Can we expand the role of surgery in stage III NSCLC?

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**SURGICAL THERAPY**

**Stage III NSCLC**

- stage III locally advanced disease
  - IIIA T3N1 usually incidental finding
    - N2 controversial
  - IIIB T4 specific indications
    - N3 unusual
- final aim = complete resection

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**COMPLETE RESECTION**

- R0 : no residual tumor
- R1 : microscopic residual tumor
- R2 : macroscopic residual tumor
**IASLC : Complete Resection Subcommittee**

**Complete resection R0**

- free resection margins proved microscopically
- systematic or lobe-specific systematic nodal dissection: \( \geq 6 \) nodes (3 mediastinal)
- no extracapsular extension in nodes removed separately or at the margin of the lung specimen
- highest mediastinal lymph node must be negative


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**NSCLC INDICATIONS FOR SURGERY**

- **Definite**: clinical stage IA T1N0
  IB T2N0
  IIA T1N1
  IIB T2N1 T3N0
  IIIA T3N1

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**NSCLC INDICATIONS FOR SURGERY**

- **Investigational**: clinical stage IIIA - N2
  IIIB - T4
  IIIB - N3

- **Exceptional**: clinical stage IV – single metastasis
  IV – multiple metastases
### SURGERY FOR NSCLC

#### Stage III

**Types of resection**

- **Stage IIIA** T3N1
  - unexpected N2
  - potentially resectable N2

- **Stage IIIB** T4 N3

#### Conclusions

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### PULMONARY RESECTIONS

- **standard**
  - lobectomy, bilobectomy
  - pneumonectomy

- **atypical, lung-sparing operations**
  - proximal: bronchoplasties
  - distal: segmentectomy, wedge excision

- **extended**
  - chest wall, diaphragm, pericardium,
  - left atrium, SVC, apex of chest (Pancoast)
sleeve resection
azygos vein
R pulmonary art.
intermediate bronchus
R main bronchus

chest wall resection

CT scan of the chest
SURGERY FOR NSCLC

Stage III

Types of resection

Stage IIIA

T3N1

unexpected N2

potentially resectable N2

Stage IIIB

T4

N3

Conclusions

T3N1 incidental, unexpected N2

- T3N1 usually incidental finding when operating T3, adjuvant chemotherapy
- unexpected, surprise N2 peroperative, frozen section
- final pathology


- thoracotomy: ≈ 20 % unexpected N2, even after mediastinoscopy
  1 nodal station, complete resection (highest node ->)
  5 year - survival: 14 - 30 %
  30 % skip metastases without N1
  importance of systematic nodal dissection

incidental, unexpected N2

- adjuvant radiotherapy:
  ↓ local recurrence, no ↑ survival
  especially indicated when multiple, extranodal N2, R1 disease

- adjuvant cisplatin-based chemotherapy:
  survival benefit (IALT 2004, ANITA 2006)

- Chest 2007; 132:243S-45S: in patients with resected NSCLC who were found to have incidental (occult) N2 disease, adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence
SURGERY FOR NSCLC
Stage III

Types of resection
Stage IIIA T3N1
- unexpected N2
- potentially resectable N2
Stage IIIB T4 N3

Conclusions

Stage IIIA- bulky N2

- 9 54-year-old
- chronic cough

mediastinoscopy +2, 3, 4R
stage IIIA-N2
induction chemotherapy
Stage IIIA- bulky N2

- reMS negative
- extrapleural lobectomy + systematic nodal dissection
- pathology: complete response
- follow-up 10 years: no recurrence or metastases

Why is downstaging important?

- prognostic factors after induction therapy
  - complete surgical resection
  - clearance mediastinal lymph nodes


Surgery for N2 disease

- EORTC 08941
  - stage IIIA-N2 NSCLC
  - phase III induction CT; in case of response: randomization between surgery and RT
  - 167 pts surgery

- Intergroup trial 0139
  - stage IIIA-N2 NSCLC
  - phase III concurrent CT/RT versus CT/RT induction + surgery
  - 164 pts surgery

Albain KS. J Clin Oncol 2005; 23 no.165-164s (abstr. 7914)
### Comparison EORTC 08941 – INT 0139

#### Induction Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>EORTC 08941</th>
<th>INT 0139</th>
</tr>
</thead>
<tbody>
<tr>
<td>chemotherapy</td>
<td>50%</td>
<td>71%</td>
</tr>
<tr>
<td>chemoradiotherapy</td>
<td>13.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>complete resection</td>
<td>56%</td>
<td>52%</td>
</tr>
<tr>
<td>expl. thoracotomy</td>
<td>N0: 13.6%</td>
<td>N0: 4.5%</td>
</tr>
<tr>
<td>ypN0/1/2</td>
<td>N2: 56%</td>
<td>N1-3: 54%</td>
</tr>
<tr>
<td>ypT0/N0</td>
<td>5.2%</td>
<td>14.4%</td>
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</tbody>
</table>

#### 30-Day Mortality

<table>
<thead>
<tr>
<th>Mortality</th>
<th>EORTC 08941</th>
<th>INT 0139</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.9%</td>
<td>5%</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>6.9%</td>
<td>R: 5.3%</td>
</tr>
<tr>
<td>Expl. Thoracotomy</td>
<td>4.8%</td>
<td>0%</td>
</tr>
<tr>
<td>90-Day Mortality</td>
<td>8.4%</td>
<td></td>
</tr>
</tbody>
</table>

#### 5-Year Survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>EORTC 08941</th>
<th>INT 0139</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>27%</td>
<td>36%</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>12%</td>
<td>22%</td>
</tr>
<tr>
<td>ypN0/1/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0: 29%</td>
<td>N0: 41%</td>
<td></td>
</tr>
<tr>
<td>N2/3: 7%</td>
<td>N1-3: 24%</td>
<td></td>
</tr>
<tr>
<td>p = .009</td>
<td>p &lt; .0001</td>
<td></td>
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Comparison
EORTC 08941 – INT 0139

Local recurrence

<table>
<thead>
<tr>
<th></th>
<th>EORTC 08941</th>
<th>INT 0139</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>32 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>55 %</td>
<td>22 %</td>
</tr>
<tr>
<td>p-value</td>
<td>p = .001</td>
<td>p = .002</td>
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</tbody>
</table>

EORTC 08941
Overall survival in randomized pts

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>165</td>
<td>167</td>
</tr>
<tr>
<td>FU, median</td>
<td>73.1</td>
<td>67.2</td>
</tr>
<tr>
<td>OS, median (m)</td>
<td>17.5</td>
<td>16.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>15.8-19.2</td>
<td>14.0-19.0</td>
</tr>
<tr>
<td>5y SR (%)</td>
<td>14.0</td>
<td>15.7</td>
</tr>
<tr>
<td>HR</td>
<td>0.84-1.35</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Intergroup 0139/RTOG 9309
Overall Survival by Treatment Arms

Dead/Total
- CT/RT/S: 145/202
- CT/RT: 155/194

Logrank p = 0.24
Hazard ratio = 0.87 (0.70, 1.10)
**Intergroup 0139/RTOG 9309**

**Progression-Free Survival by Treatment Arms**

- **CT/RT/S** 159/202
- **CT/RT** 172/194

Logrank $p = 0.017$

Hazard ratio = 0.77 (0.62, 0.96)

**Exploratory survival analysis**

- All but 1 postoperative death followed a pneumonectomy
- Hypothesized survival advantage on CT/RT/S if lobectomy performed
- Patients with lobectomy were completely matched with patients on CT/RT arm on 4 prestudy factors: KPS, age, sex, T stage

Feasible for n= 90/98

**INT 0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset**

- **MS**
  - 5 yr OS: 34 mos. 36%
  - 5 yr OS: 22 mos. 18%

Logrank $p = 0.002$
EORTC – INT trials
Lessons learnt

- Persistent ypN2 disease after induction therapy: poor prognosis
- ypN2 marker of systemic disease
- 50% in both INT and EORTC trials → ↓ survival
- Focus on pathological restaging of mediastinum (EBUS, EEUS, mediastinoscopy)
- Surgery probably beneficial: in case of mediastinal downstaging – lobectomy, complete resection

SURGERY FOR NSCLC
Stage III

Types of resection
Stage IIIA
- T3N1
- Unexpected N2
- Potentially resectable N2

Stage IIIB
- T4
- N3

Conclusions

Stage IIIB
- IIIB T4 - N3: rare indications surgical resection
- Long-term survival: complete resection
- Excellent general condition
- N2 – N3 nodes negative (SWOG 8805)
- cT4N0: 5-year survival 30%
  - Tumors of carina and distal trachea
  - Left atrium
  - Superior vena cava
  - Vertebral bodies
- Induction therapy, especially Pancoast: CT-RT
T4 – great vessels

intrapericardial resection

T4 – superior vena cava

patch, PTFE prosthesis

Stage IIIA-B
Induction chemotherapy + surgery

- Spanish Lung Cancer Group phase II 9901 trial
- 136 patients 19 centers stage IIIA-N2 and selected T4N0-1
- induction chemotherapy + surgery

- stage IIIA-N2 69 pts  stage IIIB 67 pts
- ORR 56%  90 pts operated (23 SD)  pneumonectomy 41%
- complete resection 69% operated pts, 48% all assessable pts
- † 7.8% major comp. 30%

Stage IIIA-B
Induction chemotherapy + surgery

- overall MST 16 mos. • no A IIIA-B
- complete resection (n=62) MST 49 mos
  5-year survival 41%
  stage IIIA n=33 32%
  IIIB n=29 53%
- multivariate analysis: complete resection, clinical response, age < 60 y
- 7th edition TNM T4N0-1 → stage IIIA


Case: additional lung nodule

47-year ♂
- incidently found tumor RML + additional nodule RUL

CT 270807

Case: additional lung nodule

- 3rd lesion along major fissure
  - lesion RML + RUL PET +

CT 270807
PET 290807
Case: additional lung nodule

- mediastinoscopy: intranodal metastasis 2R
- induction chemotherapy: partial response

PET 290807

Case: additional lung nodule

- chest CT: partial response RML, complete response RUL

CT 291107

Case: additional lung nodule

- PET: only slight uptake RML
- 070108: R thoracotomy
  lobectomy RML
  necrotic adenocarcinoma ypT1N1
  wedge RUL
- NSCLC, no further typing
excision nodule apex RLL
  benign nodule
- RUL: metastasis? second primary?

PET 051207
**Additional nodules T3 – T4 – M1?**

- IASLC: International Staging Committee
- preparation 7th edition TNM 2009
- large database 100,869 pts - factor T 18,198
- pT4 nodules = lobe (n=363) ≈ survival T3
- 5-year survival 28%
- better than “other” T4
- p<0.003 excluding pleural dissemination
- pM1 ipsilateral nodules ≠ lobe (n=180) ≈ survival T4
- 5-year survival 22%


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**Additional nodules**

![Graph showing survival rates](image)


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**Additional nodules proposals IASLC**

- satellite nodules
  - lobe
  - ipsilateral nodules
- pT4 ≠ lobe
- pleural dissemination
  - T4 → M1a

SURGERY FOR NSCLC
Stage III

Types of resection
Stage IIIA
- T3N1
  - unexpected N2
  - potentially resectable N2

Stage IIIB
- T4 N3

Conclusions

Can we expand the role of surgery in stage III NSCLC?

YES, we can

Stage IIIA
- T3N1 usually incidental finding, adjuvant chemotherapy
- surprise, unexpected N2: complete resection, adjuvant chemo-± radiotherapy
- potentially resectable N2: downstaging, lobectomy

Stage IIIB
- T4 specific indications; additional, ipsilateral nodules
- N3 unusual, downstaging (invasive procedure)

Final aim = complete resection, irrespective of stage

Thank you for your attention!

Antwerp