Lung and Aerodigestive malignancies

Lung Cancer

The Grim Reality of Lung Cancer

- The leading cause of cancer-related death worldwide and in the United States - “#1 cancer killer”.
- An estimated 1.8 million new lung cancer cases occurred in 2012, accounting for about 13% of total cancer diagnoses.
- Lung cancer was the most frequently diagnosed cancer and the leading cause of cancer death among males in 2012.
- Among females, lung cancer was the leading cause of cancer death in more developed countries.
- Estimated 1,095,200 new cases in men and 513,600 in women in 2008 Worldwide.
- 70% will have evidence of locally advanced or metastatic disease at presentation.
- We urgently need to improve our treatment strategies.

Lung Cancer Facts

- More people die from lung cancer than any other type of cancer. This is true for both men and women. In 2015 lung cancer is still estimated to account for more deaths than breast cancer, prostate cancer, and colon cancer combined.
- 115,610 men and 105,590 women are estimated to be diagnosed with lung cancer in the USA in 2015.
- 86,380 men and 71,660 women are estimated to die from lung cancer in USA in 2015.

COI

- I am a consultant for GSK, Merck, BMS, Pfizer.
- I receive funding for research from Novartis, the NIH.

Incidence of lung cancer by gender and region of the world

Siegel RL, Cancer Statistics; CA 2015

Torre LA, Cancer Statistics; CA 2012
Lung Cancer incidence by Histologic subtypes

Mesa et al, PLoS One. 2015

Small Cell Lung Cancer Overview

Small Cell Lung Cancer (SCLC)

- Most aggressive lung cancer type
- Median survival (no treatment) = 2-4 months
- More responsive to chemotherapy and radiation than NSCLC

Small Cell Lung Cancer Treatment: Limited Disease

- Combination chemotherapy
  - EP (etoposide + cisplatin)
  - no observed benefit of therapy longer than 4-6 cycles
- Radiotherapy
  - increases survival by about 5%
  - most effective when given early

Lung Cancer Risk After Smoking Cessation*  


Relationship to Smoking

Small Cell Lung Cancer: Staging
Small Cell Lung Cancer Treatment: Extensive Disease

- Combination chemotherapy (4-6 cycles)
  - EP/EC = etoposide + cisplatin or carboplatin
- Radiotherapy
  - no survival benefit
  - palliative only

Treatment Outcome

- **Limited disease**
  - response rate: 65%-90% (45%-75%) (CR)
  - median survival*: 10-16 months
  - 5-year survival: 18%
- **Extensive disease**
  - response rate: 70%-85% (20%-30%) (CR)
  - median survival*: 6-8 months
  - 5-year survival: 1%-2%

* Median survival untreated patients: 2-4 months.

Intergroup Trial of Concurrent Chemoradiotherapy Versus Hyperfractionated Chemoradiotherapy in Limited Stage Small-Cell Lung Cancer

Paraneoplastic Syndromes

- Small Cell
  - inappropriate secretion of ADH
  - ectopic ACTH secretion
  - neurologic-myopathic syndromes (Eaton-Lambert myasthenic syndrome)
- NSCLC
  - hypercalcemia (PTH-related-squamous)
  - skeletal-symptoms HPOA

Clinical Features and Diagnostic Work-Up

SCLC Summary

- 15% of lung cancer (on the decline)
- Worse in terms of prognosis
- Associated with paraneoplastic syndromes (SIADH, ACTH, Neuro)
- Staged as extensive versus limited
- Always scan the brain
- Chemotherapy always part of the treatment
- No surgery
- Early XRT for limited disease.
- Prophylactic Cranial irradiation if responded to therapy regardless if limited or extensive stage

Case 1 (Small Cell)

- A 75 year old female with a long standing history of smoking is presenting with confusion and hyponatremia. A LUL lung lesion is noted on CT scan and she had a surgical resection with negative margins. Pathology confirms small cell carcinoma of the lung. Her sodium level normalizes and she returns home. Her performance status is 0-1 on the ECOG scale. She is coming to you for additional advise on therapy. You would recommend:
Case 1 Answers

a. Radiation therapy to her disease location followed by chemotherapy
b. No therapy in light of her age but rather close observation
c. Chemotherapy only
d. Radiation therapy only

Stage I NSCLC

- No lymph-node metastases (N0).
- T1,N0: Tumor < 3cm, surrounded by normal lung and not in a main bronchus (Stage IA).
- T2,N0: Tumor >3cm, or involving a main bronchus but not within 2cm of the carina, or invading the visceral pleura (Stage IB).

Stage IIIB NSCLC

- Any T4: Tumor of any size invading mediastinum, heart, great vessels, trachea or carina, esophagus, vertebral body (designated T4) or more than one lesion in different lobes ipsilaterally.
- Any N3 is: Metastases to supraclavicular or contralateral mediastinal/hilar lymph nodes (designated N3).
- Also any N3 disease will define stage IIIB.
- (IIIB= T4N2 or T4N3)
- Pleural effusion or bilateral nodules is M1a not T4

Metabolic Staging (PET)

- Metabolic imaging technique (5F-fluorodeoxyglucose)
- Probably the most sensitive non-invasive method to stage NSCLC
- Sensitivity for detection of mediastinal and distal mets is 95%, specificity 83%
- CT scan values for mediastinal are 75% and 66% respectively
- Still need mediastinoscopy or biopsy for most accurate staging

Prevalence of Metastases in Lymph Nodes by Size of Node on CT scan

<table>
<thead>
<tr>
<th>Node size on CT (cm)</th>
<th>% with metastases</th>
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<tr>
<td>&lt;1</td>
<td>13%</td>
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<td>1-1.9</td>
<td>25%</td>
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<tr>
<td>2-2.9</td>
<td>62%</td>
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<tr>
<td>3-3.9</td>
<td>67%</td>
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<tr>
<td>4+</td>
<td>100%</td>
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McCLOUD, Radiology 1992
**Indications for Surgery**

- Stage I & II non-small cell
- Stage I small cell
- Stage III
  - Most T3 N1 tumors
  - Selected N2 disease
  - Occasionally T4 or N3 disease
- Stage IV
  - Solitary metastases

**Stage of NSCLC at Presentation**

- Stage I: 15%
- Stage II: 15%
- Stage IIIA: 10%
- Stage IIIB: 20%
- Stage IV: 40%

**Five Year Survival by Stage for Non-Small Cell Lung Cancer**

![Graph showing survival rates by stage]

**NSCLC: Multimodality Treatment**

**Stage IIIB NSCLC: Chemotherapy + Radiation Therapy vs Chemotherapy**

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>RT + CT</th>
<th>CT Alone</th>
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<tr>
<td>1 year</td>
<td>58</td>
<td>66</td>
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<td>2 years</td>
<td>36</td>
<td>9</td>
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<td>3 years</td>
<td>29</td>
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**Locally Advanced NSCLC stage IIIA/B**

“Concurrent Chemo-RT Improves Survival Compared to Sequential Chemo-RT”

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<th>RTOG 9410</th>
<th>MS</th>
<th>1 yr</th>
<th>2 yr</th>
<th>p</th>
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<tr>
<td>Sequential</td>
<td>14.6m</td>
<td>57%</td>
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<tr>
<td>Concurrent</td>
<td>17m</td>
<td>63%</td>
<td>35%</td>
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<table>
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<tr>
<th>West Japan</th>
<th>MS</th>
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<th>5 yr</th>
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<tr>
<td>Sequential</td>
<td>13m</td>
<td>14.7%</td>
<td>8.8%</td>
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<tr>
<td>Concurrent</td>
<td>16.5m</td>
<td>22.3%</td>
<td>15.8%</td>
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**Locally Advanced NSCLC: Definition**

(All of these are treated with concurrent therapy)

- Stage IIIA
  - Bulky N2 disease
  - Multi-station N2 disease
- Stage IIIB
  - T4 N2 or any N3 (without pleural or pericardial effusion) (if effusion exists and is positive treat only with chemotherapy)

Approximately 15-20% of NSCLC will fit into the above categories

150,000 to 200,000 cases each year globally
A 45 year old smoker presents to you with shortness of breath on exertion of 3 months duration. On physical exam he has clubbing but no cyanosis. His pulse oxymetry is 90% and he appears comfortable at rest. A cardiac work up is unremarkable. A PET/CT scan reveals a LUL mass that is involving the aorta with LN involvement in the mediastinum or hilar areas. There is no evidence of metastatic disease. A biopsy confirms a squamous cell carcinoma of the lung.

Case 2 correct answer

His staging is:
- Stage II
- Stage IIIA
- Stage IIIB (T4N2)
- Stage IV

LA-NSCLC: The Good News

Survival of good PS patients with unresected Stage III NSCLC has SIGNIFICANTLY improved over the past 20 years.

Resolved Issues In Stage IIIB NSCLC

- Chemotherapy (cisplatin-based) plus radiotherapy is superior to radiotherapy alone in good PS patients
- Chemotherapy (cisplatin-based) plus radiotherapy is superior to chemotherapy alone in good PS patients

Case 3

The patient is not interested in a clinical trial. Your recommendation for therapy outside of a clinical trial is:
- Refer to thoracic surgery as resection is his best chance for cure. Follow with chemotherapy and radiation.
- Treat with chemotherapy followed by surgical resection
- Treat with concurrent therapy (chemotherapy and radiation)

Treatment of Advanced Disease

- Stage IV
- Account for 40%
- (Use chemotherapy only for these patients) - Radiation may be added to palliate symptoms or for Brain metastases
What is the best regimen for stage IV disease?

- Phase III trial of 4 regimens (ECOG):
  - CDDP and Paclitaxel
  - Gemcitabine and CDDP
  - Docetaxel and CDDP
  - Paclitaxel and Carboplatin

RESULTS:
- No Significant differences found
- Newer agents are needed eg anti-angiogenesis

Case 4

- A 73 year old male with a negative past medical history presents with weakness and SOB and was found to have a large RLL mass with pleural effusion that is obliterating the right lung. A CT scan of the chest abdomen and pelvis reveals multiple areas of metastatic disease including bilateral adrenal metastases, and liver metastases. A diagnosis of adenocarcinoma of the lung is confirmed. He is seeking advice and wishes to be treated. Even though tired he can still perform his daily activities and has an estimated PS of 2 on the ECOG scale. Your recommendation is:
  a - Proceed to radiation therapy to treat the chest symptoms and help his breathing
  b - Proceed with palliative measures only in light of his poor performance and extensive disease and discuss hospice care.
  c - Offer chemotherapy with a doublet agent in addition to draining of the effusion and possible pleurodesis after his lung expands.

Surgical Pathological Stage

<table>
<thead>
<tr>
<th>Months after Treatment – Cumulative Percent Surviving</th>
<th>sStage</th>
<th>12 (%)</th>
<th>24 (%)</th>
<th>36 (%)</th>
<th>48 (%)</th>
<th>60 (%)</th>
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<tr>
<td>IA (511)</td>
<td>94</td>
<td>86</td>
<td>80</td>
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<td>IB (549)</td>
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<td>IIB (375)</td>
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<td>56</td>
<td>46</td>
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<tr>
<td>IIIA (399)</td>
<td>64</td>
<td>40</td>
<td>32</td>
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</table>

Overall comparison, P<0.05

Adjuvant therapy can be recommended for all stages between IB and III A (for IB more definite indication if lesion is >4 cm)
Indications for adjuvant therapy

• Any disease that is resected except stage IA
• Stage IB: may be indicated

Case 5

• A 65 year old female presents with chest discomfort. On CT scan she has a RUL mass that abuts the pleura and is 6 cm in size. She has a CT guided biopsy confirming an adenocarcinoma. Her PET scan confirms the RUL mass and uptake in the ipsilateral hilar area confirmed by biopsy with an SUV of 10. She has a T2bN1 stage Ib disease.

• You recommend the following

Case 5 Answers

a- Chemotherapy followed by a lobectomy and Lymph node dissection
b- Lobectomy with LN resection followed by chemotherapy
c- Lobectomy with LN resection followed by radiation therapy
d- Lobectomy with LN dissection followed by chemotherapy and radiation

NSCLC in 2015

• Never-smokers are a subset of NSCLC
• Targeted therapies are standard approaches
• Multi-modal therapy is used to improve outcome
• Molecular profiling is integrated into routine care
• Early diagnosis is now based on CT screening
Mechanisms of EGFR resistance

Yu et al, CCR, 2013

Cancer Immunotherapy

- Genetic mutations that underlie cancer cell transformation also render them recognizable as foreign by the body immune effector cells
- Cancer cells may evade immune surveillance through aberrant PD-L1 expression
- Inhibiting the PD-L1/PD-1 interaction can restore anti-tumor immunity


Head and Neck Cancer

- Recognize the classic risk factors: tobacco and smoking
- Recognize HPV as a rising risk for OP cancers
- Recognize the standard of care for locally advanced disease: i.e. concurrent chemotherapy and radiation therapy

Human Papilloma Virus: HPV

- types -16 and -18 are most common
- HPV+ patients with HNSCC tend to be younger, non-smokers, and non-drinkers c/w HPV-
  - These patients also have lower risk of death compared with HPV- patients
  - While only 25% of all HNSCC patients are HPV+, more than 50% of oropharyngeal patients are HPV+
  - HPV also has high predilection for base of tongue and palatine tonsils

Head and Neck Cancer

- Estimated 49,260 cases in year 2010 in U.S.*
  - OP leading cancer in U.S.
  - >11,460 deaths & 3% of all cancers
- World wide: more than 600,000 /yr
  - 10% of all cancers worldwide
- Typically > 50 yrs old, tobacco and alcohol users
- HPV related: younger age, multisexual partners and oral sex
- Histology: >90% squamous cell
- Early-stage disease (I, II) curative > 80%
- Locally advanced disease has poorer prognosis and their 5-yr survival rate < 50%

*Oral cavity, pharynx, & larynx

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### Outcomes

- **Early Stages (I & II):**
  - Accounts for 1/3rd of patients
  - Curative results with surgery or radiation 60 - 80%
  - Second primary tumors: (SPTs) is the current focus

- **Locally advanced stages (III & IV):**
  - 2/3rd of patients
  - Multimodal treatment
  - 40 - 80% local recurrence
  - 10 - 30% distant disease

### Case 6 (HNCA)

Mrs. EUH is a 50 year old female who is a chronic heavy smoker and who presents with hoarseness of one month duration. On laryngoscopic exam she is found to have a laryngeal tumor with vocal cord fixation, that does not invade the paraglottic space or thyroid cartilage. She has a single ipsilateral lymph node metastases noted on CT scan of 2 cm. She is staged as T3N1 or stage III glottic tumor. She is interested in non surgical therapy and is very concerned about long-term side effects.

- You would recommend

### Case 6 (HNCA) Answers

a. A total Laryngectomy
b. Induction chemotherapy followed by radiation therapy or surgery for residual disease
c. Concurrent chemotherapy and radiation therapy
d. Laser surgery

### Approved chemotherapy agents

- Most widely used: Cisplatin with radiation
- Also Taxanes: Paclitaxel, Docetaxel
- Catuximab which is an epithelial growth factor receptor (EGFR) monoclonal antibody is the only approved targeted agent for head and neck cancer

### Esophageal CA

- Gender: 7X Male > Female
- Incidence of squamous cell cancer:
  - Increases with age
  - Median age 69
- Race:
  - SCC: 3X AAs > Caucasians
  - Adenocarcinomas more common in Caucasians
- Geography
  - Incidence 20 - 30 X China > U.S.
  - Esophageal “cancer belt” China to Middle East
- Disease site
  - Squamous cell carcinoma upper and body
  - Adenocarcinoma lesions closer to GE junction

### Overall Survival

- [Graph showing overall survival data](source: Gillison M, et al, AACR 2016)
Esophageal Cancer incidence Worldwide

Source: Cancer Statistics, Jemal et al 2010

Esophageal CA

- Recognize that adenocarcinoma incidence is increasing in USA
- Recognize that Barrett’s (epithelial metaplasia) is a precursor for adenocarcinomas

EC - treatment

- If resectable: add chemotherapy only or chemotherapy and radiation before or after surgery.
- If unresectable: chemotherapy and radiation simultaneously (concurrent setting)
- If metastatic: consider chemotherapy only if patient has good performance eventhough disease is incurable.

Case 7 (EC)

- A 45 year old male with a history of reflux disease presents with difficulty swallowing of 3 months duration and swelling in his left lower extremity. An doppler ultrasound of his extremity confirms a DVT. An endoscopic exam with Endoscopic Ultrasound confirms an adenocarcinoma of the distal esophagus that is staged as T3N2 disease. He is interested in the most aggressive therapy. In addition to starting anticoagulation your recommendation is the following:

Case 7 (EC)

a- Surgical resection followed by adjuvant chemotherapy and radiation
b- Chemotherapy only followed by surgical resection
c- Concurrent chemotherapy and radiation therapy
d- Concurrent chemotherapy and radiation therapy followed by surgical resection
e- All of the above are possible correct answers

“Mr. Osborne, may I be excused? My brain is full.”
Key to clinical cases

- Case 1: c
- Case 2: c
- Case 3: c
- Case 4: c
- Case 5: b
- Case 6: c
- Case 7: e

APPENDIX (STAGING)

Current NSCLC Staging

<table>
<thead>
<tr>
<th>T/M</th>
<th>Tumor ≤ 2 cm</th>
<th>Tumor &gt;2 but ≤ 3 cm</th>
<th>Tumor &gt;3 but ≤ 5 cm</th>
<th>Tumor &gt;5 but ≤ 7 cm</th>
<th>Tumor &gt;7 cm</th>
<th>Tumor with invasion</th>
<th>Multiple nodules in the same lobe</th>
<th>Tumor extension in mediastinum or major organs</th>
<th>Nodules in different ipsilateral lobes</th>
<th>Pleural dissemination</th>
<th>Nodules in contralateral lung</th>
<th>Distant metastasis outside of chest</th>
</tr>
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<tbody>
<tr>
<td>T1a</td>
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Current NSCLC Staging (cont)

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</tbody>
</table>

NSCLC: Staging and Prognosis

NSCLC: Stage I and Stage III

Stage I and IIb
Stage III and IIIB

NSCLC: Stage IIIA and Stage IIIB*

Stage IIIA
Stage IIIB

* Adapted from, Mountain CF. Chest. 1986;89(suppl 4):225S-233S.