Peripheral Lung Lesion: Potential Pulmonary Adenocarcinoma?

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Disclosures

• No relevant disclosures
Goals and Methods

Stratify a peripheral lung lesion into the potential adenocarcinoma spectrum.

Explain predictive values of imaging characteristics (in conjunction with location, growth pattern, background lung disease, patient demographics, etc.).

Via rad-path correlation, illustrate peripheral adenocarcinoma spectrum.

Characterize adenocarcinoma behavior and discuss prognosis.

Briefly outline diagnostic pitfalls along with short differential, practical tips and current challenges in diagnosis and management.

*This review considers current recommendations of the International Association of Lung Cancer (IASLC), American Thoracic Society (ATS), European Respiratory Society (ERS), and American Association of Family Physicians as well as incorporating criteria proposed in the Fleischner Society Recommendations for Solitary and Sub-Solid Nodules.*
PERIPHERAL LUNG LESION

Solid
- Incidence: 62%-81%
- Most common etiology: benign subpleural lymph node.
- Risk of primary malignancy: 
  \( \leq 1\text{cm} \) – 15%
  \( \leq 2\text{ cm} \) – 42%
  > 2 cm – 50-75%

Part-solid
- Incidence: 7%
- Transient (benign): 38-70%
- Most common appearance of lung adenocarcinoma (48-63%)
- Degree of invasion is related to size of solid component.

Groundglass
- Incidence: 12%
- Most are benign (infectious or inflammatory)
- Lung adenocarcinoma: 18-59%
- If adenocarcinoma – non-invasive spectrum, nearly 100% cure with resection

*Peripheral lung adenocarcinoma often presents as a nodule (<3cm), mass (\( \geq 3\text{ cm} \)) or pneumonia-like opacity. Can be multilobar.
Solitary pulmonary nodule (SPN), initial detection on CT

**BENIGN**
- Size ≤4-7 mm
- Age ≤35-40 y.o.
- Central, lamellar, diffuse, or popcorn calcifications
- Presence of macroscopic fat (-40 to -120 HU)
- Polygonal shape or long-to-short axis ≥1.68
- Smooth margins (60% benign)

**WORRISOME**
- Size > 0.8-2 cm
- Age ≥ 45-50 y.o.
- No calcifications or macroscopic fat
- Air-bronchogram (14% benign)
- Corona radiata, coarse spiculations, lobulated margins, or pleural tag*

*Characteristics of nodules commonly representing primary lung adenocarcinoma:*
- Upper > lower lungs in smoker; probably lower > upper lobes in non-smoker (esp. female).
- Higher risk: smoking history within past 15 years; chronic lung disease; exposure to radon, diesel fumes, uranium, or asbestos.
- 43%-50% in ≥ 50 year-old patients. Highest incidence at 60-80 years old. F > M with incidence in females increasing worldwide.
- Corona radiata: PPV approximately 90%.
- 60% subpleural in location (overlap with most frequent benign nodule, a lymph node).

*Lobulated borders*: PPV 80% (41% benign, 50-80% malignant)
*Coarse spiculations*: 34% benign vs. 22% malignant
*Pleural tag*: 27% benign vs. 17%
*Cavitation*: likely benign if wall thickness 1-4 mm
Most common solitary nodule ≤ 1.5 cm: **Perifissural Lymph Node (PFN).** Benign if elongated, polygonal/triangular, well-defined, broad base against fissure

Adapted from: Radiology 2012: 265:611-616

Not PFN: irregular borders, air-bronchogram

Typical PFN

Other Benign Nodules (*courtesy of Dr. J. Kanne, Univ of Wisconsin)

- densely calcified granuloma
- fat-containing Hamartoma *
- ≤1.5 cm, triangular, broad base against the pleura
Smooth borders, homogenous:
Only 40% malignant.
Ddx: granuloma, inflammatory nodule, hamartoma, AVM, carcinoid.

Lobulated borders: suggest uneven growth.
**PPV of adenocarcinoma, 80%.**
Ddx: hamartoma (25%), carcinoid, lymphoma.
N.B. Pleural tag – benign or malignant feature.

Coarse spiculated margins: benign scarring, desmoplastic reaction, interstitial or lymphatic infiltration.
**PPV of adenocarcinoma, 60-85%.**

Corona radiata (fine marginal spicules): neoplastic infiltration or fine fibrosis.
**High PPV of adenocarcinoma, 88-94%.**
Ddx: focal scar/fibrosis, sclerosing hemangioma (rare).

Cumulative risk Increases if combined with one or more:
- ≥45-50 y.o.,
- emphysema,
- tobacco exposure
- lung fibrosis
- upper lobe
- ≥ 2 cm
- lower nodule count
- hemoptysis
- PET positive
Homogeneity and cavitation

Homogenous:
- 55% benign
- 20% malignant

True cavitation:
- Overlap in malignant and benign etiologies.

Pseudocavitation (a.k.a. air-bronchogram):
- Lung adenocarcinoma
- Lymphoma
- Inflammatory/infectious pseudotumor
Solitary pulmonary nodule: follow-up

**Current approach:**

**Fleishner Society Recommendations:**
- No growth for 2 years – benign (B9).

**Diameter, Volume, and Doubling time (DT):**
- **Volume**: based on assessment of sphere $\frac{4}{3}\pi R^3$
- $26\%$ change = 1 doubling. $< 50 \text{ mm}^3$ – B9.
- Lung cancer DT – 1-18 months (median 149 days $= 5$ mo).
- B9 lesion: $< 30 \text{ days} \text{ or } > 465 \text{ days}$.
- **Diameter**: max or perpendicular or both.
  - $\geq 2\text{ mm} \text{ or } 25\%$ size change is significant.

**Contrast Nodule Enhancement**:  
- Dynamic protocol (1-5 min $q$ 1 min, Bayraktaroglu et al.): $< 15\text{HU}$ – B9 in 99%.
- Nodule wash-in and wash-out (Jiang et al.): net enhancement $\geq 20$ – malignant in 79%.

**Assessment with PET/CT and biopsy** (discussed later).

**Current Issues:**

No growth for 2 years – only 65% PPV of benignity.

6% solid adenocarcinomas shrink before subsequent growth.

DT $< 1$ mo: some lymphomas or fast growing metastasis.

Dynamic nodule enhancement, criteria:
- Nodule $> 5\text{mm}$
- Spherical
- Homogenous (no necrosis, fat or calcium)
- No motion or beam hardening artifact.
Assessment of Nodule Volume

- Analysis of nodule volume enhances ability to correctly predict malignancy in 88% of subjects compared to Swensen model utilizing linear diameter alone (Mehta et al., 2014)
  - 94.6% sensitivity 98.3% specificity for malignancy with nodules > 500 mm³ demonstrating volume doubling time < 400 days or new solid component (van Klavern et al., 2009)

*Interscan measurement variability can be reduced through the use of commercially available post processing software which semi-automates maximum diameter and volumetric calculation.

*Images courtesy of Dr. Jane Ko, MD, NYU Langone Medical Center
Nodule Enhancement

✓ Malignant nodules demonstrate significantly greater enhancement than benign lesions.

✓ Enhancement of > 15 HU 98% sensitive (58% specific) in determination of malignancy (Swensen et al., 2000).

✓ Bayraktaroglu et al. (2008) confirmed lung nodule enhancement ≤ 15 HU strongly indicative of benignity and demonstrated statistical significance in peak attenuation differences between benign and malignant lesions following contrast administration (54 ± 23.10 HU in benign vs. 82.44 ± 19.56 HU in malignant)

*Images courtesy of Dr. Jane Ko, MD, NYU Langone Medical Center
Part-solid pulmonary nodule (PSN), initial encounter on CT

Solid and ground-glass components, in various proportions.

Most common presentation of lung adenocarcinoma, 48-63%.

- Henschke et al.: 63% PSN malignant vs 7% solid nodules.
- Smaller overall size, smaller solid part, non-lobulated and non-spiculated borders – significant predictors of low grade lesion (Lee et al. Radiology 2013).

In addition to lung adenocarcinoma, DDX:

(* denotes most common)
- Extrathoracic malignancy (GI, melanoma, RCC)
- Lymphoproliferative disease
- Organizing pneumonia*
- Atypical infection*
- Focal lung fibrosis*
- Endometriosis
Management of incidental part-solid nodule(s)

- Most common appearance of adenocarcinoma in young non-smoker.
- Clinical scenario is important for pre-test probability (acute infection, immune status etc.).
- Growth of solid component needs to be carefully scrutinized.

<table>
<thead>
<tr>
<th>Solitary</th>
<th>Multiple</th>
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<tbody>
<tr>
<td>Initial 3-mo CT follow-up</td>
<td>Initial 3-mo CT to F/U dominant nodule(s)</td>
</tr>
<tr>
<td>Further annual follow-up ≥ 3 years</td>
<td>Further annual follow-up ≥ 3 years</td>
</tr>
<tr>
<td>If persistent or growing solid component ≥5 mm or overall increasing density, biopsy or resection should be considered.</td>
<td>Tissue diagnosis if non-resolving or growing solid component ≥ 5 mm or overall increasing density.</td>
</tr>
<tr>
<td>PET/CT is an option for ≥10 mm lesions but can be inconclusive.</td>
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Follow-up part-solid lesion

**CT:** low dose, contiguous, best with 1 mm slices.

**Lesion size:** total - on lung windows, solid part - on soft tissue windows.

**Malignancy or progression:**
*Increasing density and/or growing solid part*

CTR (consolidation/tumor ratio) – solid part/max size (including GG part) ratio (Suzuki et al. 2011) useful in indentifying adenocarcinoma in situ
- Noninvasive adenoca: ≤2 cm with CTR ≤0.25.

Adenocarcinoma, volume doubling time (solid nodule, Song et al. *Radiology* 2014):
- <5 mm → 934.7–4617.7 days
- > 5 mm → 376.4–941.5 days.

**Favorable features** (well-differentiated tumor and/or slow growth) in stage Ia:
- Cystic or bubble-like lucencies
- Intra-tumoral air-bronchogram
- Extensive GG component
- Lack of pleural retraction

FDG-18 PET/CT can be inconclusive but increasing SUV correlates with invasion.
**Incidence:** 12% vs. 81% solid or 7% part-solid lesions.

**Malignant:** 18-59% vs. 48-63% part-solid.

**DDx:**

**Transient:** inflammatory focus, focal hemorrhage, residual edema.

**Persistent:** focal fibrosis, developing adenocarcinoma spectrum.

**Additional DDx for lesion ≤ 1 cm:**

**atypical adenomatous hyperplasia (AAH)**
- Focal cell proliferation with mild-to-moderate atypia of type II pneumocytes and/or Clara cells.
- No invasive or metastatic potential.
Ground-glass lesion, follow-up

Doubling time for adenocarcinoma: 813 ± 375 days (Hasegawa et al. Br J Radiol 2000). If presented with fast growing GG lesion, consider other etiologies.

Contiguous scan, best with 1 mm slices and multiplanar reconstructions.

Fine needle biopsy: low diagnostic yield, 35% for < 1cm and 50% for over 1 cm. If lesion ≥3 cm and persists or transforms into part-solid lesion- surgical approach should be considered.

Takashi et al (Jpn J Radiol 2012): predictors of growth
- Size > 10 mm
- Lobulated borders
- Bubble-like appearance
(Also: female gender, younger age, never smoker)

Adapted from D.P.Naidich et al. Radiology 2013; 266

<table>
<thead>
<tr>
<th>Solitary pure ground-glass nodule</th>
<th>Multiple pure ground-glass nodules</th>
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</thead>
<tbody>
<tr>
<td>≤ 5 mm → no CT follow-up.</td>
<td>≤ 5 mm → F/U at 2 and 4 years.</td>
</tr>
<tr>
<td>&gt; 5 mm → initial CT at 3 mo; if persists – annual CT ≥ 3 years.</td>
<td>&gt;5 mm → initial CT at 3 mo; if persists – annual CT ≥ 3 years.</td>
</tr>
<tr>
<td></td>
<td>If dominant lesion – consider lung-sparing surgery for diagnosis.</td>
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PET-CT: limited role, could be misleading and therefore not recommended.
Ground-glass lesion, follow-up

- Scrutinize for developing solid part (17% of lesions), increasing density, or subtle growth.
- Monitoring for >3 years may be warranted.
- No clear role of PET/CT for groundglass lesion but upgrades the lesion to more worrisome if positive and potentially has prognostic implication for further lesion progression (as in the case here).

70 y.o. female never smoker with incidental LUL GG lesion that has doubled in size in 5 years. Lack of solid component in 2010 with positive FDG-18 PET/CT.
3 years later: irregular solid component (> 5 mm), increasing density and further growth.
Pathology confirmed invasive adenocarcinoma.
## Spectrum of pulmonary adenocarcinoma

<table>
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<tr>
<th>Histologic form</th>
<th>Pathologic Findings</th>
<th>CT findings</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Adenocarcinoma in situ (AIS)</td>
<td>( \leq 3 ) cm, pure lepidic growth w/o stromal/vascul/pleural invasion, only rarely mucinous.</td>
<td>Usually GG, occasionally bubble-like or part-solid.</td>
<td>Excellent. 100% cure with resection, no metastatic potential.</td>
</tr>
<tr>
<td>Minimally invasive adenocarcinoma (MIA)</td>
<td>( \leq 3 ) cm, predominantly lepidic growth with ( \leq 5 ) mm focus of invasion, only rarely mucinous.</td>
<td>Sub-solid +/- ( \leq 5 ) mm central solid component.</td>
<td>Excellent. 100% cure upon resection, no metastatic potential.</td>
</tr>
<tr>
<td>Lepidic predominant adenocarcinoma</td>
<td>( \geq 1 ) focus of invasion ( \geq 5 ) mm, predominant lepidic growth (spread along alveolar walls).</td>
<td>Usually part solid but may be GG or bubble-like.</td>
<td>Best prognosis among invasive forms. 5-year disease free survival (DFS): 75-85%.</td>
</tr>
<tr>
<td>Acinar, papillary/micropapillary, or solid predominant</td>
<td>Invasive + small lepidic component.</td>
<td>Usually solid +/- a small nonsolid component.</td>
<td>Acinar/papillary: 84% DFS. Micropapillary: 67% DFS. Solid: 70% DFS.</td>
</tr>
<tr>
<td>Invasive mucinous</td>
<td>Mucinous, predominant lepidic growth. If multifocal – called multicentric.</td>
<td>Solid or sub-solid Single or multifocal. Can show aerogenous spread.</td>
<td>76% DFS. Low histologogic grade but intermediate prognosis due to frequent multifocality.</td>
</tr>
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</table>

**Spectrum of lung adenocarcinoma: Pre- or minimally invasive**

**Groundglass lesions:**
- AAH and AIS

**Subsolid lesion with < 5 mm solid part or small bubble-like lesion:**
- MIA and AIS.

**Adenocarcinoma-in-situ (AIS) and atypical adenomatous hyperplasia (AAH):**
- Definitive diagnosis on resection
- Low diagnostic yield on FNA
- Excellent prognosis.

**Minimally invasive adenocarcinoma (MIA):**
- Definitive diagnosis on resection
- Low diagnostic yield on FNA
- Excellent prognosis.

AIS: growth along alveolar walls w/o invasion, papillary, micropapillary formations, or intra-alveolar atypical cells.

MIA: predominantly lepidic pattern of growth (spread along alveoli), overall size of tumor $\leq 3$ cm, and invasion to a depth $\leq 5$ mm.
Spectrum of lung adenocarcinoma: Invasive

**Acinar** (LEFT IMAGE): round and oval malignant glands (some examples) invading stroma.

**Solid** (RIGHT IMAGE): invasive growth in solid aggregates (some examples) without distinct glandular lumens.

**Lepidic** (LEFT IMAGE): mantling of air spaces - “lepidic” growth (some examples) by single layers or limited strata of only modestly atypical cuboidal or columnar epithelial cells.

**Micropapillary** (RIGHT IMAGE): within the airspaces, the tumor is growing in micropapillary groups (some examples) lacking fibrovascular cores.
Spectrum of lung adenocarcinoma: Invasive

**Mucinous (LEFT IMAGE):**
Spreads by acinar, papillary, or lepidic growth. Often multifocal. Malignant cells with intracytoplasmic mucin (arrowhead) as opposed to reactive epithelial cells with a terminal bar and cilia (arrow).

**Solid pseudosquamous a.k.a. squamoid (RIGHT IMAGE):**
Immunohistochemical staining would be positive for TTF-1 and Napsin-A, and negative for p40 and CK 5/6.
Pathologic features of adenocarcinoma

Immunohistochemistry used to confirm diagnosis of adenocarcinoma
- Adenocarcinoma: (+) TTF-1 and Napsin A vs. Squamous cell carcinoma: (+) p40, p63 and CK5/6.

Histologic prognostic factors
- Poor disease free survival: tumor size $\geq 2.5 \text{ cm}$, solid and micropapillary subtypes
- Poor overall survival and recurrence in patients with limited resections: micropapillary subtype
- High risk factors: close margin in limited resection, micropapillary component, vascular or pleural invasion, high stage
- Good prognosis: stage I lepidic predominant adenocarcinoma.

Genetic Profile
- Driver gene alterations in adenocarcinoma: EGFR, KRS, BRAF, ERBB2/HER2, ALK, ROS1, RET, NTRK1 and NRG1
- Most clinically relevant due to targeted drugs: EFGR and ALK
- Specifics
  - Invasive mucinous adenocarcinoma: show KRAS mutations and lack EGFR
  - EGFR mutations: more common in Asians, females, and non-smokers; non-mucinous adenocarcinoma with lepidic and papillary growth; TTF-1 positive tumors
  - KRAS mutations: solid pattern
  - ALK mutations: acinar pattern including cribriform pattern and signet ring cell tumors.

Pathologic grading is an independent prognostic predictor for high risk group.
Accuracy for predicting lymphatic involvement increases with incorporation of radiologic size.
Imaging variants of adenocarcinomas

**BBBLE-LIKE LESION**
- Low/intermediate grade (in-situ, min invas or invasive predominantly lepidic).
- Increasing density suggests progression.
- DDx: lymphoma, sarcoidosis, round pneumonia, organizing pneumonia, focal fibrosis.

**PNEUMONIA-LIKE ADENOCARCINOMA**
- Can present with constitutional and infection-like symptoms.
- Short-term imaging follow-up is important. If non-resolving, then DDx:
  - Infiltrative lung adenocarcinoma
  - Lymphoma
  - Organizing pneumonia
- If adenocarcinoma – usually mucinous.
Imaging variants of adenocarcinomas

ADENOCARCINOMA WITHIN THE SCAR
✓ Challenging diagnosis.
✓ Suspicious features:
  - size progression
  - developing convex borders
  - increasing spiculations/lobulations
  - positive FDG-18 PET/CT.

MULTILOBAR WITH VARIOUS DEGREE OF INVASION
✓ Multiple lesions considered de novo cancers rather than metastases.
✓ Most aggressive lesions demonstrate:
  - Size >2 cm
  - Solid or part-solid (with solid part > 5 mm) and fine spiculated margins.

PET/CT is beneficial to N and M staging rather than additional characterization of lesions here.
Imaging variants of adenocarcinomas

**CYSTIC ADENOCARCINOMA**

- Challenging diagnosis.
- Suspect when focus of clustered cysts with GG halo or nodular thickening.
- Higher suspicion when:
  - Spiculated nodule present
  - Progressed internal nodularity
  - Growth of clustered cysts.

**ABSCESS-LIKE ADENOCARCINOMA**

- Challenging diagnosis.
- Resolution of presumed abscess should be documented in every case.
- Clinical scenario is not always helpful (can present with infection-like symptoms).
- Wall thickness: > 5 mm – could be malignant.
FDG-PET/CT

Sensitivity: 72-95%. Specificity: 83%.
Recommended use in pre-test probability of 5-60% and indeterminate 10 mm nodule.
False (-): size <8-10 mm, low histologic grade/well differentiated tumor.
False (+): granulomatous inflammation, infection, carcinoid.
Higher SUVmax reflects increased degree of invasion and worse prognosis in adenocarcinoma.

Slowly progressing pneumonia-like mucinous invasive adenocarcinoma with mildly (+) PET/CT.

N.B. Inconclusive PET/CT does not exclude malignant nature.

Morphologic progression of adenocarcinoma correlates with increasing activity on PET/CT as well as increasing invasiveness and decreasing survival.
Increased SUVMax correlates with tumor invasiveness in clinical stage IA patients post resection (Okada et al 2011):

- Elevation of SUVmax reflects cellular proliferation and aggressiveness.
- SUVMax detects patients at high risk of recurrence after curative resection.
  - 3 year disease free survival: 96% with SUVmax ≤ 2.5 vs. 77% with SUVmax ≥ 2.5
- Nodal metastasis and recurrence rate < 1% among patients with SUVmax ≤ 1.5.

FDG-PET/CT demonstrates utility as preoperative predictor for post surgical outcomes, with sublobar resection a viable option in patients with SUVmax ≤ 1.5.

SUVmax and CTR are significantly correlated with non-invasive pathology (AIS) despite part-solid appearance on CT (Hattori et al 2013):

- AIS is found in 40% of part solid nodules with SUVMax ≤ 1.0 and CTR (consolidation/tumor ratio i.e. solid part/max lesion size) ≤ 0.40.
  - Pathological lymphovascular invasion was not present in any patient in this subgroup.
# Probability of malignancy


<table>
<thead>
<tr>
<th>Low (&lt;5%)</th>
<th>Intermediate (5-60%)</th>
<th>High (&gt;60%)</th>
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</table>
| - Young (<35 y.o.)  
- No smoking history or known cancer  
- Smaller nodule size  
- Regular margins and/or non-upper lobe location. | Combination of low and high features  
*This category perhaps should also be used for Asian females without significant smoking history presenting with subsolid nodule* | - Older (≥60 y.o.) and heavy smoker  
- Prior Hx of lung cancer (within last 5 years) or family Hx of lung cancer  
- Larger nodule (≥2 cm), part-solid or solid  
- Irregular/spiculated borders  
- Upper lobe location. |
| No or low PET FDG uptake for nodule ≥ 8 mm | Low-moderate PET/FDG uptake* | Intensely hypermetabolic nodule |
| Bronchoscopy or non-surgical biopsy: specific benign results | Non-diagnostic bronchoscopy or non-surgical biopsy results | Bronchoscopy or non-surgical biopsy are suspicious for cancer |
| • Complete/near complete resolution on first F/U CT  
• *Stable ≥2 years or progressive decrease size for solid nodule  
• *Stable ≥3-5 years or progressive decrease in size of solid part for part-solid nodule | • Dedicated F/U imaging and clinical assessment  
• Worsening clinical scenario (eg. hemoptysis, increasing CEA, weight loss etc.), high risk nodule morphology, growth, or increasing FDG uptake -> surgical consult | • Clear evidence of growth or developing irregular margins on follow-up CT for solid lesion  
• Increasing solid part or increasing density of sub-solid lesion. |

- *20% of lung cancers decrease in size before subsequent growth.  
- If pre-test probability > 60% - PET should not be used for confirmation but rather for staging.
Summary

- Improved understanding of imaging and pathologic characteristics of pulmonary adenocarcinoma allows better stratification of peripheral lung lesions.
- IASLC/ATS/ERS classification emphasizes key radiographic findings correlating with pathologic invasiveness and behavior, thus guiding treatment and aiding prognosis.
- Near 100% cure with resection of non-invasive spectrum adenocarcinoma

When to suspect adenocarcinoma
- Part solid ground glass nodule or persistent pure ground glass lesion.
  - High consolidation/tumor ratio and increased SUVMax on PET correlates with higher grade/invasion.
- Solid nodule size > 0.8-2 cm without calcifications or macroscopic fat in age ≥ 45-50 y.o
  - Significantly increased risk with history of smoking, chronic lung disease, inhalational exposure.
- Corona radiata, spiculation, and lobulated margins: high positive predictive value
- Use of nodule volume doubling time enhances predictive value over axial evaluation.
17. Takahashi M et al. Tumor invasiveness as defined by the newly proposed IASLC/ATS/ERS classification has prognostic significance for pathologic stage IA lung adenocarcinoma and can be predicted by radiologic parameters. The Journal of thoracic and cardiovascular surgery. 2014;147(1):54-9.