Overview

- Epidemiology
- Screening
- Diagnosis
- Staging
- Treatment
- Cases
Epidemiology

- Leading cause of cancer death in men and women worldwide
- 25% never smokers
- Prognosis is poor
Risk Factors

• Causal relationship between smoking and lung cancer well established

• Other risk factors: environmental tobacco smoke, radon, arsenic, air pollution, asbestos, silica, cooking fumes, and family history
Screening

• 75% of patients with lung cancer are incurable at diagnosis

• Prevention is the most effective strategy to reduce burden in the long term

• Potential benefit of screening to detect early cancers that can be cured
Screening

• National Lung Screening Trial (NLST): low dose CT (LDCT) vs. chest x-ray screening in high risk group (current or ex-smokers age 55 to 74; at least 30 pack-years)

• 20% reduction in lung cancer mortality with LDCT screening
Screening

• Generalizability of NLST findings uncertain:
  – demographic of trial patients
  – expertise of academic centres
  – cost effectiveness
  – risk of false-positive findings

• Multiple studies ongoing to confirm NLST findings and screening pilot programs in development
Diagnosis and Staging
Suspected Lung Cancer

**Clinical Staging**
- History & Physical Exam
- Imaging
- Tumour Sample
- Multidisciplinary Team

**Pathologic Diagnosis**
- Smoking history
- PS and weight loss
- CXR, CT (PET)
- Bronchoscopy/EBUS
- CT guided biopsy
- Pleural fluid
- Surgery, Radiation, Systemic Therapy
Clinical Staging

- To evaluate extent of disease involvement and identify targetable lesion for biopsy
Clinical Staging

- History and Physical
- CXR
- CBC, lytes, Cr, LFTs, Ca, alb, INR/PTT, CEA
- CT chest
- PET scan if:
  - Potentially curative treatment (stage I, II or III)
  - For staging prior to resection of solitary brain met
  - For radiation planning
Tissue Diagnosis

• Goal is to obtain adequate tissue to confirm diagnosis and perform molecular testing if indicated

• Ideally should target biopsy that will yield most advanced site of disease
Tissue Diagnosis

- Often difficult to obtain adequate tissue

- Surgical resection > Core biopsy > Bronchoscopy or EBUS > FNA or Fluid cytology
EBUS

- Relatively new procedure for tissue diagnosis and lymph node staging
- Can perform trans-bronchial needle aspirates (TBNAs) to obtain tissue from lungs and lymph nodes
- Allows for improved visualization for difficult to reach areas and to access small lymph nodes
Tissue Diagnosis

- Non-small cell lung cancer (NSCLC) – 85%
  - Adenocarcinoma (ADC)
  - Squamous cell (SCC)
  - Large cell (LC)

- Small cell lung cancer (SCLC) – 10-15%
Clinical Features and Histology

Central SCLC, SCC

Peripheral ADC
Treatment
General Principles

• Treatment is based on multiple factors
  – Stage
  – Histologic subtype
  – Tumour location
  – Age, comorbidities, performance status, weight loss
General Principles

• Identify goals of care: Palliative vs Curative

• Local Therapy: Surgery, Radiation

• Systemic Therapy: Chemotherapy, Targeted Rx

• Supportive Care: PleurX, opioids, home care, advanced care planning
# NSCLC: Treatment and Outcomes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>5 yr survival</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Surgery +/- Chemo</td>
<td>50%</td>
</tr>
<tr>
<td>II (IIIA)</td>
<td>Surgery +/- Chemo</td>
<td>40%</td>
</tr>
<tr>
<td>IIIA</td>
<td>ChemoRT +/- Surgery</td>
<td>20-30%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>ChemoRT or RT alone</td>
<td>5-10%</td>
</tr>
<tr>
<td>IV</td>
<td>Chemo +/- Targeted Therapies</td>
<td>1%</td>
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NSCLC: Targeted Therapies

- Recent discovery of subsets of NSCLC with mutations that drive cancer growth and spread
- These lung cancers are highly responsive to treatments that target these mutations
- More frequent in never smokers
- Metastatic non-squamous NSCLCs are routinely tested for EGFR and ALK
SCLC: Treatment and Outcomes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>5 yr survival</th>
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<tbody>
<tr>
<td>Limited</td>
<td>ChemoRT + PCI</td>
<td>10-20%</td>
</tr>
<tr>
<td>Extensive</td>
<td>Chemo +/- RT</td>
<td>1-2%</td>
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</table>
Cases

- Adjuvant NSCLC
- Locally Advanced NSCLC
- Metastatic NSCLC
Case 1

58 year old woman, smoker

- Presents with atypical chest pain Aug 2014
Case 1

- Referred to Respirology
- Bronchoscopy Aug 29 2014 – non-diagnostic
- EBUS Sep 8 2014 – non-diagnostic
- EBUS Sep 24 2014 – atypical cells
- What next?
Case 1

- Consult Thoracic Surgery
- PET - no nodal or distant disease (cT1N0)
- LUL lobectomy Nov 2014
- Pathology
  - pT1a (1.7cm) poorly differentiated adenocarcinoma
  - pN2 (5 and 7L nodes positive)
  - Stage IIIA
Case 1

- 5-year survival without chemo 30%; with chemo 40%
- CT head negative
- Postoperative chemo: cisplatin/vinorelbine x 4
- Referred to ?Post-operative RT (N2 disease)
Case 1 Key Points

• ~30% of patients are diagnosed with operable disease

• Tissue diagnosis can be difficult and consider referring to avoid delays and repeat procedures

• Surgical resection for tissue diagnosis and treatment may be required
Case 1 Key Points

• For operable disease, PET and pathologic nodal staging (EBUS) required

• Clinical (pre-op) and pathologic (post-op) stage can differ

• Adjuvant chemotherapy provides modest benefit in resected stage I-III NSCLC

• Post-operative RT for resected N2 disease is controversial
Case 2

48 year old man, 30 pack-year ex-smoker

• Cough June 2014
• Treated as GERD with PPI
• Heartburn better, but persistent cough
Case 2

- PFTs Nov 2014 normal
- Referred to Respirology Jan 2015
Case 2

- Bronchoscopy Feb 2015 VGH: non-diagnostic

- EBUS Feb 2015 VGH:
  - Squamous cell ca RLL
  - Station 4R, 7, 11R nodes +
  - 4L node non-diagnostic
Case 2

- R neck and bilateral mediastinal nodal involvement
- CT head negative
- Clinical stage IIIB (T2N3)
Case 2

- Concurrent chemoRT Apr 2015
- Cisplatin/Etoposide x 2 cycles during RT (60Gy; 6 weeks)
- Plan is to complete further 2 cycles of chemo after RT
- Goals of treatment are curative, but recurrence rate is very high ~90%
Case 2 Key Points

• CXR as a screening and diagnostic tool can be limited

• Consider CT and/or Respirology consult with persistent cough if high risk

• Delays from symptom onset to diagnosis and treatment common

• Multiple bottle-necks = need for multidisciplinary rapid access clinic
Case 2 Key Points

- Concurrent chemoRT is an option for fit patients with locally advanced disease that is amenable to high dose RT (60Gy)

- Stage IIIA NSCLC 5-year OS is 20% with concurrent chemoRT

- Stage IIIB NSCLC 5-year OS is 5-10%
Case 3

56 year old woman, smoker

Presents with cough and scant hemoptysis
Case 3

- CT Feb 2015: LUL mass, left hilar, mediastinal, adrenal and liver involvement
- EBUS Mar 2015 – NSCLC (adenoca)
- PET and CT head – brain and bone mets
- Palliative RT to lung and brain Mar 2015
- Molecular testing: EGFR/ALK negative
- Cisplatin/pemetrexed chemo x 1 cycle April 2015
Case 3

Pre-chemo

Post cycle 1
Case 3

- Switched to 2\textsuperscript{nd}-line docetaxel
- Rapid clinical deterioration
- Transition to best supportive care
Case 3 Key Points

• Median survival of met NSCLC is 6 months without treatment

• First-line platinum-based chemotherapy prolongs survival by 3-6 months

• Response rates to 1st-line chemotherapy 30-50%

• Rapidly progressive disease on 1st-line chemotherapy = poor prognosis
Case 4

88 year old Asian female lifelong never smoker

- Chest pain Oct 2014
- Dec 2014 CT: LUL mass, bilateral lung nodules, extensive bone metastases
- Family History: brother lung cancer age 81; sister lung cancer at age 63; sister uterine cancer age 31
- No known exposures
- Biopsy: NSCLC (adenoca); EGFR mutation positive (L858R)
EGFR mutations in Lung Cancer

- **Diagram:**
  - EGFR signaling pathway:
    - EGFR activates Ras, which in turn activates RAF, MEK, and ERK, leading to proliferation.
    - EGFR also activates SOS and GRB2, which activate PI3K and Akt, leading to cell survival.
    - STAT3 and STAT5 have other effects.

- **Bar Chart:**
  - 58% of lung cancers have EGFR mutations.
  - 13% do not have EGFR mutations.
Case 1

Baseline

8 weeks post gefitinib
Case 4 Key Points

- Activating EGFR mutations are present in 15% of NSCLC in North America; 60% in Asian never smokers
- Presence of EGFR mutation predicts response to EGFR inhibitor therapy (gefitinib, erlotinib)
- Resistance ultimately develops
- Early results from clinical trials of newer generation EGFR inhibitors promising
Case 5

32 year old female never smoker
Presents with blurring of vision left eye and intermittent cough
Ophthalmology: metastatic lesions to left eye
Case 5

• CT showing collapse of L lung, brain, eye, and liver mets

• Core biopsy liver: adenoca consistent with lung primary

• ALK testing (IHC and FISH) positive
Gene Fusions
- Promoter of 5' gene fusion partner drives expression of developmentally silenced ALK
- 5' fusion partner dimerization domains mediate activation of ALK

Ligand-induced dimerization
- Developmentally regulated
- Adult human expression restricted to small intestine, nervous system and testes

Activating Mutations
- Neuroblastoma
- Anaplastic Thyroid Carcinoma
- In cancers that occur in tissues that normally express full length ALK?
- Or re-express full-length ALK during malignant transformation?

Proliferation
Differentiation
Anti-apoptosis

Case 5

- Started on crizotinib
- Elected to hold off on RT to brain and eye
- CXR 4 weeks on crizotinib
- Eye lesion improving
Case 5 Key Points

- ALK-positive NSCLCs are highly responsive to ALK inhibitor therapy (crizotinib)
- CNS response to crizotinib have been observed
- However, resistance ultimately develops
- Clinical trials with newer generation ALK inhibitors are underway
## Metastatic NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Non-squamous</th>
<th>Squamous</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>EGFR+</td>
<td>ALK+</td>
</tr>
<tr>
<td><strong>1&lt;sup&gt;st&lt;/sup&gt;-line</strong></td>
<td>Gefitinib/Erlotinib</td>
<td>Crizotinib</td>
</tr>
<tr>
<td><strong>2&lt;sup&gt;nd&lt;/sup&gt;-line</strong></td>
<td>Platinum doublet</td>
<td>Platinum doublet</td>
</tr>
<tr>
<td><strong>3&lt;sup&gt;rd&lt;/sup&gt;-line</strong></td>
<td>Pemetrexed or Docetaxel</td>
<td>Pemetrexed or Docetaxel</td>
</tr>
</tbody>
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Summary Recent Advances

2005 to present...

• NLST and LDCT screening
• First PET scan at BCCA
• EBUS for nodal staging
• Minimally invasive surgeries
• Targeted radiation techniques (stereotactic RT) for inoperable stage I disease
• Approval of molecular testing and targeted therapies for EGFR+ and ALK+ metastatic NSCLC
Future Directions

2015 and beyond...

• Better understanding of risk factors for lung cancer in never smokers
• Guidelines for LDCT screening in high risk groups
• Improved techniques for rapid diagnosis and treatment (liquid biopsy)
• Towards personalized genomics and targeted therapies
• Ongoing studies of immunotherapy
Thank You