Minimally Invasive Treatment in NSCLC
- The Japanese Experience and Approach -
Masahiro Tsuboi, M.D., Ph.D.
Group Chair,
Lung Cancer Surgical Study Group in Japan Clinical Oncology Group (JCOG),
Associate-Professor,
Department of Thoracic Surgery & Oncology,
Tokyo Medical University & Hospital
Chief, Department of Thoracic Surgery,
Kanagawa Cancer Center

Surgical Outcome for NSCLC in Japan

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>72.1</td>
<td>77.0</td>
<td>79.5</td>
<td>83.3</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td>49.9</td>
<td>60.1</td>
<td>60.1</td>
<td>66.4</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
<td>48.7</td>
<td>53.8</td>
<td>59.9</td>
<td>60.1</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0</td>
<td>40.6</td>
<td>43.6</td>
<td>42.2</td>
<td>47.2</td>
</tr>
<tr>
<td>IIB</td>
<td>T3N0M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N1M0</td>
<td>35.8</td>
<td>38.0</td>
<td>29.8</td>
<td>32.8</td>
</tr>
<tr>
<td>IIIIB</td>
<td>TanyN2M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>TanyNanyM1</td>
<td>20.8</td>
<td>27.0</td>
<td>20.0</td>
<td>23.2</td>
</tr>
</tbody>
</table>

Asamura H, et al. JTO 2008

What was happened in the past decade?

- Improving of the perioperative care
  - Dry side management
  - No blood transfusion ....
- Changing of the distribution on the histrologic type
  - The increase of the adenocarcinoma (c.f.; Sq; decreasing)
  - The pathological definition of the non-invasive adenocarcinoma; Noguchi classification ....
- The introduction of the CT-screening in clinical practice
  - (since 1994 ??)
  - More smaller lesion was detected?
- Adjuvant therapy ?? etc..

The changes of the number of the patients with cT1 (< 2cm)N0 NSCLC in TMU; 1982-1999
Minimally Invasive Treatment = Limited Resections for Small-sized Lung Cancer: Present Status and Future Directions

- Historical background for limited resection
- Review of literature
- Possible candidates for limited resection
- Future directions

Extent of Parenchymal Resection for Lung Cancer

- Anatomical lobectomy
- Lymph node dissection

Cahan W, J Thorac Surg 1960;39:555

Sublobar resection for lung cancer?

- Wide wedge
- Segementectomy

Lobectomy

Sublobar resection (limited resection)

Pro and Con for Lob & Sub-Lob Resection for T1N0 NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Sublobar Resection</th>
<th>Lobar Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>N</td>
<td>5-year Survival (%)</td>
</tr>
<tr>
<td>Pro lobectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCI [13]</td>
<td>122</td>
<td>37.2*</td>
</tr>
<tr>
<td>Warren [22]</td>
<td>66</td>
<td>40</td>
</tr>
<tr>
<td>Miller [23]</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>Martin [24]</td>
<td>62</td>
<td>49</td>
</tr>
<tr>
<td>Pro sublobar resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exert [25]</td>
<td>109</td>
<td>89</td>
</tr>
<tr>
<td>Pulleto [24]</td>
<td>61</td>
<td>36</td>
</tr>
<tr>
<td>Read [27]</td>
<td>113</td>
<td>84</td>
</tr>
<tr>
<td>Landiavano [26]</td>
<td>101</td>
<td>42</td>
</tr>
<tr>
<td>Chadia [17]</td>
<td>130</td>
<td>93</td>
</tr>
<tr>
<td>Kodama [21]</td>
<td>46</td>
<td>93</td>
</tr>
<tr>
<td>Koke [26]</td>
<td>76</td>
<td>89</td>
</tr>
</tbody>
</table>

* Histologically significant.

LSICG = Lung Cancer Study Group
NA = not available

### Pro and Con for Lob & Sub-Lob Resection for T1N0 NSCLC: recent series

<table>
<thead>
<tr>
<th>First author, year, [reference]</th>
<th>Study period</th>
<th>Number of patients</th>
<th>Type of resection</th>
<th>5-year survival (or other as specified)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada 2006</td>
<td>1992-2001</td>
<td>262</td>
<td>Lobectomy</td>
<td>89.1%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>305</td>
<td>Segmentectomy or wedge</td>
<td></td>
<td>89.6%</td>
<td></td>
</tr>
<tr>
<td>Okumura 2007</td>
<td>1980-2002</td>
<td>1241</td>
<td>Lobectomy</td>
<td>pT1NM0 &lt;= 2 cm in diameter, (excluding large cell carcinomas): 81% &gt; 2 cm: 78% NS for tumors &lt;= 2 cm S for tumors &gt; 2 cm (p = 0.057)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>Segmentectomy</td>
<td>pT1NM0 &lt;= 2 cm in diameter, (excluding large cell carcinomas): 81% &gt; 2 cm: 58%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Risk & Benefit balance

**Lob vs. SEG-WWR**

*based on JCOG0201 data*

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy</th>
<th>Segment.</th>
<th>WWR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts.</td>
<td>562</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (0.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Morbidity</td>
<td>27 (4.8%)</td>
<td>0</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td>Ope. Time</td>
<td>175 m.</td>
<td>187.5 m.</td>
<td>93 m.</td>
</tr>
<tr>
<td>Bleeding</td>
<td>78.5 ml</td>
<td>90 ml</td>
<td>10 ml</td>
</tr>
<tr>
<td>Trans. blood</td>
<td>2.1%</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

### Lobectomy vs Limited Resection for T1N0 NCLC: Summary

- So far lobectomy is a standard mode of resection for stage I lung cancer.
- The morbidity and mortality for lobectomy is tolerable for most of the patients.
- Many retrospective studies are suggesting the equivalent efficacy of limited resection for stage I lung cancer, especially new T1a; 2cm or less in size.

### Are these results applicable for the present-day T1N0 populations?
"GGO" (ground glass opacity)

- Recognized on high-resolution CT
- Localized or focal lesion
- Mild (moderate) increase of CT density, which do not obscure lung structures

"Non-solid GGO"

"Part-solid (mixed) GGO"
AAH (atypical adenomatous hyperplasia)

BAC (bronchioloalveolar carcinoma)

“Solid nodule”

Invasive adenocarcinoma
Radiological-Pathological Correlation

Solid component of GGO represents the feature of invasive growth.

Pathology-CT Correlation

Non-solid GGO -------
  - AAH (atypical adenomatous hyperplasia)
  - BAC (bronchioloalveolar carcinoma)
Part-solid GGO -------
  - BAC (bronchioloalveolar carcinoma)
  - Adenocarcinoma with mixed subtypes (invasive)
Solid -------
  - Adenocarcinoma with mixed subtypes (invasive)

Prognostic Significance of the Size of Central Fibrosis


Prognosis of GGO-BAC tumors:

FIGURE 7. Survival curves according to the WHO classification. The 5-year disease-free survival rates are 100% (BAC), 72.4% (mixed subtypes), 55.6% (solid), and 42.9% (papillary), respectively.
Characteristics of GGO-BAC

1. Female predominance
2. No history of tobacco smoking
3. Multicentricity
4. Indolent nature of non-solid GGO

Results of resection for GGO lesion(s)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>No. Pt</th>
<th>Methods</th>
<th>Prognostic factors</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jang</td>
<td>1996</td>
<td>Radiology</td>
<td>14</td>
<td>-</td>
<td>Focal area of GGO</td>
<td>Not reported</td>
</tr>
<tr>
<td>Aoki</td>
<td>2001</td>
<td>Radiology</td>
<td>127</td>
<td>3cm</td>
<td>GGO &gt; 0.5</td>
<td>96%</td>
</tr>
<tr>
<td>Kodama</td>
<td>2001</td>
<td>Lung Cancer</td>
<td>104</td>
<td>2cm</td>
<td>Visual GGO &gt; 0.5</td>
<td>100%</td>
</tr>
<tr>
<td>Takamochi</td>
<td>2001</td>
<td>JTCVS</td>
<td>269</td>
<td>Ad</td>
<td>TDR &amp; CEA</td>
<td>100%</td>
</tr>
<tr>
<td>Kim/Johkoh</td>
<td>2001</td>
<td>AJR</td>
<td>224</td>
<td>3cm Ad</td>
<td>GGO extent</td>
<td>Not reported</td>
</tr>
<tr>
<td>Matsuguma</td>
<td>2002</td>
<td>JTCVS</td>
<td>111</td>
<td>cIA</td>
<td>Visual GGO &gt; 0.5</td>
<td>100%</td>
</tr>
<tr>
<td>Takushima</td>
<td>2002</td>
<td>Lung Cancer</td>
<td>64</td>
<td>2cm</td>
<td>CT GGO &gt; 0.57</td>
<td>100%</td>
</tr>
<tr>
<td>Suzuki</td>
<td>2002</td>
<td>ATS</td>
<td>69</td>
<td>cIA Ad</td>
<td>GGO &gt; 50%</td>
<td>100%</td>
</tr>
<tr>
<td>Okada</td>
<td>2003</td>
<td>ATS</td>
<td>167</td>
<td>TDR</td>
<td>TDR &amp; GGO &gt; 0.5</td>
<td>100%</td>
</tr>
<tr>
<td>Ohde</td>
<td>2003</td>
<td>Lung Cancer</td>
<td>98</td>
<td>3cm Ad</td>
<td>Dimension GGO &gt; 50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

SAME SIZE, BUT NOT SAME CANCER (different stage of tumor progression)

Sub-solid GGO ≠ Solid Adenocarcinoma
What Should Be the Intervention for GGOs?

Factors Affecting the Strategy
- Character of lesion
  - (non-solid vs. solid GGO)
- Size
- Location

BASIC STRATEGY
- Indolent cancer (tumor)
  - Careful watching
- Non-invasive cancer
  - Minimally-invasive cancer
    - Limited resection
  - Invasive cancer
    - Radical resection

STRATEGY for Management of GGOs
- Non-solid
  - Follow-up, obligation for 3 months
  - 15<=Size
    - Disappear
    - F/U
    - Lobectomy/Segmentectomy
  - Size>15mm
    - Inner
    - Outer
    - Lobectomy/Segmentectomy
    - Segmentation/WW

- Part-solid
  - 15<=Size
    - Inner
    - Outer
    - Lobectomy/Segmentectomy
    - Segmentation/WW
  - Size>15mm
- * If frozen diagnosis suggests invasive feature, lobectomy may be performed.
**Intervention for GGO-BACs**

1. **Non-solid GGO:**
   - 10-15 mm ≥ Careful Watching by HI-RESO CT
   - 10-15 mm < Wide wedge/Segmentectomy

2. **Part-solid GGO:**
   - 10-15 mm ≥ Segmentectomy/Wide wedge
   - 10-15 mm < Lobectomy (Segmentectomy)
   - 50% (solid part) < Lobectomy

* In case of inner location, lobectomy is recommended.

**Part-solid, Lobectomy**

**Non-solid, Lobectomy**

**Technical issues of Limited Resection**
Pro & Con for Lob vs. Limited Resection for T1N0 NCLC

The intraoperative decision of the surgical margin is very important.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>5-year Survival (%)</th>
<th>Local Recurrence (%)</th>
<th>N</th>
<th>5-year Survival (%)</th>
<th>Local Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro lob resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCSC [19]</td>
<td>122</td>
<td>44</td>
<td>37.7%</td>
<td>129</td>
<td>69%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Yamanouchi [20]</td>
<td>66</td>
<td>43</td>
<td>22.7%</td>
<td>109</td>
<td>77%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Miller [34]</td>
<td>35</td>
<td>59</td>
<td>7%</td>
<td>78</td>
<td>71%</td>
<td>13%</td>
</tr>
<tr>
<td>Naruke [34]</td>
<td>62</td>
<td>59</td>
<td>9%</td>
<td>113</td>
<td>77%</td>
<td>24%</td>
</tr>
<tr>
<td>Pro-van Sliedrecht</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over [20]</td>
<td>180</td>
<td>69%</td>
<td>Na</td>
<td>97</td>
<td>75%</td>
<td>Na</td>
</tr>
<tr>
<td>Petrelli [21]</td>
<td>65</td>
<td>55%</td>
<td>36%</td>
<td>411</td>
<td>69%</td>
<td>38%</td>
</tr>
<tr>
<td>Reed [37]</td>
<td>115</td>
<td>84%</td>
<td>6.4%</td>
<td>150</td>
<td>74%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Luchtenbrinck [30]</td>
<td>102</td>
<td>82%</td>
<td>39%</td>
<td>187</td>
<td>70%</td>
<td>9%</td>
</tr>
<tr>
<td>Oda [17]</td>
<td>150</td>
<td>91%</td>
<td>Na</td>
<td>150</td>
<td>70%</td>
<td>Na</td>
</tr>
<tr>
<td>Kikawara [22]</td>
<td>46</td>
<td>95%</td>
<td>2.2%</td>
<td>77</td>
<td>88%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Kikawara [30]</td>
<td>76</td>
<td>87%</td>
<td>13.7%</td>
<td>158</td>
<td>80%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

* Statistically significant at the 0.05 level.

Easy vs. Difficult Location for Limited Resection

Basic strategy for Segmentectomy

Critical issues:
- How to manage the intersegmental vein
- How to decide surgical margin?

Typical segmentectomy
Convenient Segmentectomy

Radical Segmentectomy - 1

Radical Segmentectomy - 2

Wide Wedge resection
How to make intersegmental faces?

Which is the prior procedure for the preservation of the postoperative pulmonary function?

What is the most suitable procedure for preserving lung function?

Stapling vs. Direct dividing

Technical standardization and Consensus for Sublobar resection should be needed soon.

ESTS is considering this project as the postgraduate course in 2009.

STS/AATS/ACOSOG ?

Non-surgical approach as Minimally Invasive Tx.
New Possibilities for GGOs or small-sized NSCLC Other than Surgery

- Radiation therapy
  - SBRT, Radiosurgery
- Ablations
  - RFA, Microwave
  - Cryotherapy

Background

- Japanese investigators’ reports; equivalent to surgery?
  - many censored cases/insufficient f/u
  - pts selection/more peripheral lesions
  - many post hoc subgroup analyses

We do NOT have prospective data in operable pts with T1N0M0 NSCLC.

JCOG 0403
A PHASE II STUDY OF STEREOTACTIC BODY RADIATION THERAPY IN PATIENTS WITH T1N0M0 NON-SMALL CELL LUNG CANCER

- To evaluate the safety and efficacy of SBRT for T1N0M0 NSCLC
  - SBRT as a standard care in medically inoperable pts
  - SBRT as a treatment option in operable pts
- Primary endpoint, 3-year overall survival
- Sample size, 165 (started on 20/07/2004)
  - operable, 65
  - inoperable, 100

Eligibility Criteria

- Pathologically proven NSCLC
- T1N0M0
- Medically inoperable or operable (refused surgery)
- PS 0-2
- PaO2 > 60 torr
- FEV1.0 > 700 ml
- Signed informed consent

Operability is judged by surgeons
JCOG 0403
A PHASE II STUDY OF STEREOTACTIC BODY RADIATION THERAPY IN PATIENTS WITH T1N0M0 NON-SMALL CELL LUNG CANCER

✓ Treatment
- 4-10 MV X rays
- 48 Gy in 4 fractions over 4-8 days
- prescribed to the isocenter
- heterogeneity corrected dose
- algorithm, pencil beam; NOT superposition
- CTV = GTV
- PTV = ITV + 5 mm
- MLC margin, 5 mm
- 5-10 static beams or multiple arc beams ≥ 400 deg

Future Directions

Kid’s park
**BASIC STRATEGY for Surgery in small-sized NSCLC**

- Non-invasive cancer
  - Minimally-invasive cancer
    - Limited resection
- Invasive cancer
  - Radical resection

**Critical issues Lob vs. SEG-WWR**

- Really less invasive?
  - Operative time, Hospital stay
  - Morbidity/mortality
- Really preserving lung function?
  - Short-time function vs. Long-term function

**Clinical trials for Minimally Invasive approach in Japan**

What is a standard procedure for cT1aN0M0 NSCLC?

**JCOG/WJOG trials for stage IA (T1aN0M0) NSCLC**

- 0%<Solid<25%
  - One-arm, wide wedge resection (phase II)
- 25%<Solid<100%
  - Lobectomy vs. Limited (Seg) (phase III)
Study 1: JCOG0804/WJOG4507L; Phase II Trial of Limited Resection (Wide wedge resection) for Possible Early Adenocarcinomas (GGO – Part-solid GGO); (Single-arm study)

- Subject ---- Non-solid GGO or part-solid GGO
  Solid part < 25%
- Why one arm? ----- Very few event (cancer-related death) to perform comparative study
- Intervention ----- Wide Wedge resection
- Endpoint ------ Recurrence-free survival rate at any site
- Sample size----300 patients

Study 2: JCOG0802/WJOG4607L; Phase III Randomized Trial between Lobectomy and Limited Resection for Small-sized carcinoma (Part-solid GGO – Solid 2cm or Less)

- PI: Asamura H.
- Peripheral carcinoma, <= 2 cm Negative hilar node
- Lobectomy
- Segmentectomy
- Stratified factors:
  Institute, Gender, Histology (Ad vs, Non-ad), Solid or non-solid
- Endpoints:
  Primary: OS
  Secondary: pulmonary function
  Sample size: 1,100

Comparison of CALGB140503 with JCOG0802/WJOG

- CALGB140503: Intergroup; Phase III Randomized Trial between Lobectomy and Sublobar Resection for Small-sized carcinoma
  - PI: Altorki N
  - Peripheral carcinoma, <= 2 cm Negative hilar node
  - Lobectomy
  - Sublobar resection (segmentectomy/ wedge)
  - Stratified factors:
    Tumor size, Histology (Sq vs. non-sq?), Smoking status
  - Endpoints:
    Primary: DFS
    Secondary: OS, pulmonary function
  - Sample size: 1,300

- JCOG0802/WJOG:
  - Peripheral small (2cm or less) NSCLC without pure GGO lesion
  - Peripheral small (2cm or less) NSCLC without non-invasive lung cancer on Chest CT-scan
  - Trial design: Randomized phase III / non-inferiority trial
  - Target number: 1297 cases (908 cases after randomization) / 5 years / 3.25 years
  - Standard arm: Lobectomy
  - Investigational arm: Wedge resection or Segmentectomy
  - Primary endpoint: Progression Free Survival
  - Secondary endpoints: OS, Local recurrence rate, Distant recurrence rate, Postope. pulmonary function at 6 months (FRV1.0, FVC)
  - Sample size: 1,100

Comparison:

<table>
<thead>
<tr>
<th></th>
<th>CALGB140503</th>
<th>JCOG0802/WJOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Peripheral small (2cm or less) NSCLC without pure GGO lesion</td>
<td>Peripheral small (2cm or less) NSCLC without non-invasive lung cancer on Chest CT-scan</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized phase III / non-inferiority trial</td>
<td>Randomized phase III / non-inferiority trial</td>
</tr>
<tr>
<td>Target number:</td>
<td>1297 cases (908 cases after randomization) / 5 years / 3.25 years</td>
<td>1100 cases / 3 years / 5 years</td>
</tr>
<tr>
<td>Standard arm</td>
<td>Lobectomy</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>Investigational arm</td>
<td>Wedge resection or Segmentectomy</td>
<td>Segmentectomy</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Progression Free Survival</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>OS, Local recurrence rate, Distant recurrence rate, Postope. pulmonary function at 6 months (FRV1.0, FVC)</td>
<td>Postope. pulmonary functions at 3 months and 1 year, DFS, Local recurrence rate, Adverse events, hospitalization, chest drainage term, Operative time, bleeding amount, number of auto-staplers</td>
</tr>
</tbody>
</table>
Comparison of CALGB140503 with JCOG0802/WJOG

<table>
<thead>
<tr>
<th>Eligibility criteria (2nd registration during operation)</th>
<th>CALGB140503</th>
<th>JCOG0802/WJOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymph node metastasis by frozen diagnosis: Right (#4, #7, #10), Left (#5, #6, #7, #10)</td>
<td>Frozen; not mandatory. No non-curative factor, such as malignant pleural effusion and dissemination, both Lobectomy and Segmentectomy are possible</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Pure GGO, Carcinoid tumor</td>
<td>Carcinoid tumor</td>
</tr>
</tbody>
</table>

Stratified factors

- Tumor size (1.5 > vs. 1.5 cm=<)
- Smoking history
- Histology

Stratified factors

- Institute
- Histology (aden. Vs. non-adeno.)
- Gender
- Age (70 y.o.>, vs. 70=<)
- Thin-slice CT findings (solid vs. non-solid)

Postoperative follow-up

CT: 8, 12 months, and then every year
CT: every 6 months

Conclusions

- Many retrospective studies are suggesting the equivalent efficacy of limited resection for stage I lung cancer.
- Prospective clinical trials are on going.
  - New standard approach of small-sized NSCLC will be established.
- Technical consensus for sub-lobar resection should be needed in the worldwide.

Thank You for Your Attention.
Lobectomy vs. Limited Resection for T1N0 NSCLC: A Lung Cancer Study Group
Ann Thorac Surg 1995; 60: 615-23

267 Pts. randomized
247 Pts. Eligible for analysis

Randomize

Peripheral carcinoma on CXR, < 3 cm Negative hilar node

Lobectomy

Limited resection

Endpoints:
Primary: OS
Secondary: pulmonary function
Sample size: 80 deaths and 70 recurrences to occur with a power of .90 to detect a 1.8 fold difference in median survival

Reports on the Comparison btwn Lobectomy & Limited Resection for T1N0 NCLC:
A Lung Cancer Study Group

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>No. of limited resection</th>
<th>No. of lobectomy</th>
<th>Survival difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffmann and Ransdell (1980)</td>
<td>RS</td>
<td>33 (W)</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>Read et al (1990)</td>
<td>RS</td>
<td>113 (87S+6W)</td>
<td>131</td>
<td>NS (CSS)</td>
</tr>
<tr>
<td>Date et al (1994)</td>
<td>MPS</td>
<td>16 (65+10W)</td>
<td>16</td>
<td>Lobectomy better</td>
</tr>
<tr>
<td>Warren and Faber (1994)</td>
<td>RS</td>
<td>66 (S)</td>
<td>103</td>
<td>Lobectomy better</td>
</tr>
<tr>
<td>Harpole et al (1995)</td>
<td>RS</td>
<td>75 (W)</td>
<td>193</td>
<td>NS (CSS)</td>
</tr>
<tr>
<td>LCSG (1996)</td>
<td>RCT</td>
<td>122 (82S+40W)</td>
<td>125</td>
<td>NS</td>
</tr>
<tr>
<td>Kodema et al (1997)</td>
<td>RS</td>
<td>46 (W)</td>
<td>77</td>
<td>NS</td>
</tr>
<tr>
<td>Landreneau et al (1997)</td>
<td>RS</td>
<td>102 (W)</td>
<td>117</td>
<td>NS</td>
</tr>
<tr>
<td>Pastirino et al (1997)</td>
<td>RS</td>
<td>53 (S+W)</td>
<td>367</td>
<td>NS</td>
</tr>
<tr>
<td>Kwiatkowski et al (1998)</td>
<td>RS</td>
<td>58 (S+W)</td>
<td>186</td>
<td>Lobectomy better</td>
</tr>
<tr>
<td>Gkado et al (2003)</td>
<td>RS</td>
<td>70 (S)</td>
<td>139</td>
<td>NS</td>
</tr>
<tr>
<td>Koike et al (2003)</td>
<td>RS</td>
<td>74 (60S+14W)</td>
<td>159</td>
<td>NS</td>
</tr>
<tr>
<td>Campione et al (2004)</td>
<td>RS</td>
<td>21 (S)</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Keenan et al (2004)</td>
<td>RS</td>
<td>94 (S)</td>
<td>147</td>
<td>NS</td>
</tr>
</tbody>
</table>

Lobectomy vs. Limited Resection for T1N0 NSCLC:
A Lung Cancer Study Group
Ann Thorac Surg 1995; 60: 615-23

- Lobectomy (125) vs. Limited (122) (82, Seg; 40, Wedge)
- Survival was improved in the Lob group but was of borderline statistical significance.
- Local-regional recurrence rate showed a 3-fold increase with limited resection.
- 25% of pts. of clinically staged as T1N0 were found to have positive mediastinal LN.
**Lobectomy vs Limited Resection for T1N0 NSCLC:**
A Lung Cancer Study Group
Ann Thorac Surg 1995; 60: 615-23

**CONCLUSION:**
Lobectomy with systematic hilar/mediastinal LN sampling/dissection should remain the standard surgical treatment for clinical T1N0 tumors.

**Critiques:**
- A meta-analysis of 14 comparative studies between lobectomy and limited resection for stage I lung cancer
- 13 retrospective studies and 1 randomized study
- Stages, IA only (9), IA+IB (5)
- Endpoint, a combined survival difference at 1, 3, and 5 years
**Lobectomy vs Limited Resection for T1N0 NCLC:**
A meta-analysis of 14 comparative studies

*Nakamura H et al. Br J Cancer 2005; 92: 1033-7*

**Results:**
- 1YS; 0.7%
- 3YS; 1.9%
- 5YS; 3.6%

**Conclusion:**
While survival after lobectomy was slightly better than that after limited resection at 1, 3, and 5 years postoperatively, the differences were not statistically significant.

---

**Cautious note:**
- Application of meta-analysis method for retrospective studies
- Heterogeneity among studies (indication for surgery)
- Publication bias

**Results of careful watching**

(1) Demographic data
SEX: male (50, 36.8%), female (86, 61.2%)
AGE: 62.1 years (35 - 81)
FOLLOW-UP PERIOD: 29.9M (6.6-83.7)

(2) Type of lesion
Non-solid 97 (71.3%)
Part-solid or SC 32 (23.5%)
Solid 7 (5.2%)

(3) Size
1cm or less 80 (58.8%)
More than 1cm 56 (41.2%)

(4) History of previous lung cancer
Yes 14 (10.3%)
No 122 (89.7%)

Fate of GGOs According to CT Appearance (1998-2004): N=136

Fate of GGOs According to History of Previous Lung Cancer (1998-2004): N=136

Fate of GGOs According to Size (1998-2004): N=136
Predictors of Increase in Size

Multivariate analysis

<table>
<thead>
<tr>
<th>Probability</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size (mm: continuous variable)</td>
<td>0.002</td>
<td>1.437</td>
</tr>
<tr>
<td>Shape of tumor (irregular vs round)</td>
<td>1.014</td>
<td>24.889</td>
</tr>
</tbody>
</table>

Summary so far

1. Sub-centimeter lung tumors showing non-solid GGO on HRCT tend to be stable in size.
2. Shape of tumor and tumor size were significant predictors for increase in size of GGO tumors.
3. GGO tumors found in patients who had a history of lung cancer tend to grow up fast.

% PAPILLARY ADENOCARCINOMA
BY MAJOR SUBTYPE

<table>
<thead>
<tr>
<th>Prominent Subtype</th>
<th>Kim et al N=36</th>
<th>Takano et al N=66</th>
<th>Nakamura et al N=130</th>
<th>Motoi et al N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinar</td>
<td>5 (14%)</td>
<td>18 (27%)</td>
<td>5 (4%)</td>
<td>30 (30%)</td>
</tr>
<tr>
<td>Papillary</td>
<td>17 (47%)</td>
<td>30 (45%)</td>
<td>62 (48%)</td>
<td>37 (37%)</td>
</tr>
<tr>
<td>BAC</td>
<td>7 (19%)</td>
<td>9 (14%)</td>
<td>15 (12%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Solid</td>
<td>7 (19%)</td>
<td>5 (8%)</td>
<td>21 (16%)</td>
<td>25 (25%)</td>
</tr>
</tbody>
</table>

Nakamura Y: Ca Sci 98:1006-1013

A Natural History of Peripheral Adenocarcinomas
(Well differentiated histology)

PURE GGO
Complex GGO with solid component
INDOLENT!
Solid tumor with vascular and bronchial convergence
Solid tumor
Does GGO Grow?

Yes.

GGO, enlarged

Feb 7/ 2001  July 7/ 2003

Jan 21/ 2001  Jan 15/ 2003
Does GGO *Always* Grow?

No, not *always*.