Lung cancer
– diagnosis, staging and treatment of early/locally advanced disease

Prof. Rafal Dziadziuszko,
Dept. of Oncology and Radiotherapy,
Medical University of Gdańsk, Poland
Conflict of Interest Disclosure:

Honoraria for advisory boards and lectures:

- Roche
- Pfizer
- Astra-Zeneca
- Novartis
- Bristol-Myers Squibb
- Seattle Genetics
- MSD
- Takeda
Lung cancer

- Responsible for about one-third of all cancer deaths
- Accounts for more deaths than breast cancer, prostate cancer and colon cancer COMBINED
- ~85% of patients who develop lung cancer will die of the disease
10 top causes of lung cancer

1. smoking
2. smoking
3. smoking
4. smoking
5. smoking
6. smoking
7. smoking
8. smoking
9. smoking
10. other causes
Epidemiology and tobacco control
Lung cancer mortality in selected countries

http://www-dep.iarc.fr/WHOdb/WHOdb.htm; slide courtesy of Dr. J. Didkowska
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

Table 7. Cause of Death on the Death Certificate, According to Screening Group.*

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Low-Dose CT Group</th>
<th>Radiography Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number/total number (percent)</td>
<td>number/total number (percent)</td>
<td>number/total number (percent)</td>
</tr>
<tr>
<td>Neoplasm of bronchus and lung†</td>
<td>427/1865 (22.9)</td>
<td>503/1991 (25.3)</td>
<td>930/3856 (24.1)</td>
</tr>
<tr>
<td>Other neoplasm</td>
<td>416/1865 (22.3)</td>
<td>442/1991 (22.2)</td>
<td>858/3856 (22.3)</td>
</tr>
<tr>
<td>Cardiovascular illness</td>
<td>486/1865 (26.1)</td>
<td>470/1991 (23.6)</td>
<td>956/3856 (24.8)</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>175/1865 (9.4)</td>
<td>226/1991 (11.4)</td>
<td>401/3856 (10.4)</td>
</tr>
<tr>
<td>Complications of medical or surgical care</td>
<td>12/1865 (0.6)</td>
<td>7/1991 (0.4)</td>
<td>19/3856 (0.5)</td>
</tr>
<tr>
<td>Other</td>
<td>349/1865 (18.7)</td>
<td>343/1991 (17.2)</td>
<td>692/3856 (17.9)</td>
</tr>
</tbody>
</table>
WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

Edited by
William D. Travis, Elisabeth Brambilla, Allen P. Burke, Alexander Marx, Andrew G. Nicholson
Lung cancer: Common histological diagnoses

- Non-small cell lung cancer (NSCLC) ~ 85%
  - squamous-cell carcinoma
  - adenocarcinoma
  - large cell carcinoma
  - NSCLC NOS (not-otherwise specified)
- Small cell lung cancer (SCLC) ~ 15%
Lung cancer:
Rare histological diagnoses (~5%)

- Large-cell neuroendocrine carcinoma
- Carcinoid (typical/atypical)
- Sarcomatoid carcinoma
- Salivary gland type carcinomas (mucoepidermoid, adenoid cystic carcinoma)
- Pulmonary blastoma
Lung cancer symptoms

- Associated with local growth
- Associated with distant metastases
- General and paraneoplastic symptoms
Local lung cancer symptoms

- Persistent cough
- Haemoptysis
- Shortness of breath
- Recurrent pneumonia
- Chest, shoulder, or back pain
- Wheezing
- Hoarseness
- Swelling in the neck and face
  (superior vena cava syndrome, SVCS)
- Difficulty swallowing - dysphagia
Symptoms associated with distant metastases

- Bone pain (rib, spine...)
- Pathological fracture
- Spinal cord compression symptoms
- Enlarged lymph nodes (cervical, supraclavicular...)
- Pain in the upper abdomen
- Headaches and dizziness
General symptoms

- Weight loss and anorexia
- Fatigue and weakness
- Fever
## NSCLC vs SCLC: major differences
(simplified picture...)

<table>
<thead>
<tr>
<th>Feature</th>
<th>NSCLC</th>
<th>SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor growth</td>
<td>Relatively slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Type of growth</td>
<td>Mainly loco-regional</td>
<td>Rapid dissemination</td>
</tr>
<tr>
<td>Sensitivity to chemotherapy</td>
<td>Low/moderate</td>
<td>High</td>
</tr>
<tr>
<td>Main treatment modality</td>
<td>Surgery</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>
Diagnostic procedures in NSCLC: first steps

• Clinical history (smoking, symptoms, weight loss, performance status ...)
• Clinical examination
• Chest radiography/CT scan
## Diagnostic procedures in NSCLC: second step

<table>
<thead>
<tr>
<th>Examination</th>
<th>Patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoscopy</td>
<td>All patients</td>
</tr>
<tr>
<td>Transthoracic fine/core needle biopsy</td>
<td>Peripheral tumor</td>
</tr>
<tr>
<td>CT chest and upper abdomen</td>
<td>All patients</td>
</tr>
<tr>
<td>Bone scan</td>
<td>If symptoms present</td>
</tr>
<tr>
<td>Brain CT or MRI</td>
<td>Stage II - III patients</td>
</tr>
<tr>
<td>PET/CT</td>
<td>All patients considered for radical surgery or radiotherapy</td>
</tr>
</tbody>
</table>
Additional diagnostic procedures in NSCLC

- USG-guided nodal fine needle aspiration (to confirm nodal involvement)
  - transbronchial (EBUS)
  - transesophageal (EUS)
- Thoracoscopy (if pleural effusion)
- Biopsy of peripheral lymph nodes or other metastatic lesions
- Cardiac evaluation - Echocardiogram
- Pulmonary function tests
- 6-minute walking test
A bronchoscope is used to view the airways and check for any abnormalities.
Bronchoscopy devices
Mediastinoscopy
Transthoracic fine needle aspiration or core needle biopsy
Transthoracic fine/core needle biopsy
Lung cancer stages
The Eighth Edition Lung Cancer Stage Classification

Frank C. Detterbeck, MD, FCCP; Daniel J. Boffa, MD; Anthony W. Kim, MD, FCCP; and Lynn T. Taneue, MD, FCCP

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

Journal of Thoracic Oncology  Vol. 11 No. 1: 39-51
Lung cancer stages and survival, TNM 8ed.

![Graph showing survival rates across different stages of lung cancer.](image)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Events / N</th>
<th>MST</th>
<th>24 Month</th>
<th>60 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>68 / 781</td>
<td>NR</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>IA2</td>
<td>505 / 3105</td>
<td>NR</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>IA3</td>
<td>546 / 2417</td>
<td>NR</td>
<td>90%</td>
<td>77%</td>
</tr>
<tr>
<td>IB</td>
<td>560 / 1928</td>
<td>NR</td>
<td>87%</td>
<td>68%</td>
</tr>
<tr>
<td>IIA</td>
<td>215 / 585</td>
<td>NR</td>
<td>79%</td>
<td>60%</td>
</tr>
<tr>
<td>IIB</td>
<td>605 / 1453</td>
<td>66.0</td>
<td>72%</td>
<td>53%</td>
</tr>
<tr>
<td>IIIA</td>
<td>2052 / 3200</td>
<td>29.3</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>IIIB</td>
<td>1551 / 2140</td>
<td>19.0</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>IIIC</td>
<td>831 / 986</td>
<td>12.6</td>
<td>24%</td>
<td>13%</td>
</tr>
<tr>
<td>IVA</td>
<td>336 / 484</td>
<td>11.5</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>IVB</td>
<td>328 / 398</td>
<td>6.0</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Goldstraw P. et al., J Thorac Oncol 2016
NSCLC
NSCLC stage at presentation

- Stage I: 10%
- Stage II: 9%
- Stage III: 21%
- Stage IV: 60%
Treatment strategy for non-small-cell lung cancer

- Stage I
- Stage II
- Stage IIIA
- Stage IIIB
- Stage IV

Surgery

Radiotherapy

Systemic therapies
Stage I - II NSCLC
Surgery
Surgery

- Lobectomy is a golden standard, sublobar resections (segmentectomy or wedge resections) should be reserved for patients with compromised pulmonary function
- Sublobar resections are currently evaluated vs. lobectomy in tumors <2 cm in clinical trials
- Pneumonectomy should be avoided, but this is sometimes not possible
- VATS procedures are common in tumors <4 cm (decreased pain and faster recovery)
Postoperative radiotherapy by stage

Hazard Ratio

Stage
1
2
3

Nodal status
0
1
2

Test for trend
$c^2_{(1)} = 13.194$, $p = 0.0003$

Test for trend
$c^2_{(1)} = 5.780$, $p = 0.016$

Lancet 1998; 352: 257
Postoperative chemotherapy: metaanalysis of phase III studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Events / No. of Patients</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>569 / 1,088</td>
<td>0.95</td>
<td>(0.81 to 1.12)</td>
</tr>
<tr>
<td>ANITA</td>
<td>458 / 840</td>
<td>0.82</td>
<td>(0.68 to 0.98)</td>
</tr>
<tr>
<td>BLT</td>
<td>186 / 307</td>
<td>0.95</td>
<td>(0.71 to 1.27)</td>
</tr>
<tr>
<td>IALT</td>
<td>980 / 1,867</td>
<td>0.91</td>
<td>(0.81 to 1.04)</td>
</tr>
<tr>
<td>JBR10</td>
<td>197 / 482</td>
<td>0.71</td>
<td>(0.54 to 0.94)</td>
</tr>
<tr>
<td>Total</td>
<td>2,390 / 4,584</td>
<td>0.89</td>
<td>(0.82 to 0.96)</td>
</tr>
</tbody>
</table>

Pignon, J Clin Oncol 2008;26:3552-3559
Postoperative chemotherapy by stage

Pignon, J Clin Oncol 2008;26:3552-3559
Stereotactic body radiotherapy (SBRT) for stage I NSCLC
Results of SBRT in stage I NSCLC

Local relapse-free survival

Regional relapse-free survival

Dissemination-free survival

Overall survival
Stage III NSCLC

IIIA

IIIB
Stage III NSCLC

- Up to 30% of NSCLC patients present at diagnosis with stage III disease
- Most of them are not amenable for primary surgery
- Results following surgery or radiotherapy as a single modality alone are poor
- Multimodality therapy increases outcomes
Stage IIIA (N2):

Surgery?
Radiotherapy?
Chemotherapy?
A combination?
Stage IIIA (N2): major phase III studies

- Intergroup US 0139
  
  RT-CT $\rightarrow$ R $\rightarrow$ Surgery $\rightarrow$ CT $\rightarrow$ CT

- EORTC 08941
  
  CT $\rightarrow$ R $\rightarrow$ RT $\rightarrow$ Surgery $\rightarrow$ CT
Intergroup 0139/RTOG 9309
Results by treatment arm

Albain et al. Lancet 2009
EORTC 08941: Results by treatment arm

P=0.61

Surgery

Radiotherapy

Time to progression

P= 0.60

Surgery

Radiotherapy

Overall survival

Stage IIIA (N2): conclusions

- Pulmonary resection after response to induction chemotherapy or chemoradiotherapy does not improve survival

- Combined chemotherapy and radiotherapy remains the standard treatment in the majority of stage III (N2) patients. Surgery is considered for very selected patients in specialized centers (e.g. single stage N2)

- Current clinical trials evaluate induction chemo-immunotherapy followed by surgery
Inoperable locally advanced NSCLC
Concurrent versus sequential chemoradiation: metaanalysis of survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>RT + Conc CT</th>
<th>RT + Seq CT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 8831</td>
<td>45/46</td>
<td>39/45</td>
<td></td>
<td>2.4</td>
<td>20.9</td>
<td>1.12</td>
<td>0.73 to 1.72</td>
</tr>
<tr>
<td>WJLCC</td>
<td>131/156</td>
<td>142/158</td>
<td>-16.8</td>
<td>67.3</td>
<td></td>
<td>0.78</td>
<td>0.61 to 0.99</td>
</tr>
<tr>
<td>RTOG 9410</td>
<td>180/204</td>
<td>189/203</td>
<td>-20.5</td>
<td>91.1</td>
<td></td>
<td>0.80</td>
<td>0.65 to 0.98</td>
</tr>
<tr>
<td>GMMA Ankara</td>
<td>15/15</td>
<td>15/15</td>
<td>-1.0</td>
<td>7.0</td>
<td></td>
<td>0.87</td>
<td>0.41 to 1.82</td>
</tr>
<tr>
<td>GLOT-GFPC NPC</td>
<td>87/102</td>
<td>96/103</td>
<td>-9.9</td>
<td>45.0</td>
<td></td>
<td>0.80</td>
<td>0.60 to 1.07</td>
</tr>
<tr>
<td>EORTC 08972</td>
<td>63/80</td>
<td>66/78</td>
<td>-0.5</td>
<td>31.9</td>
<td></td>
<td>0.98</td>
<td>0.69 to 1.39</td>
</tr>
<tr>
<td>Total</td>
<td>521/603</td>
<td>547/602</td>
<td>-46.4</td>
<td>263.1</td>
<td></td>
<td>0.84</td>
<td>0.74 to 0.95</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 3.24$, $P = .66$, $I^2 = 0$

Auperin et al  J Clin Oncol 2010; 28:2181
Concurrent radiochemotherapy in stage III NSCLC: PROCLAIM Trial

Survival probability

Time from randomisation (months)

Patients at risk:
Pemetrexed + cisplatin: 301 282 268 239 221 194 178 157 145 126 98 75 67 56 46 42 33 25 19 14 10 3 1 0 0
Etoposide + cisplatin: 297 278 262 232 216 201 179 164 140 113 97 82 69 56 49 46 31 26 22 16 10 6 3 1 0

HR (95%CI) 0.98 (0.79, 1.20)
Log-rank p=0.831

Mediana OS (95%CI), mies.
Pemetrexed + cisplatin: 26.8 (20.4, 30.9)
Etoposide + cisplatin: 25.0 (22.2, 29.8)
Durvalumab (anti-PDL1 antibody) consolidation after radiochemotherapy in stage III NSCLC

PACIFIC trial

Graph showing the comparison of overall survival between Durvalumab and Placebo groups. The median overall survival is reported with 95% CI, and the 12-month and 24-month overall survival rates are also provided with 95% CI. The stratified hazard ratio for death is 0.68 (99.73% CI, 0.47–0.997) with a two-sided P-value of 0.0025.