Advances in the Management of Early Stage Lung Cancer

“Sir, the following paradigm shifts occurred while you were out.”

Frank Detterbeck MD
Thoracic Surgery, Yale University, Thoracic Oncology Program
Potential Conflicts of Interest

- Olympus – member of Data Safety Monitoring Board for study of endobronchial valves for emphysema
- Medela – research grant on chest drainage device
- Chair of ACCP Evidence-Based Lung Cancer Guidelines
- IASCLC Staging and Prognostic Factors Committee (Chair of several subcommittees)
Overview

• Setting the Stage – How the world is changing
• The Nature of Early Stage Lung Cancer
• GGO – slow down and take a deep breath
• Advances in Surgery
• SBRT – a valuable addition
• Approach to the compromised patient
Setting the Stage: How the world is changing
Improvement in Survival over Time

There has been a major improvement in Survival between the 1990-1999 and the 1999-2000 datasets.

IASLC datasets, using the 7th edition classification in both...
Changes in Size: Japan Registry

Surgical Patients

- 1994:
  - 3cm: 49%
  - 2cm: 23%
  - Other sizes: 28%

- 1999:
  - 3cm: 55%
  - 2cm: 30%
  - Other sizes: 15%

- 2004:
  - 3cm: 63%
  - 2cm: 38%
  - Other sizes: 7%
CT scans performed in US by Year

Brenner NEJM 2007;357:2277-84
Change in Stage IV NSCLC: NCDB

Community Hosp (100-649 Ca/Yr)
Community Hosp (>650 Ca/Yr)
Teaching Hosp Cancer Program

Ref: Morgensztern D et al
J Thor Onc.2010; 5(1):29-33
Trends in NSCLC (California Cancer Registry)

Ref: Chee Arch Int Med 2008;168:1541-9
Survival Trends in NSCLC (California Ca Regis)

Survival by PET vs No PET 1999-2004

Ref: Chee Arch Int Med 2008;168:1541-9
Changing Survival over Time

Why?

Reasons probably include:

- Earlier detection
- Changing spectrum of disease → Cohort includes more indolent tumors
- Better staging
- Better treatment modalities → Higher cure rate, prolonged survival with incurable Ca
- ↓ inappropriate (or no) treatment
- ↓ competing causes of death
The Nature of Early Stage Lung Cancer
Adenocarcinoma Subclassification

Atypical Adenomatous Hyperplasia (AAH) – (precancerous lesion)

Adenocarcinoma in situ (AIS)

Minimally Invasive Adenocarcinoma (MIA) (<5mm invasive component)

Invasive Adenocarcinoma
Lepidic, Acinar, Papillary, Micropapillary, Solid
(Usually mixed – shown is Acinar predominat)

But is there really a 1:1 correlation?
## Correlation of CT & Pathology

<table>
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<tr>
<th>N pts:</th>
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<th>9</th>
<th>46</th>
<th>156</th>
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</table>

### NOS

- **Excl AAH**
- **Excl LPA**

### Combined categories

- **Benign diagnoses excluded in all**

### Annotations

- **Song 14**
- **Lee 13**
- **Lim 13**
- **Son 14**
- **Zhang 15**
- **Zhang 14**
- **Xiang 14**
- **Fourmel 17**
- **Hattori 17**

### Categories

- **AAH**
- **AIS**
- **MIA**
- **LPA**

### Diagnoses

- **0%**
- **10%**
- **20%**
- **30%**
- **40%**
- **50%**
- **60%**
- **70%**
- **80%**
- **90%**
- **100%**

### Percentages

- **70%**
- **80%**
- **90%**
- **40%**
- **50%**
- **60%**

### Pure GGO and > 50% GGO

- **pure GGO**
- **> 50% GGO**
## Prediction of Adeno Subtype

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>GGN type</th>
<th>Size (mm)</th>
<th>Slice Thickness (mm)</th>
<th>Window for Solid part</th>
<th>Total Size</th>
<th>Solid Size</th>
<th>Density</th>
<th>Mass</th>
<th>margin</th>
<th>Air Bronch</th>
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<td><strong>Adeno vs AIS / MIA</strong></td>
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<td>Part</td>
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<td>≤2</td>
<td>MW</td>
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<td>Y</td>
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<td>N</td>
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<tr>
<td>Zhang 15</td>
<td>237</td>
<td>Both</td>
<td>&lt;20</td>
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<td>Y</td>
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<td>Son 14</td>
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<td>Pure + &lt;5</td>
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<td>Lim 13</td>
<td>46</td>
<td>Pure</td>
<td>≥10</td>
<td>2.5</td>
<td>MW</td>
<td>y</td>
<td>-</td>
<td>N</td>
<td>y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>MIA vs AAH / AIS</strong></td>
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<td>N</td>
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<tr>
<td><strong>AIS vs AAH</strong></td>
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<td>≤2</td>
<td>MW</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

N = Not Signif; Y = Stst signif by MVA; y = inconsistently signif in different models
### STAGE I ADENOCARCINOMA (N=514)

#### RECURRENCE-FREE SURVIVAL

<table>
<thead>
<tr>
<th>Histologic Type (N)</th>
<th>5 Year RFS %</th>
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</thead>
<tbody>
<tr>
<td>AIS (1), MIA (8)</td>
<td>100</td>
</tr>
<tr>
<td>Lepidic NM (29)</td>
<td>90</td>
</tr>
<tr>
<td>Papillary (143)</td>
<td>83</td>
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<tr>
<td>Acinar (232)</td>
<td>85</td>
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<td>Mucinous Adca (13)</td>
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<tr>
<td>Colloid (9)</td>
<td>71</td>
</tr>
<tr>
<td>Solid (67)</td>
<td>71</td>
</tr>
<tr>
<td>Micropapillary (12)</td>
<td>64</td>
</tr>
</tbody>
</table>

Caveat: Study includes everything from pure GGN to solid spiculated lesions
Outcomes of Adeno Subtypes

All studies show: AIS/MIA survival is consistently excellent. Most studies include the full spectrum from pure GGO to pure solid. Only study focused on mostly GGN shows that for these tumors the pathologic adenocarcinoma subtype doesn’t matter.

Pure GGN + <5mm solid portion

Would survival be just as good without resection?

5-yr DFS
AIS 100% (n=38)
MIA 100% (n=61)
Adeno 98% (n=92)

Son JY PLOS One 2014;9;(8)
Whole vs Solid Tumor Size by CT

Tsutani  JTCVS 143:607-12, 2012
Solid/Invasive Component is Key

Lymphatic Invasion

Vascular Invasion

Pleural Invasion

Pathologic Invasiveness

Node Involvement

502 cla Adeno pts, R0 CT 1-2mm thickness Lung windows, max Ø DFS predicted by solid size, PET, N+ (not whole size) in MV anal.

Tsutani JTCVS 2012;143:607-12
Solid/Invasive Component is Key

Multiple multivariate analysis studies have shown that the size of the solid or invasive component is key

- Predicts Recurrence-Free Survival (RFS)\(^1,2,3,5,6\)
- Predicts N\(^{+1,4}\)
- Predicts Lymph, Vasc, Pleural invasion\(^1,3\)

- Size of GGO component has no value\(^1,2,3,4,5,6\)

- Maybe also of prognostic value: Pleur Inv\(^2\); PET\(^1,3,6\); N\(^{+1}\); CEA\(^2\); Ly Inv\(^3\); Air Bronchogram\(^4\);

**8th Edition Size Measurement**

**Clinical Size Measurement**
- 8th Ed: cT determined by largest dimension of solid component
- long axis dimension, lung window setting, 1 mm slices

**Pathologic Size Measurement**
- 8th Ed: pT determined by largest dimension of invasive component (or the % that is invasive if several sites); also record largest dimension of lepidic component

If interspersed components, measure total size and % solid / invasive
Ground Glass Opacities:
Slow Down and
Take a Deep Breath
Genetic Features of Multifocal Adeno

Mutation of:
- KRAS
- EGFR

68% smokers
72% non-smokers

↓ rate of KRAS with de-differentiation suggests that AAH with KRAS mutation doesn’t progress

Opposite for EGFR mutation

Mutually exclusive KRAS & EGFR mutations suggests different pathways

Also correlation w smoking

↑ rate of KRAS with Mod-Poorly differentiated Adeno suggests it doesn’t develop from AAH maybe different mechanism?

Sakamoto J Pathol 2007;212:287-94
There is evidence for different types of GGNs with different biologic behavior.
Only Some GGNs Grow

Patients with a Lung Cancer and additional sub-solid GGNs over time

Ref: Kobayashi J Thor Oncol 2013;8:309-14
Only Some GGNs Grow

Patients with a Lung Cancer and additional sub-solid GGNs over time

Ref: Kobayashi J Thor Oncol 2013;8:309-14
Do All GGNs Grow?

AAH w KRAS mutation: not destined to grow? (Associated with smoking?)
   A manifestation of the ability of KRAS to induce senescence?

AAH w EGFR mutation: progression to lepidic Adeno No assoc w smoking?
How well can we determine growth?

Solid Nodules

Poor inter- & intra-observer consistency for differences of <1.5-2 mm

20% error for presence/absence of 1 volume doubling for 5mm nodule and slice thickness of 2.5mm in phantom

Bottom line:

Sub-Solid Nodules (GGN)

Especially GGN are difficult – indistinct borders,

Bottom line:

• Use thin slices (1.25 mm)
• Don’t trust changes <2 mm
• Don’t compare apples to oranges (i.e. PET-CT to diagnostic CT, 5 mm slices to 1.25 mm slices)

When in doubt, get another data point!
Challenges in Assessing Growth

How well can we determine growth?

Ignore differences less than 2 mm
Use thin slice CT (1.25mm)
Compare like to like (type of scan, setting, slice thickness)
  Don’t trust diagnostic CT compared to PET/CT
  Don’t trust thick vs thin slices
  Don’t use MIP images, different window settings

Bottom line: when there is doubt, don’t cut it out
⇒ get more data points
### Incidence of Progression by %GGO and Time

<table>
<thead>
<tr>
<th>Growth in:</th>
<th>0-1 yr</th>
<th>1-2 yr</th>
<th>2-3 yr</th>
<th>3-4 yr</th>
<th>4-10 yr</th>
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<tbody>
<tr>
<td>No change</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>% of Resections</th>
<th>AIS/MIA</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>96%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>33%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>27%</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>99.2% Stage Ia</td>
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<td></td>
</tr>
</tbody>
</table>

**Prospective, Long-Term Study**

Patients followed for 10-15 years (accrued 2000-2005); Pure or part-solid GGO ≤ 3 cm

Progression defined as either growth or increased consolidation (usually ~2-3 mm ↑)

Proportion of consolidation assessed on lung windows

Sawada Chest 2016;
Progression of GGO (Prospective Study)

Prospective multicenter study 2009-11; median f/u 4.3 yrs
Patients with pure GGN or with ≤ 5mm solid component  (n = 1253)
Defined as pure, heterogeneous (consolidated on lung window) or part-solid (mediastinal window) on 1.25 mm slice CT

Central expert radiology and pathology review (of changing or resected cases)

Growth was defined as:
• ↑ in max diam of ≥2mm of GG portion
• ↑ in max diam of ≥2mm of solid portion (either lung or mediast window)
• New solid portion (either lung or mediast window)

74% CT & 6% CXR screening, 17% incidental;
60% never-smoker; 31% multiple

Kakinuma J Th Onc 2016;11:1012-28
Progression of GGO (Prospective Study)

Patients with pure GGN or with \( \leq 5\text{mm} \) solid component \( (n = 1253) \)

Growth of max Size of Solid Component \( \geq 2\text{mm} \)

Multivariate predictor:
- Pure – initial size,
- Hetero – none
- Part-solid – initial size

Part solid GGN \( (n=104) \) on mediast. window \( (<5\text{mm}) \)
- Pure GGN \( (n=1053) \)
- Heterogeneous GGN \( (n=81) \)

Kakinuma J Th Onc 2016;11:1012-28
Progression of GGO (Prospective Study)

Patients with pure GGN or with ≤ 5mm solid component (n = 1253)

Final Results (% of 1253 GGNs):
- 7.4% resected
- 1% Adeno; 3.3% MIA, 2.7% AIS, 0.5% AAH
- All Adeno were part-solid on CT
- 98% Stage Ia (2% stage Ib)
- No recurrences (median f/u 3 yrs)
- No new nodules developed

Kakinuma J Th Onc 2016;11:1012-28
GGN Management Recommendation

Triggers for Intervention
This is a moving target - my current recommendation:

<table>
<thead>
<tr>
<th>GGN Type</th>
<th>Follow-Up Schedule</th>
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</thead>
<tbody>
<tr>
<td>Pure GGN</td>
<td>LDCT q 12 mo</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>CT q 6 mo x 2 years; if stable revert to LDCT q 12 mo</td>
</tr>
<tr>
<td>Part-solid GGN (2-5 mm solid portion on MW)</td>
<td>CT q 3 mo x 1 year; if stable revert to CT q 6 mo</td>
</tr>
</tbody>
</table>

Note: CT should be done with 1.25 mm slice thickness

a Assuming no doubt about measurement (generally requires \( \geq 2 \) interval scans)

b Speculative recommendation, based on limited data
Criteria for Multifocal GG/L Category

Clinical Criteria

Tumors should be considered multifocal GG/L lung cancer if:
There are multiple sub-solid nodules (either pure ground glass or part-solid), with at least one suspected (or proven) to be cancer.

- This applies whether or not the nodules have been biopsied
- This applies if the other nodule(s) are suspected to be AIS, MIA or LPA

- GGN lesions <5mm or lesions suspected to be AAH are not counted.
# Multifocal GG/L Adenocarcinoma

## Systematic Literature Review:

<table>
<thead>
<tr>
<th>First Author</th>
<th>N</th>
<th>pN2</th>
<th>% Re-sec</th>
<th>% Multi-focal</th>
<th>CT appearance (% ground glass)</th>
<th>% BAC&lt;sup&gt;a&lt;/sup&gt; Histology</th>
<th>% 5-year Survival</th>
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<tr>
<td>Ishikawa</td>
<td>93</td>
<td>8</td>
<td>100</td>
<td>87</td>
<td>26 51 22</td>
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<td>87 93</td>
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<tr>
<td>Vazquez&lt;sup&gt;b&lt;/sup&gt;</td>
<td>49</td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100</td>
<td>100</td>
<td>42 23 34</td>
<td>74 12</td>
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<td>6</td>
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<td>84</td>
<td>28 43 29</td>
<td>69&lt;sup&gt;d&lt;/sup&gt; 31</td>
<td>93 -</td>
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<tr>
<td>Ebright</td>
<td>29&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100</td>
<td>100</td>
<td>- - -</td>
<td>66 34</td>
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<tr>
<td>Mun&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0</td>
<td>100</td>
<td>93</td>
<td>0 - -</td>
<td>14 86</td>
<td>100&lt;sup&gt;f&lt;/sup&gt; 100&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>100</td>
<td>100</td>
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<td>14 57</td>
<td>64 64</td>
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<td><strong>Average</strong></td>
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<td>&lt;50%</td>
<td>&gt;50%</td>
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<td></td>
<td>26</td>
<td>51</td>
<td>22</td>
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</tbody>
</table>


<sup>a</sup>bronchioloalveolar carcinoma (term was in use at the time these papers were written)

<sup>b</sup>involving primarily pts detected by CT screening for lung cancer  

<sup>c</sup>N1 and N2 combined

<sup>d</sup>Includes adenocarcinoma  

<sup>e</sup>pts with pneumatic (infiltrative) adenocarcinoma excluded
### Multifocal GG/L: Recurrence Pattern

#### Systematic Literature Review:

<table>
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<tr>
<th>1st Author</th>
<th>N</th>
<th>Type</th>
<th>New 1º</th>
<th>Lung</th>
<th>N2,3</th>
<th>L+D</th>
<th>D</th>
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<tr>
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<td>50</td>
<td>30</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Ebright\textsuperscript{u}</td>
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<td>&lt;50% GG</td>
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<tr>
<td>Ishikawa</td>
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<td>Multifocal</td>
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<td>(18)\textsuperscript{c}</td>
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<td>(15)\textsuperscript{c}</td>
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<td>(30)\textsuperscript{c}</td>
</tr>
<tr>
<td><strong>Average\textsuperscript{e}</strong></td>
<td>64</td>
<td><strong>23</strong></td>
<td><strong>5</strong></td>
<td><strong>6</strong></td>
<td></td>
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</tbody>
</table>


\textsuperscript{u}included pts with unifocal disease \hspace{1cm} \textsuperscript{b}involving primarily pts detected by CT screening
\textsuperscript{c}data for new primary cancers not reported \hspace{1cm} \textsuperscript{d}pre-1999 definition
\textsuperscript{e}excluding values in parentheses
Multifocal GG/L Tumors - Management

Less investigation needed to confirm clinical stage

Manage each nodule individually →
• Observe if it doesn’t meet criteria for intervention
• Resect if meets criteria for intervention (prefer segmentectomy)

Rationale:
• often indolent, many do not progress
• low propensity for nodal or distant metastases,
• higher propensity for development of new lung cancers
Advances in Surgery
Minimally Invasive Surgery

- 5 cm incision
- No rib spreading
- Additional 5 & 10 mm incisions
Operative Mortality (%)

<table>
<thead>
<tr>
<th>VATS</th>
<th>Open</th>
</tr>
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<td>3961</td>
<td>NS</td>
</tr>
<tr>
<td>1513</td>
<td>.02</td>
</tr>
</tbody>
</table>

Specific data not reported
Peri-Operative Complications (%)

### VATS
- Study: Cheng 07
- Study: Chen 13
- Study: Yan 09

### Open
- Study: Paul 13
- Study: Yang 16
- Study: Falcoz 16
- Study: Cao 12
- Study: Cao 13
- Study: Paul 10
- Study: Scott 10
- Study: Hores 09
- Study: Villamizar
- Study: Lee 13
- Study: Ilonen 11
- Study: Jeon 13
- Study: Scott 10
- Study: Ceppa 12
- Study: Ceppa 12
- Study: Farjah 09
- Study: Park 12
- Study: Swanson 12
- Study: Licht 13
Metaanalysis: VATS vs Open

36 Studies (3 randomized), 3384 patients, 1995-2007

Intraoperative Outcomes: Safe
6% conversion, no Δ transfusion, periop Mortality ~1%
↓ Bl loss (80 ml), ↑ OR time (16 min)

Peri-operative Complications: Better
↓ Complications, ↓ Hosp days

Postoperative Pain, Quality of Life: Better
↓ Pain (any measure x >3 mo.), ↑ FEV1
↑ return of function, trend to ↑ QOL

Oncologic Aspects: Equal or Better
no Δ node staging, ↑ Delivery of adjuvant chemotherapy

Long-Term Outcomes: Equal
↑ long-term survival

Approach Used for Lobectomy
Outcomes according to Specialization

- Gen Surgeon
- Gen Surgeon
- Gen Surgeon

Hosp Mort: Thoracic, Cardiac
Hosp Mort: Thoracic, Cardiac
Ov Surv: Thoracic, Cardiac

- Schipper Lobe
- Schipper Pneum
- Schipper Seg
- Goodney
- Farjah
- Ellis
- Li
Outcomes according to Hospital Type

- Non-Teaching Hosp
  - Meguid Ov
  - Meguid Pneum
  - Meguid Lobe
  - Meguid Segm
  - Cheung
  - Romano Lobe/Seg
  - Romano Pneum
  - Simunovic

- Teaching Hosp
  - Meguid Ov
  - Meguid Pneum
  - Meguid Lobe
  - Meguid Segm
  - Cheung
  - Romano Lobe/Seg
  - Romano Pneum
  - Simunovic

- Non-Teaching
  - Hospital Mortality
  - Overall Survival

- Teaching
  - Hospital Mortality
  - Overall Survival
Outcomes according to Case Volume

- Hospital Mortality
- Overall Survival

Low Volume:
- Adjusted Odds Ratio

High Volume:
- Adjusted Odds Ratio

Authors:
- Hollenbeck
- Bilimoria
- Finlayson L
- Finlayson Pn
- Birkmeyer L
- Birkmeyer Pn
- Cheung
- Romano L/S
- Romano P
- Hannan
- Urbach
- Khuri
- Osada
- Freixinet
- Simunovic
- Bach
- Begg
- Kim
- Sioris
- Tanaka
- Li
Trends in SEER for pI \( \leq 2\) cm NSCLC

Segmentectomy may be appropriate for some patients

- **1987-97**
  - \( n = 1961 \)

- **1998-2004**
  - \( n = 3327 \)

- **2005-08**
  - \( n = 3509 \)

MVA: HR 1.41 (1.21-1.65)

Wedge-HR 1.19 (1.01-1.41)

Seg – HR 1.04 (0.80-1.36)

Wedge-HR 1.09 (0.79-1.50)

Seg – HR 0.83 (0.47-1.45)

Yendamuri J Surg Res 2013;183:27

Wedge/Seg 23.9%

Wedge-HR 1.09 (0.79-1.50)

Seg – HR 0.83 (0.47-1.45)

< 1 cm 8.8%

BAC 16% No nodes Bx 22.2%

< 1 cm 10.1%

BAC 16.8% No nodes Bx 16.6%

< 1 cm 10.6%

BAC 15.6% No nodes Bx 14%

Predates codes for W vs Seg
Meta-analysis: Intentional Segment vs Lobe

Systematic Review (up to Dec 2013), metaanalysis Subgroup of Intentional Segment vs Lobe for stage I (7 studies, 1550 pts; > stage I in 5.8% Seg; 4.4% lobe;)
No Difference in OS or DFS

Overall Survival – HR 1.04 (0.66-1.63)
Meta-analysis: Intentional Sublobar vs Lobe

Systematic Review, metaanalysis (12 studies, 2745 pts)
Intentional Wedge/Seg for stage I (> stage I in 3% SL; 6% lobe)

No Difference in OS or DFS

Size ~ 6mm smaller in wedge/Seg (~ 16 vs 22 mm)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Read</td>
<td>0.14</td>
<td>0.36</td>
<td>11.8%</td>
<td>1.15 [0.57, 2.33]</td>
<td>1990</td>
</tr>
<tr>
<td>Warren</td>
<td>0.3</td>
<td>0.91</td>
<td>3.3%</td>
<td>1.35 [0.23, 8.03]</td>
<td>1994</td>
</tr>
<tr>
<td>Ginsberg</td>
<td>0.42</td>
<td>0.22</td>
<td>17.1%</td>
<td>1.52 [0.99, 2.34]</td>
<td>1995</td>
</tr>
<tr>
<td>Kodama 1997</td>
<td>0.11</td>
<td>0.6</td>
<td>6.3%</td>
<td>1.12 [0.34, 3.62]</td>
<td>1997</td>
</tr>
<tr>
<td>Koike</td>
<td>0.08</td>
<td>0.43</td>
<td>9.8%</td>
<td>1.08 [0.47, 2.52]</td>
<td>2003</td>
</tr>
<tr>
<td>Okada</td>
<td>-0.31</td>
<td>0.22</td>
<td>17.1%</td>
<td>0.73 [0.48, 1.13]</td>
<td>2006</td>
</tr>
<tr>
<td>Kodama 2008</td>
<td>-1.31</td>
<td>0.41</td>
<td>10.3%</td>
<td>0.27 [0.12, 0.60]</td>
<td>2008</td>
</tr>
<tr>
<td>Sugi</td>
<td>0.79</td>
<td>0.67</td>
<td>5.4%</td>
<td>2.20 [0.59, 8.19]</td>
<td>2010</td>
</tr>
<tr>
<td>Ichiki</td>
<td>-1.37</td>
<td>294.88</td>
<td>0.0%</td>
<td>0.25 [0.00, 2.555E250]</td>
<td>2011</td>
</tr>
<tr>
<td>Yamashita</td>
<td>-0.2</td>
<td>0.51</td>
<td>7.9%</td>
<td>0.82 [0.30, 2.22]</td>
<td>2012</td>
</tr>
<tr>
<td>Hamatake</td>
<td>0.32</td>
<td>0.88</td>
<td>3.5%</td>
<td>1.38 [0.25, 7.73]</td>
<td>2012</td>
</tr>
<tr>
<td>Tsutani</td>
<td>-0.71</td>
<td>0.53</td>
<td>7.5%</td>
<td>0.49 [0.17, 1.39]</td>
<td>2013</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.91 [0.64, 1.29]

Overall Survival – HR 0.91 (0.64-1.29) Cao, Ann CT Surg 2014;3:134
## Types of Non-Randomized Comparisons

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Key Feature</th>
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<tbody>
<tr>
<td>Probably not confounded comparison</td>
<td>Cohorts well matched or multivariate model accounts for <em>all</em> known relevant factors</td>
</tr>
<tr>
<td>Possibly only mildly confounded comparison</td>
<td>Cohorts well matched or multivariate model accounts for most relevant factors</td>
</tr>
<tr>
<td>Probably confounded comparison</td>
<td>Inability to assess potential differences between cohorts</td>
</tr>
<tr>
<td></td>
<td>Unclear impact of demonstrated differences</td>
</tr>
<tr>
<td>Clearly confounded comparison</td>
<td>Differences in cohorts being compared</td>
</tr>
<tr>
<td></td>
<td>Known or presumed confounder is inseparable from the intervention</td>
</tr>
</tbody>
</table>
NCDB Outcomes – cT1a N0 M0 NSCLC

National Cancer Database Outcomes study, 2003 to 2011
clinical T1A N0 NSCLC, 13,606 patients
Short-term and long-term outcomes
(30-day mortality, overall survival)
Detailed analysis - included most major prognostic factors

Propensity matched by all available prognostic factors

Categorized as a possibly only mildly confounded non-randomized comparison

Ref: Khullar J Thor Onc 2015;10:1625-33
NCDB Outcomes – cT1a N0 M0 NSCLC

Propensity–matched cohorts (n = 209 each)
(age, sex, race, comorbidity; size, histology, grade;
year, hosp type, insurance, income, education, urban/rural)

Ref: Khullar J Thor Onc 2015;10:1625-33
Prospective Studies

- CALGB 140503: RCT of lobe vs sublobar for T1aN0M0 solid NSCLC
target accrual ~800

- WJOG 4607I: RCT of lobe vs Segment for T1aN0 Adeno semisolid GGO
target 1100

- JCOG 0804/WJOG 1507I: phase II, wedge or Segment for pure GGO ± minimal solid component
target accrual 330
SBRT – a Valuable Addition
Stereotactic Body Radiation Therapy
## Selected SBRT Prospective Reports

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Dose</th>
<th>Local Control %</th>
<th>Overall Surv %</th>
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</thead>
<tbody>
<tr>
<td>Kyoto</td>
<td>45</td>
<td>12 Gy x 4</td>
<td>94</td>
<td>83/72 (3-yr)</td>
</tr>
<tr>
<td>Scandinavian</td>
<td>57</td>
<td>15 Gy x 3</td>
<td>92</td>
<td>60 (3-yr)</td>
</tr>
<tr>
<td>Indiana</td>
<td>70</td>
<td>20 -22 x 3</td>
<td>88</td>
<td>43 (3-yr)</td>
</tr>
<tr>
<td>RTOG 0236</td>
<td>55</td>
<td>20 Gy x 3</td>
<td>90-97</td>
<td>56 (3-yr)</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>42</td>
<td>19 -30 x 1</td>
<td>68</td>
<td>37 (3-yr)</td>
</tr>
<tr>
<td>Torino</td>
<td>62</td>
<td>15 Gy x 3</td>
<td>88</td>
<td>57 (3-yr)</td>
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<tr>
<td>Tohoku</td>
<td>31</td>
<td>15 x 3, 7.5 x 8</td>
<td>78/40</td>
<td>71 (3-yr)</td>
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<tr>
<td>JCOG 0403</td>
<td>100</td>
<td>12 Gy x4</td>
<td>78/40</td>
<td>60 (3-yr)</td>
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<tr>
<td>VU Univ</td>
<td>676</td>
<td>Risk - adapted</td>
<td>90</td>
<td>64 (2-yr)</td>
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</table>
Retrospective comparison: Stage I NSCLC deemed ineligible for lobectomy → no significant differences in:

Local recurrence
4% SBRT v 20% wedge (p=0.07)

Regional recurrence
4% SBRT v 18% wedge

Distant Metastases
19% SBRT v 21% wedge

Cause-specific survival
93% SBRT v 94% wedge

Overall survival
72% SBRT v 87% wedge (p=0.01)

Clearly confounded non-randomized comparison
Propensity-matched retrospective review
- stage I NSCLC, included sub-lobe up to pneumonectomy
- No difference in 4-year local control (90%)
- No difference in 4-year regional control (80%)
- No difference in NSCLC-specific survival

Probably confounded non-randomized comparison
SBRT for Operable Patients
Prospective Randomized Trials

**Randomized**

ROSEL  Closed due to poor accrual
lobectomy versus SBRT

STARS  Closed due to poor accrual
lobectomy versus SBRT (cyberknife)

ACOSOG Z4099/RTOG 1021  Closed due to poor accrual
sub-lobar resection versus SBRT

SABR-Tooth – ongoing, but

STABLEMATES-ongoing, but

VALOR  - ongoing, but…
NCDB - Healthy cI NSCLC (no comorbidities)

- NCDB 2008-12 healthy cI pts: 13,562 Lobectomy, 1781 SBRT (BED 100-200)
- Propensity matched (1,781 pairs; matched for age, sex, race, T size, T site, cT stage, histotype, grade, insurance, income, education, rural/urban, facility type, location)
- Subset recommended for lobe, but refused (256 matched pairs)

Lobe recommended, P-matched
Possibly only mildly confounded non-randomized comparison
Approach to the Compromised Patient
Outcomes in Compromised Pts

STS DB 2000-10, 12,970 lobectomies for Lung Cancer

Ref: Ceppa Ann Surg 2012;256:487-93
Outcomes in Compromised Patients

STS DB Lobectomies 2009-11 (n = 13,376)

ppoFEV1 %

ppoDLCO %

% Mortality

% CardioPulmonary Complications

Ref: Burt JTCVS 2014;148:19-29
## Outcomes in Compromised Patients

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; Author, year</th>
<th>n</th>
<th>Source</th>
<th>Criteria</th>
<th>% Op Mort</th>
<th>% Complicati all</th>
<th>% Complicati pulm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VATS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandri 15</td>
<td>141</td>
<td>Leeds</td>
<td>&gt;75 yr, CAD, FEV1/DLCO &lt;50</td>
<td>1.5</td>
<td>21&lt;sup&gt;CP&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Berry 10</td>
<td>47</td>
<td>Duke</td>
<td>ppoFEV1 ≤45%</td>
<td>-</td>
<td>-</td>
<td>13&lt;sup&gt;CP&lt;/sup&gt;</td>
</tr>
<tr>
<td>Berry 10</td>
<td>28</td>
<td>Duke</td>
<td>ppoDLCO ≤45%</td>
<td>-</td>
<td>-</td>
<td>14&lt;sup&gt;CP&lt;/sup&gt;</td>
</tr>
<tr>
<td>Burt 14</td>
<td>210</td>
<td>STS</td>
<td>ppoFEV1 30-40%</td>
<td>0</td>
<td>-</td>
<td>13&lt;sup&gt;CP&lt;/sup&gt;</td>
</tr>
<tr>
<td>Burt 14</td>
<td>127</td>
<td>STS</td>
<td>ppoDLCO 30-40%</td>
<td>1.7</td>
<td>-</td>
<td>14&lt;sup&gt;CP&lt;/sup&gt;</td>
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<tr>
<td>Zhang 15</td>
<td>350</td>
<td>Sys Rev</td>
<td>ppoFEV1/DLCO ≤40%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.5</td>
<td>39</td>
<td>26</td>
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<tr>
<td>Ceppa&lt;sup&gt;c&lt;/sup&gt; 12</td>
<td>-</td>
<td>STS</td>
<td>ppoFEV1 ≤40%</td>
<td>-</td>
<td>-</td>
<td>18</td>
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<tr>
<td>Burt 14</td>
<td>58</td>
<td>STS</td>
<td>ppoFEV1 20-30%</td>
<td>3</td>
<td>-</td>
<td>12&lt;sup&gt;CP&lt;/sup&gt;</td>
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<tr>
<td>Burt 14</td>
<td>24</td>
<td>STS</td>
<td>ppoDLCO 20-30%</td>
<td>2.9</td>
<td>-</td>
<td>16&lt;sup&gt;CP&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Open</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berry 10</td>
<td>40</td>
<td>Duke</td>
<td>ppoFEV1 ≤45%</td>
<td>-</td>
<td>-</td>
<td>45</td>
</tr>
<tr>
<td>Berry 10</td>
<td>27</td>
<td>Duke</td>
<td>ppoDLCO ≤45%</td>
<td>-</td>
<td>-</td>
<td>37</td>
</tr>
<tr>
<td>Burt 14</td>
<td>260</td>
<td>STS</td>
<td>ppoFEV1 30-40%</td>
<td>3.5</td>
<td>-</td>
<td>22&lt;sup&gt;CP&lt;/sup&gt;</td>
</tr>
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<td>Burt 14</td>
<td>148</td>
<td>STS</td>
<td>ppoDLCO 30-40%</td>
<td>4.4</td>
<td>-</td>
<td>18&lt;sup&gt;CP&lt;/sup&gt;</td>
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<tr>
<td>Zhang 15</td>
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<td>Sys Rev</td>
<td>ppoFEV1/DLCO ≤40%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.8</td>
<td>58</td>
<td>46</td>
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<tr>
<td>Ceppa&lt;sup&gt;c&lt;/sup&gt; 12</td>
<td>-</td>
<td>STS</td>
<td>ppoFEV1 ≤40%</td>
<td>-</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Burt 14</td>
<td>45</td>
<td>STS</td>
<td>ppoFEV1 20-30%</td>
<td>7.5</td>
<td>-</td>
<td>22&lt;sup&gt;CP&lt;/sup&gt;</td>
</tr>
<tr>
<td>Burt 14</td>
<td>30</td>
<td>STS</td>
<td>ppoDLCO 20-30%</td>
<td>5.5</td>
<td>-</td>
<td>21&lt;sup&gt;CP&lt;/sup&gt;</td>
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</table>
## Outcomes in Older Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>N</th>
<th>Morbidity %</th>
<th>Mortality %</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>lobe</td>
<td>SL</td>
<td>lobe</td>
</tr>
<tr>
<td>Kilic</td>
<td>Stage I, age &gt;75</td>
<td>106</td>
<td>78</td>
<td>25</td>
<td>11.5</td>
</tr>
<tr>
<td>Okami</td>
<td>Stage IA, age &gt;75</td>
<td>79</td>
<td>54</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Dell'Amore</td>
<td>Stage I-IIA age &gt;75</td>
<td>218a</td>
<td>71</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Shirvani</td>
<td>Stage I SEER-MC</td>
<td>7215</td>
<td>1496</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liu</td>
<td>Stage I, age &gt;70</td>
<td>122</td>
<td>45</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*a includes lobectomy and bilobectomy; b 3 year
Limited Lung Resection: Outcomes

<table>
<thead>
<tr>
<th>Surgical Technique</th>
<th>Low-Risk Pts</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>% Op.</td>
<td>% 5yr Surv</td>
<td></td>
</tr>
<tr>
<td>Open Lobe</td>
<td>1-4</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>VATS Lobe</td>
<td>1</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Open Segment</td>
<td>0-1</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Open wedge</td>
<td>0-1</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

*Source: SWAG*
Conclusions
All Beasts come in many Varieties
Tailored Approach: Summary

Binary treat/not treat thinking is inadequate
We know how to identify less aggressive lung cancers
Lung cancer may be a family of different cancers
We should weigh the behavior of (indolent) lung cancer vs co-morbidities
Observation allows you to assess behavior, weigh factors
Waiting for solid component >2mm (on mediastinal windows) is safe, may be best approach
Collect enough data points to be confident, given the variability in assessing small differences, different scans
Advances in Stage I NSCLC

Consider changes in overall outcomes, understanding of the nature of the cancer in question

Focus on solid/invasive component

Don’t overtreat inconsequential or well-behaved cancers

Multifocal GG/L adeno is an easily identified entity – treat each lesion separately as indicated

Surgical advances: VATS, possibly segmentectomy (but be careful about margins!)

SBRT: clearly less morbidity, a good alternative in patients in whom surgical risk deemed to be high

Be critical of confounding factors when assessing evidence