Disclosures

NONE
Objectives

• Epidemiology and risk for lung cancer
• Lung Cancer Screening
• Advancements in managing locally-advanced disease
• Advancements in management of metastatic disease
  • molecular marker driven therapy
  • immunotherapy

Lung Cancer Epidemiology

Total Cases = 234,030
Lung Cancer Epidemiology

Total Cases = 234,030

Total Deaths = 154,050

Oregon Specific Projections for 2018

- 3140 new cases
- 2000 deaths
Lung Cancer Epidemiology

Lifetime Probability of Developing Lung Cancer

• 1 in 15 men
• 1 in 17 women

Non-smokers

Never-smoker definition
= less than 100 cigarettes in a lifetime

15-20% of all lung cancers occur in never smokers (and light former smokers)
Lung Cancer Screening

Prior attempts to screen for lung cancer
- CXR
- Sputum cytology

Ineffective screening tools for lung cancer

National Lung Screening Trial

- NCI funded
- Initiated 2002 (enrolled 2002-2004), Published Aug 2011
- Randomized trial comparing annual low-dose, non-contrast CT versus CXR
- Enrolled 53,454 patients among 33 participating institutions
National Lung Screening Trial

Eligibility:
1. 55-74 years old
2. $\geq 30$ pack year history of smoking
3. Quit tobacco $\leq 15$ years ago

Exclusion criteria:
1. History of prior lung cancer
2. CT chest $\leq 18$ months prior to enrollment
3. Hemoptysis
4. Unexplained weight loss ($\geq 15\#$ in prior year)

53,454 enrolled
- 26,722 randomized to CT screening
- 26,732 randomized to CXR

- Additional data collected for smoking history/cessation
- Cost effectiveness, quality of life measures collected
National Lung Screening Trial

- Imaging yearly x 3 years
- Positive Scan
  - Any nodule ≥ 4mm
  - Any non-calcified nodule or mass
  - Adenopathy
  - Effusions
- Any abnormalities stable after 3 years (on CT chest) were reclassified as minor

NLST Baseline Characteristics

Summary

- 43% Young (55-59 year old)
- 60% Male
- 91% White
- 50% Current Smokers
### NLST

**Stage and Histologic Type of Lung Cancers in the Two Screening Groups, According to the Result of Screening**

<table>
<thead>
<tr>
<th>CT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Lung Cancer Diagnosed</td>
<td>1060 cases</td>
</tr>
<tr>
<td>Lung Cancer Confirmed after positive screening</td>
<td>649</td>
</tr>
<tr>
<td>Lung Cancer Confirmed after negative screening</td>
<td>44</td>
</tr>
<tr>
<td>Lung Cancer Confirmed in patients who missed screening or confirmed after trial screening phase complete</td>
<td>367</td>
</tr>
</tbody>
</table>

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**Table 1: Stage and Histologic Type of Lung Cancers in the Two Screening Groups, According to the Result of Screening**

<table>
<thead>
<tr>
<th>Stage</th>
<th>CT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>520 (416 = IA)</td>
<td>289 (196 = IA)</td>
</tr>
<tr>
<td>Stage II</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>Stage III</td>
<td>221</td>
<td>231</td>
</tr>
<tr>
<td>Stage IV</td>
<td>226</td>
<td>335</td>
</tr>
</tbody>
</table>

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**Notes:**
- The screening mammogram only captured the breast images to better assess the result of screening.
- The stage was not known in the case of 32 cancers after a positive mammogram and 1 patient was diagnosed with lung cancer after a positive mammogram.
- The results were based on the trial screening phase and only 2 patients were diagnosed with lung cancer during the initial trial screening phase.
- The results were based on a total of 1270 patients who were followed up on the screening study and only 2 patients were diagnosed with lung cancer.
- The results were based on patients who were followed up on the screening study and only 2 patients were diagnosed with lung cancer.

**Source:** NLST investigators. NEJM 2011;365(5):395-409
NLST
Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer

20% reduction in mortality in low dose CT screening group

Limitations of the NLST

- Participating institutions are recognized for cancer and radiologic expertise
- Low surgical mortality in NLST centers
- CT scanning technology has advanced compared to timing of the trial
- Participants were more likely healthy compared to average former or current smoker
  - 94 million current or former smokers USA
  - 7 million meet NLST inclusion criteria
Limitations of the NLST

▪ Reduction in disease-specific mortality possibly underestimated
  – 3 years of screening
▪ High rate of false positives
  – Most interventions were additional imaging versus procedures
▪ Over diagnosis
  – LESS LIKELY given overall similar rates of cancer between 2 groups (minimal, if any, effect)

NLST investigators. NEJM 2011;365(5):395-409

NLST Conclusions

▪ CXR screening is ineffective compared to low-dose CT screening
▪ Screening is NOT a substitute for primary prevention through smoking cessation
▪ Screening with chest CT will reduce disease specific mortality
▪ Screening may lead to additional imaging and procedures, with potential complications
▪ High number of false positive scans- psychological impact

NLST investigators. NEJM 2011;365(5):395-409
NLST Conclusions and Next Steps

- Issues of payment, implementation, cost-effectiveness, as well as addressing barriers to screening not published
  - Anxiety
    - Most abnormalities are not lung cancer
  - Expense
  - Underrepresented in NLST – women, people of color

Lung Cancer Screening Take Home Points

Candidates:
- 55-77 years old
- ≥ 30 pk yrs
- Quit within 15 yrs
- Medically fit

Stop screening:
- >15 yrs since cessation
- 77 years old
- No longer able or unwilling to undergo surgery
Lung Cancer Screening Tools

- Lung Cancer Alliance risk calculator - [Am I at Risk of Lung Cancer](#)
- American Lung Association - [Risk Calculator](#)
- National Comprehensive Cancer Network guidelines for patients - [Lung Cancer Screening](#)
- University of Michigan - [https://shouldiscreeen.com](#)

What about all of the radiation exposure?

- Risk of radiation-induced cancer
  - 1 in 2000 per 10 mSv scan
- Increased risk over time (younger people at increased risk given life expectancy)
- Potential greater susceptibility in women

http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115329.htm
What about all of the radiation exposure?

<table>
<thead>
<tr>
<th>Diagnostic Procedure</th>
<th>Typical Effective Dose (mSv)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray (PA film)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>1.5</td>
</tr>
<tr>
<td>I.V. urogram</td>
<td>3</td>
</tr>
<tr>
<td>Upper G.I. exam</td>
<td>6</td>
</tr>
<tr>
<td>Barium enema</td>
<td>8</td>
</tr>
<tr>
<td>CT head</td>
<td>2</td>
</tr>
<tr>
<td>CT chest</td>
<td>7</td>
</tr>
<tr>
<td>CT abdomen</td>
<td>8</td>
</tr>
<tr>
<td>Coronary artery calcification CT</td>
<td>3</td>
</tr>
<tr>
<td>Coronary CT angiogram</td>
<td>16</td>
</tr>
</tbody>
</table>

Unfortunate Reality

Most lung cancer is diagnosed as stage IV = incurable disease

Is there a reason to treat if incurable?
Why we treat stage IV lung cancer

Quality of life is improved for patients with stage IV NSCLC who receive chemotherapy compared to BSC
- data from 287 patients, published 1999
  (OLD CHEMO = more toxic)
- median survival 5.9 and 8.1 months (for two different chemotherapy regimens) and 4.1 months for BSC
- improvement in quality of life scores at each assessment period for chemotherapy arm only

Chemotherapy prolongs life AND improves quality of life

Lung Cancer 2018

Treatment landscape shifting rapidly based on:
• Advancing histologic and molecular analysis
• Rapid experimentation, adoption, and approval of novel medications

NEJM
• 2014-2018 23 research articles with lung cancer in title
• 2009-2013 12 research articles with lung cancer in title
Non-small cell lung cancer sensitizing mutations

EGFR
- Multiple oral TKIs
- survival ~ years prior to needing chemotherapy

ALK
- Multiple oral TKIs, each with control 7-12 months
- Estimated survival now ~ 5 years!

ROS-1
- Proven survival with oral TKIs

BRAF (V600E)
- Combination TKI therapy approved

Emerging Mutations
- MET amplification
- MET exon 14 skipping mutation
- RET rearrangements
- HER2 mutations

Case 1
59 yo former light smoker presented with cough and dyspnea

September 2015
Case 1

Diagnosed with - Pulmonary adenocarcinoma with ALK translocation

Started Crizotinib (oral TKI) 10/2015

Staging MRI brain revealed innumerable (asymptomatic) brain metastases
- received whole brain radiation October 2015

Case 1

Progressed in January 2017
Started 2nd line alectinib (oral TKI) – continues, NED

July 2018
Non-small cell lung cancer without driver mutation

Rapid evolution of treatment paradigm for NSCLC without mutations

- Immunotherapy as 1st line therapy if PD-L1 expression >50%
- Chemotherapy + immunotherapy as 1st line therapy if PD-L1 expression <50%

Survival without systemic therapy = 6 months
Survival with therapy = 10-16 months -> this is changing

Immunotherapy

Case 2
53 yo 30 pack year smoker presented with left arm swelling and hoarse voice

October 2015

Case 2
Received 2 cycles standard of care chemotherapy
Worsening dyspnea, new plethora

October 2015  December 2015
Case 2
Palliative radiation for SVC obstruction
February 2016 -switched to niovlumab

Evolution of immunotherapy in treatment of lung cancer

In one short talk...
2nd line Anti-PD-1 in Stage IV Squamous Cell Lung Cancer

**Nivolumab**

- FDA approved for squamous cell carcinoma in 2015
- 272 patients stage IV progressed after 1st line therapy
- randomized nivolumab versus docetaxel
- OS: 9.2 mos nivolumab versus 6.0 mos docetaxel
- Response rate: 20% with nivolumab versus 9% docetaxel
- Grade 3/4 AE: 7% nivolumab versus 55% with docetaxel

What is the role for anti-PD-1 treatment in non-squamous NSCLC in the 2nd line?
2\textsuperscript{nd} line Anti-PD-1 in NSCLC (any histology)

**Pembrolizumab**

- 495 patients with stage IV NSCLC
- phase I study
- collected PD-L1 expression from tumors

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2\textsuperscript{nd} line Anti-PD-L1 in NSCLC (any histology)

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2nd line Anti-PD-1 in NSCLC (any histology)


Median OS: 12 mo
Previously treated OS: 9.3 mo
Previously untreated OS: 16.2 mo

1st line immunotherapy for stage IV NSCLC

1st line immunotherapy for stage IV NSCLC

KEYNOTE 024
- Randomized phase 3 trial
- Pembrolizumab q3 week versus physician choice 1st line platinum doublet chemotherapy
- 305 patients enrolled, untreated stage IV NSCLC (any histology)
- >50% PD-L1 expression
- no EGFR mutation or ALK translocation


1st line immunotherapy for stage IV NSCLC

Overall Survival in the Intention-to-Treat Population

OS:
Not reached in either arm

Median duration of response:
IO – not reached
Chemo – 6.3 mos

1st line immunotherapy for stage IV NSCLC

Led to FDA approval for single-agent pembrolizumab as 1st line therapy for stage IV NSCLC with >50% PD-L1 expression

What about the patients with <50% expression of PD-L1?
Anti-PD-1 with Chemotherapy in Stage IV Squamous Cell Lung Cancer

KEYNOTE 407
- Randomized phase 3 trial
- Platinum doublet chemotherapy q3 weeks, 1:1 randomized to concurrent pembrolizumab or placebo
- 559 patients enrolled, untreated stage IV squamous NSCLC
- Stratified by PD-L1 expression
- No EGFR mutation or ALK translocation
Anti-PD-1 with Chemotherapy in Stage IV Squamous Cell Lung Cancer

Overall Survival in the Intention-to-Treat Population

OS:
• 15.9 mos in combined
• 11.3 mos in chemo only


Anti-PD-1 with Chemotherapy in Stage IV Non-squamous NSCLC

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

ORIGINAL ARTICLE


Gandhi et al. NEJM 2018; 379: 2078-2092
Anti-PD-1 with Chemotherapy in Stage IV Non-squamous NSCLC

KEYNOTE 189
• Randomized, double-blind, phase 3 trial
• Platinum doublet chemotherapy q3 weeks; 2:1 randomized to concurrent pembrolizumab versus placebo
• 616 patients enrolled, untreated stage IV non-squamous NSCLC
• Stratified by PD-L1 expression
• No EGFR mutation or ALK translocation

OS at 12 months:
- 69.2% combo
- 49.4% chemo alone
- HR for death 0.49 (0.38-0.64)
Immunotherapy side effects

Typical side effects:
- Thyroid dysfunction
- Pruritus +/- rash
- Arthralgias/myalgias
- Temperature elevation
- Fatigue

Uncommon but severe side effects:
- Colitis
- Pneumonitis
- AKI/CKD
- Multiple endocrine complications
- Neurologic complications

Management of side effects

- Grade severity
- Continue treatment if mild
- If moderate/severe, hold treatment (possibly permanently) and treat with high dose steroids

Steroids should be AVOIDED if at all possible during treatment with immunotherapy

Immunotherapy for Stage III NSCLC

‣ First major addition to management of stage III disease in 15 years

‣ 709 patients with inoperable stage III disease treated with concurrent chemoradiation
  • treated with consolidation therapy
  • 2:1 durvalumab versus placebo
  • Phase 3 trial
  • treatment q2 weeks for up to 12 months after completion of concurrent chemoradiation

Antonia et al. N Engl J Med September 2018; Online NEJM.org
Immunotherapy for Stage III NSCLC

Antonia et al. N Engl J Med September 2018; Online NEJM.org
Immunotherapy for Stage III

Progression free survival
- Durvalumab = 16.8 months
- Placebo = 5.6 months

Median time to death or distant metastases
- Durvalumab = 28.3 months
- Placebo = 16.2 months

Median OS
- Durvalumab = NR
- Placebo = 28.7 months

Prior standard of care was NO CONSOLIDATION

Case 3
70 year old former smoker (138 pack years)
Stage IIIA squamous cell lung cancer
Inoperable
Treated with standard chemoradiation followed by
Immunotherapy with durvalumab

September 2017
August 2018
Next “big” work in lung cancer treatment

- Role for tumor mutation burden guiding treatment
- Immunotherapy in earlier stages of disease
- Combinations of immunotherapy
- Predicting likelihood of benefit of therapies
- Predicting risk of toxicity of therapies
- Epigenetics
- Role of Microenvironment

Reducing Incidence of Lung Cancer

- Tobacco prevention
- Tobacco cessation
- Reducing/eliminating 2nd hand exposure
- MORE research for growing population of never smoker with lung cancer
- Addressing environmental exposures (radon, diesel exhaust, other chemical exposures)
THANK YOU!

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