Lung Cancer
Clinical and Biological Considerations

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Thoracic Surgery Dept
Outline

• Epidemiology
• Clinical Presentation
• Disease staging
• Screening
• Overview of Treatment
  – Targeted therapy
Histologic Types of Lung Ca

- Small Cell Ca – 15%
- Non-Small Cell Ca – 85%
  - Adenocarcinoma
  - Squamous Cell Ca
  - Large Cell Ca
  - Others
    - Bronchioloalveolar, Carcinoid, Adenosquamous, etc
### Incidence & Mortality 2016

#### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>180,890</td>
<td>246,660</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>117,920</td>
<td>106,470</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>70,820</td>
<td>63,670</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>58,950</td>
<td>60,050</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>46,870</td>
<td>49,350</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,170</td>
<td>32,410</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>39,650</td>
<td>29,510</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>34,780</td>
<td>26,050</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34,090</td>
<td>25,400</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>28,410</td>
<td>23,050</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>841,390</strong></td>
<td><strong>843,820</strong></td>
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</table>

#### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>85,920</td>
<td>72,160</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,120</td>
<td>40,450</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,020</td>
<td>23,170</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,450</td>
<td>20,330</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>18,280</td>
<td>14,240</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,130</td>
<td>10,470</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,720</td>
<td>10,270</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,820</td>
<td>8,890</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,520</td>
<td>8,630</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,440</td>
<td>6,610</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>314,290</strong></td>
<td><strong>281,400</strong></td>
</tr>
</tbody>
</table>
Demographics - Males

- Deaths
• Deaths

• 600% rise from 1930 to 1997
Epidemiology of Lung Cancer

• Leading cause of cancer death
• Risk Factors
  – Age
  – Tobacco
  – Occupational agents
    • Asbestos, Radon, Arsenic, Chromium, etc
  – Genetic factors
Epidemiology of Lung Cancer

- **Risk Factors**
  - ? Gender
    - Conflicting results
  - Race
    - ↑ risk in African Americans & Native Hawaiians
  - Diet
    - Fruits & vegetables intake lower the risk
    - ID of specific nutritional elements - elusive
  - COPD/Pulmonary fibrosis
## Impact of Age

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Malignant (%)</th>
</tr>
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<tbody>
<tr>
<td>35–44</td>
<td>15</td>
</tr>
<tr>
<td>45–49</td>
<td>26</td>
</tr>
<tr>
<td>50–59</td>
<td>41</td>
</tr>
<tr>
<td>60–69</td>
<td>50</td>
</tr>
<tr>
<td>70–79</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 19–5. INCIDENCE OF MALIGNANCY IN SOLITARY PULMONARY NODULES RELATED TO AGE
Smoking and Lung CA

- **Billions of Cigarettes Smoked**
- **Deaths from Lung Cancer**

Graph showing the increase in billions of cigarettes smoked and deaths from lung cancer over the years from 1900 to 1990.
Incidence (per 100,000)

- Non-Smoke
- 1 PPD
- 2 PPD
Smoking kills 512,000 people a year, from many different diseases

- 185,000 cancer*
- 108,000 respiratory
- 75,000 other
- 144,000 vascular (heart disease, stroke and other diseases of the arteries and veins)

*includes 138,000 (89%) of the 155,521 lung cancer deaths
About one in three of all cancer deaths is due to smoking

- 185,000 (33%) from smoking
- 115,000 (40%) from smoking
- 70,000 (26%) from smoking

- 553,000 total cancer deaths
- 286,000 male
- 267,000 female

United States, year 2000

www.deathsfromsmoking.net
Smoking causes about three times as many deaths as all non-medical causes put together.

- 512,000 smoking
- 151,268* non-medical

United States, year 2000

- Murder / assault
- Suicide
- Road accidents
- Plane crashes
- Train crashes
- Accidents at work
- Accidents at home
- Other natural disasters
- Poisoning
- Drowning
- Fires
- Floods / storms
- Other accidents
- *in year 2000

www.deathsfromsmoking.net
Low Smoking Exposure

- Mutations TK domain of EGFR
- Adenocarcinomas
- Well Differentiated
- Women > Men
- Non-smokers
Evaluation

- Clinical
- Laboratory
- Radiographic
- Physiologic
- Diagnostic
Clinical Manifestations

• Factors which Affect Symptoms
  – Location
  – Extension
  – Mets
  – Hormonal syndromes
Symptoms-Pulmonary

- Pulmonary
  - Cough
  - Hemoptysis
  - Dyspnea
  - Fever
  - Chest pain
Symptoms-Extrapulmonary

- Extra Pulmonary
  - Pleural effusion - dyspnea
  - Recurrent Nerve - Hoarseness
  - SVC Syndrome
  - Dysphagia
Symptoms-Extrathoracic

• Extra Thoracic
  – Hypertrophic pulmonary osteoarthropathy
  – Cervical Lymph Node Mets
  – Bone Pain
  – CNS Symptoms
Symptoms-General

• Non-specific
  – Weight loss
  – Weakness

• Hormonal
  – Cushing’s Small Cell
  – SIADH Adeno or poorly diff
  – Parathormone, Hypercalcemia SCCA
Symptoms-General

- Asymptomatic - 5 to 15%
- Others
  - Neuromyopathies (Eaton-Lambert)
  - Dermatoses
  - Vascular
  - Hematologic
Physical Findings

- Will depend on extent of disease
- Cachexia
- Lymphadenopathy
- Clubbing
- Pulmonary findings
- Manifestations of metastases
Laboratory

- Non-specific findings
- Anemia
- Hypercalcemia
- Elevated CEA level
- Abnormal LFTs
- Elevated ALP
Imaging

- CXR (OLD FILMS!)
- CT Scan
- MRI
- Bone Scan
- PET Scan
PET Scan Imaging

- 97% Sensitive
- 78% Specific
- > 1 cm
## Disease Staging

### TNM Staging – 7th edition

<table>
<thead>
<tr>
<th>T/M</th>
<th>Subgroup</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1a</td>
<td>Ia</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T1</td>
<td>T1b</td>
<td>Ia</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T2</td>
<td>T2a</td>
<td>Ib</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T2</td>
<td>T2b</td>
<td>IIa</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T3</td>
<td>T3 &gt; 7</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T3</td>
<td>T3 _Inv</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T3</td>
<td>T3 _Satell</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T4</td>
<td>T4 _Inv</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
<td>IIIb</td>
</tr>
<tr>
<td>T4</td>
<td>T4 _ipsi Nod</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
<td>IIIb</td>
</tr>
<tr>
<td>M1</td>
<td>M1a _Contra Nod</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1</td>
<td>M1a _Pl Disem</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>
T Status

• T1a <2
• T1b >2-3
• T2a >3-5
• T2b >5-7
• T3 > 7cm
• TX Primary tumor cannot be assessed, eg sputum positive
• T0 No evidence of primary tumour
• Tis Carcinoma in situ
N
Status
Nodal Status

NX- Can’t Assess
N0- No regional nodes
N1- Peribronchial
N2- Ipsilateral mediastinal
N3- Contralateral mediastinal
Nodal Status

NX- Can’t Assess
N0- No regional nodes
N1- Peribronchial
N2- Ipsilateral mediastinal
N3- Contralateral mediastinal

Lung Cancer '2012
Nodal Status

NX- Can’t Assess
N0- No regional nodes
N1- Peribronchial
N2- Ipsilateral mediastinal
N3- Contralateral mediastinal
M Status

• M0 No distant metastasis
• M1 Distant metastasis
  • M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusions
  • M1b Distant metastasis
Lung Staging - Mets

- Lymph Nodes 96%
- Bones 48%
- Adrenals 40%
- Liver 41%
- Kidneys 19%
- Heart 15%
- Opposite lung 13%
Survival by Stages
Pathologic

<table>
<thead>
<tr>
<th>Stages</th>
<th>Deaths / N</th>
<th>MST 5-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1168 / 3666</td>
<td>119 73%</td>
</tr>
<tr>
<td>IB</td>
<td>1450 / 3100</td>
<td>81 58%</td>
</tr>
<tr>
<td>IIA</td>
<td>1485 / 2579</td>
<td>49 46%</td>
</tr>
<tr>
<td>IIB</td>
<td>1502 / 2252</td>
<td>31 36%</td>
</tr>
<tr>
<td>IIIA</td>
<td>2896 / 3792</td>
<td>22 24%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>263 / 297</td>
<td>13 9%</td>
</tr>
<tr>
<td>IV</td>
<td>224 / 266</td>
<td>17 13%</td>
</tr>
</tbody>
</table>
Tumor Growth I
Stepwise Model
We underestimate what we don’t see
Stage at Presentation

- All Races
- White
- African American

Lung & Bronchus
- Localized: 16, 16, 14
- Regional: 35, 35, 36
- Distant: 41, 41, 43

Female Breast
- Localized: 61, 62, 51
- Regional: 31, 30, 37
- Distant: 6, 6, 9

Colon & Rectum
- Localized: 39, 40, 35
- Regional: 36, 37, 35
- Distant: 19, 19, 24
Purpose of Lung Cancer Screening

- Detect asymptomatic, early stage disease that is amenable to curative therapy
- Improved outcomes
  - Survival
  - Quality of Life
The Shift in Stage of Lung Cancer with LDCT Screening

- Stage I/II: Current and Screened
- Stage III: Current and Screened
- Stage IV: Current and Screened
• **N=53,500**
  • Randomized

• **Low Dose CT**
  • Annual x 2

• **Chest Roentgenogram**
  • Annual x 2

→ **354 Deaths**
→ **442 Deaths**

**20% Reduction**

**Radiology**: Volume 258: Number 1—January 2011
### Summary of Screening Criteria Presented by Professional Organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screening Criteria</th>
</tr>
</thead>
</table>
| NCCN         | • NLST Criteria (55-74 years, 30 Packyear (PY))  
                • ≥ 50, 20 PY with additional risk factor (Cancer History, COPD, FH, work exposure, pulmonary fibrosis) |
| ACS          | • NLST Criteria with Expertise in LDCT  
                • Multidisciplinary Team  
                • Vigorous Smoking Cessation |
| ALA          | • NLST Criteria with Expertise in LDCT  
                • Encourage Smoking Cessation  
                • No Chest X-ray  
                • Multidisciplinary Team |
| ACCP/ASCO    | • NLST Criteria  
                • Smoking Cessation ≥ 15 Years Ago  
                • Multidisciplinary Team |
### Summary of Screening Criteria Presented by Professional Organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screening Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>AATS</td>
<td>• NLST Criteria (55-79 years, 30 PY)</td>
</tr>
<tr>
<td></td>
<td>• ≥ 50, 20 PY with additional risk factor (Moderate COPD, Cancer History, FH, work exposures)</td>
</tr>
<tr>
<td></td>
<td>• No suggested limits on numbers of LDCTs</td>
</tr>
<tr>
<td></td>
<td>• Lifelong surveillance for aerodigestive cancer survivors</td>
</tr>
<tr>
<td>AAFP (January 2014)</td>
<td>• Insufficient evidence to recommend for or against screening for lung cancer</td>
</tr>
<tr>
<td></td>
<td>• Potential for screening from ages 55-80</td>
</tr>
<tr>
<td></td>
<td>• Physicians must engage in shared decision making regarding the benefits, potential harms, and costs from screening</td>
</tr>
</tbody>
</table>
Recommendations for Lung Cancer Screening Programs

• Experienced management of nodule surveillance
• Multidisciplinary team
• Referral centers with experienced radiologists and pulmonologists
• Must be integrated with comprehensive smoking cessation program
Lung Cancer Multidisciplinary Team

- Medical Oncology
- Pulmonology
- Prevention
- Radiation Oncology
- Nuclear Medicine
- Thoracic Surgery
- Diagnostic Radiology
- Pulmonary Pathology
Obtaining Tissue for Diagnosis

- CT guided needle biopsy
- Endobronchial biopsy
- Endobronchial Ultrasound
- Navigational bronchoscopy
- Thoracoscopic biopsy
Treatment Modalities

- Surgery
- Radiotherapy
- Chemotherapy
- Targeted Therapy
- Endobronchial Interventions
- Palliative Procedures
Surgical Management

• Approach
• Video Assisted Thoracic Surgery (VATS)
• Thoracotomy
  – Posterolateral
  – Anterior
• Median Sternotomy
Surgical Management

• Lobectomy (+ lymphadenectomy)
• Larger resections
  – Bilobectomy, Pneumonectomy
• Lesser resections
  – Segmentectomy, wedge resection
Minimally Invasive Lobectomy
Robot-Assisted Lobectomy
The da Vinci SI Surgical Robot (bedside cart)
The da Vinci Robot
Features

• *EndoWrist* Instruments provide enhanced dexterity, precision and control:
  – 7 degrees of freedom
  – 90 degrees of articulation
  – *Intuitive* motion and finger-tip control
  – Motion scaling and tremor reduction
Surgical Contraindications

- Inadequate cardiopulmonary reserve
- Malignant pleural effusion
- Recurrent laryngeal nerve paralysis
- Small cell carcinoma
- Contralateral lymph node mets
- Distant mets
Non-Surgical Therapies

• Chemotherapy
• Radiotherapy
• Combination therapy
  – Neoadjuvant (prior to surgery)
  – Palliative
  – Definitive
  – Adjuvant (after surgery)
Chemotherapy

- Traditional chemotherapeutic agents are systemic cytotoxic drugs
- Platin-based therapy
  - Cisplatin
  - Carboplatin
- Typically a doublet
  - Combination of 2 chemotherapeutic agents
Targeted Therapy

• Markedly improved understanding of molecular pathways in NSCLC
• Identification of “Driver Mutations”
• Design of small molecules to interfere with the products of these mutated genes
• Often more effective & less toxic than traditional chemotherapy
Molecular targets in non-small cell lung cancer

Pathways for molecularly targeted therapy in non-small cell lung cancer.

Original, courtesy of Dr. Joel Neal.
The EGFR family
- EGFR (ErbB1, HER1)
- ErbB2 (HER2, neu)
- ErbB3 (HER3)
- ErbB4 (HER4)

Binding of soluble extracellular ligand → dimerization → intracellular TK domain activation/phosphorylation → downstream signaling → promotion of cell proliferation, motility and invasion

EGFR mutated in ~10% of NSCLC in the US and 35% in East Asia (overall 26%)

Confers poor prognosis
Receptor Tyrosine Kinases (RTKs) Activation
EGRF Signaling

- Growth factor binding to EGFR results in activation of the MAPK signaling pathway (RAS-RAF-MEK-ERK) and the PI3K pathway (PI3K-AKT-mTOR).
EGFR Mutations

Mutations above the schematic are associated with sensitivity to EGFR TKIs

Mutations listed below the schematic are associated with EGFR TKI resistance
EGFR Mutations

• More often occur in adenocarcinomas in female never-smokers
• Typically, non-overlapping with other oncogenic mutations found in NSCLC (i.e. KRAS mutations, ALK rearrangements, etc.)
• Both prognostic and predictive
• Identifies the subset of patients responsive to TKIs
Pharmacologic targeting of the EGFR signaling pathway

- Two basic approaches
  - Anti-EGFR monoclonal antibodies (mAbs)
  - Small molecule Tyrosine Kinase Inhibitors (TKIs)
- Limited efficacy in unselected NSCLC
Anti-EGFR mAbs

- Bind to the extracellular domain of EGFR
- Competitive occlusion of the ligand binding region
- Inhibit ligand-induced phosphorylation of the catalytic region
- Blocks the intracellular signaling cascade
- Cetuximab (Erbitux®) & Panitumumab (Vectibix®)
  - Effective in combination with chemotherapy
  - No validated predictive biomarker
Small molecule TKIs

- Response is predictable based on activating EGFR somatic mutations
- Gefinitib (Iressa®) and Erlotinib (Tarceva®)
  - Reversible inhibitors of the EGFR kinase
  - Bind to the ATP-binding site thus preventing phosphorylation and downstream signaling
  - Superior to chemotherapy in pts with tumors that bear activating EGFR mutations
  - EGFR amplification (detected by FISH in 20-40% of NSCLCs) adds to the response rates
Small molecule TKIs

- A small proportion of pts show a radiographic response with no detectable EGFR mutation
  - Need for new biomarkers
NSCLC Patients selection for EGFR TKIs

**POSITIVE SELECTION**
- Never smokers
- Females
- Adenocarcinoma (BAC)
- East-Asians

**NEGATIVE SELECTION**
- Smokers
- NSCLC Non-ADKs

EGFR

**Mutations**
- Activating mutations (ex 18-21)
- T790M

**signal transduction pathway**
- RAS wt
- PLCE
- RasGDS
- BRAF
- MEK
- ERK

**Cellular response**
- Genes transcription

**MET amplification**
- PI3K
- AKT
- mTOR
Mechanisms of Resistance

- 2 types
  - Primary or *de novo* resistance
  - Secondary or acquired
- Both types related to EGFR mutations
  - mainly affecting exon 20 - Small insertions or duplication; T790M mutation
Mechanisms of Resistance

• Newer irreversible EGFR inhibitors (pan-Erb inhibitors) may overcome T790M-mediated resistance

• Other genomic alterations can coexist with EGFR mutations
  – Mutations of PIK3CA
  – Loss of function of the inhibitor PTEN
  – Altered IGFR signaling
Mechanisms of Resistance

- In EGFR wild type tumors, downstream genetic lesions may cause TKI resistance
  - KRAS mutations; 17% of NSCLC
  - BRAF mutations; rare (2%)
  - PIK3CA mutations (3%)
  - Loss of PTEN expression
  - Activating mutations of the AKT gene
  - Amplified MET mediates PIK3CA activation via ErbB3 activation
Mechanisms of Resistance

• T790M mutation and MET amplification account for 70% of acquired resistance to EGFR inhibitors in NSCLC
• Strong rationale for combination anti-EGFR /anti-MET approach
• EML4-AKT fusion protein
  – Product of gene translocation
  – Induces constitutive dimerization & activation of the ALK kinase domain
Conclusion

• NSCLC is extremely heterogeneous
  – As an entity
  – Even within an individual patient
• Targeted therapy results are mixed and not fully understood
• Current biomarkers seem inadequate
• Modest improvements in survival have been achieved
• The holy grail of markedly effective, personalized NSCLC therapy is still elusive
Radiotherapy

- Therapy using ionizing radiation to control or kill malignant cells
  - 3D Conformal RT
  - Intensity-modulated radiation therapy (IMRT)
  - SBRT
SBRT
Stereotactic Body Radiation Therapy
Endobronchial Therapy

• Interventions within the airway via flexible or rigid bronchoscopy

• Used for very early (non-invasive) or obstructive disease
  – Laser fulguration
  – Photodynamic therapy
  – Cryotherapy
  – Stent insertions
PleurX Catheter
PleurX Catheter
Management of Advanced Lung Cancer

- Platin-based combination chemotherapy
- Conformal 3-D radiotherapy
- Molecularly targeted therapy
- Airway obstruction relief – Lasers, PDT, stents

- Management of Pleural Effusions
- Pain Control & other aspects of Palliative care – dyspnea, psychosocial problems, etc
Long-term Care

- Surveillance
- Survivorship – Fertility, Cognitive challenges, other disabilities
- End of Life Planning – Proxy, Hospice (home or institutional), Intubation or not, DNR (Do Not Resuscitate), etc