Nodules: Mass


- Nodule mass = [HU + 1000] x nodule volume (ml)
- Physical density (mg/ml)
- Mass can enable early detection of growth in malignant nodules

Selected Topics: Pulmonary Nodule

- CT protocol
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Management of Pulmonary Nodules

- Multidisciplinary team (pulmonary, thoracic surgery, diagnostic and interventional radiology)
- Shared decision making with the patient
- Patient preferences and comorbidities
- Imaging
- Institutional approaches

Further Evaluation > 7 mm Solid Nodule

For low to moderate risk surgical candidates

- Patient preference/ Shared decision making process with patient / Patient comorbidities

   Very Low prob (< 5%)
   FU CT
   3, 6, 12, 24 mo (low dose)

   Low /mod (5-65% pretest prob)
   If - or mild
   PET staging
   Surgery

   High prob >65%
   If mod or intense
   PET Staging
   Biopsy

Likelihood of Malignancy (%)

**Fleischner: Incidental Small Solid Nodules**

<table>
<thead>
<tr>
<th>Size</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
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<tbody>
<tr>
<td>≤ 4 mm</td>
<td>No FU</td>
<td>12 mo. If no Δ, no further FU</td>
</tr>
<tr>
<td>&gt;4-6 mm</td>
<td>12 mo. If no Δ, no further FU</td>
<td>6 - 12 mo. If no Δ, 18-24 mo. FU</td>
</tr>
<tr>
<td>&gt;6-8 mm</td>
<td>6 - 12 mo. If no Δ, 18 - 24 mo. FU</td>
<td>3 - 6 mo. if no Δ, 12 - 24 mo. FU</td>
</tr>
<tr>
<td>&gt;8 mm</td>
<td>CT FU at 3, 9, 24 mo / Dynamic CT / PET scan / Biopsy (One or more)</td>
<td></td>
</tr>
</tbody>
</table>

*No smoking history or other risk factor (family history, asbestos, environmental)*

**Fleischner Criteria (Solid Nodules) Exceptions**

- **Hx of malignancy**
  - FU earlier, more frequent, longer than 2 years (depends on tumor cell type, histological grade, stage)
- **Fever (infection)**
- **Subsolid nodule, air bronchograms:**
  - FU > 2 years (longer intervals)
  - Worrisome morphology (despite small size)

**Fleishner SSNs: Solitary**


- Risk of patients not a variable
- Minimal size criteria
- Multiple nodules addressed
- Nodule morphology not emphasized

**Fleishner SSNs: Recommendation 2**

- Pure GGNs > 5 mm
  - No role for antibiotics
  - PET/CT unlikely to be of value
  - Biopsy in surgical candidates not recommended
    - Lower diagnostic yield for GGO
    - Discordance of biopsy vs. surgical specimen
  - Consistent CT technique: Low dose technique, dose modulation, iterative reconstruction for soft tissues

**Fleishner SSNs: Solitary**

Naidich et al. Radiology Jan 2013

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Additional Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 mm GGN</td>
<td>No FU</td>
</tr>
<tr>
<td></td>
<td>Contiguous 1 mm</td>
</tr>
<tr>
<td></td>
<td>sections</td>
</tr>
<tr>
<td>&gt; 5 mm GGN</td>
<td>3 mo FU, annually if no</td>
</tr>
<tr>
<td></td>
<td>change for minimum 3 years</td>
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</tbody>
</table>

**Fleishner SSNs: Solitary**

Naidich et al. Radiology Jan 2013

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Additional Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part solid</td>
<td>3 mo FU, annual FU if solid</td>
</tr>
<tr>
<td></td>
<td>part &lt;5 mm for minimum of 3 years</td>
</tr>
<tr>
<td></td>
<td>3 years. If ≥ 5 mm solid, biopsy or surgical resection</td>
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</table>
### Fleishner SSNs: Multiple

Naidich et al. Radiology Jan 2013

<table>
<thead>
<tr>
<th>Multiple</th>
<th>Recommendations</th>
<th>Additional Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure GGNs ≤ 5 mm</td>
<td>FU CT at 2 and 4 years</td>
<td>Consider alternate causes for multiple GGNs</td>
</tr>
<tr>
<td>Pure GGNs &gt;5 mm without dominant lesion</td>
<td>3 mo FU, then annually if persistent for minimum 3 yrs</td>
<td>FDG PET limited value Potentially misleading Not recommended</td>
</tr>
<tr>
<td>Dominant nodule with solid or part solid component</td>
<td>3 mo FU. If persistent, bx or surgical resection esp. if &gt; 5 mm solid</td>
<td>Consider lung sparing surgery</td>
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**Summary**

- SSNs are likely to represent adenocarcinoma if persistent
- A high percentage are transient up to 70%
- **Soft tissue** on CT correlates with aggressive features
- Variable growth patterns of subsolid nodules
- PET/CT and biopsy of limited utility
- Fleischner and ACCP guidelines useful aids for nodule management decisions

<table>
<thead>
<tr>
<th>Fleischner</th>
<th>ACCP</th>
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<tr>
<td>Differences</td>
<td></td>
</tr>
<tr>
<td>Addresses solitary and multiple subsolid nodules</td>
<td>Solitary nodules only</td>
</tr>
<tr>
<td>N/A</td>
<td>Pretest probability considered</td>
</tr>
<tr>
<td>Emphasizes degree of solid component (&gt; 5 mm vs. &lt; 5 mm)</td>
<td>Overall size of part solid nodules considered (&gt; 8 mm 3mo, PET, surgery biopsy)</td>
</tr>
<tr>
<td>Similarities</td>
<td></td>
</tr>
<tr>
<td>No follow up for pure GGNs ≤ 5 mm</td>
<td></td>
</tr>
<tr>
<td>Annual F/U for pure GGNs &gt; 5 mm</td>
<td></td>
</tr>
<tr>
<td>Emphasis on low dose CT</td>
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<tr>
<td>No emphasis on nodule morphology</td>
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