The Pathology of Lung and Colon Cancer

Dean W. Joelson, M.D.

Lung Cancer Epidemiology

- Risk Factors:
  - Smoking
  - Second-hand smoke
  - Other environmental exposures:
    - Radon gas, asbestos, diesel exhaust, etc.
    - Radiation therapy (i.e. after mastectomy for breast cancer)
    - Family history

- In 2008:
  - 204,493 people in the United States were diagnosed with lung cancer, including 211,886 men and 96,607 women.
  - 158,592 people in the United States died from lung cancer, including 88,541 men and 70,051 women.

Lung and Bronchus Cancer Incidence Rates by Race/Ethnicity and Sex, U.S., 1999–2008

Combined data from the National Program of Cancer Registries as submitted to CDC and from the Surveillance, Epidemiology and End Results program as submitted to the National Cancer Institute in November 2010.

Stage at diagnosis Stage distribution (%) 5-year survival (%)

Lung Cancer

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>Stage distribution (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to primary site)</td>
<td>15</td>
<td>52.2</td>
</tr>
<tr>
<td>Regional (spread to regional lymph nodes)</td>
<td>22</td>
<td>25.1</td>
</tr>
<tr>
<td>Distant (cancer has metastasized)</td>
<td>56</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Colon Cancer Epidemiology

- Risk factors:
  - Inflammatory bowel disease
  - A personal or family history of colorectal cancer or colorectal polyps.
  - A genetic syndrome such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (Lynch syndrome).
  - Lifestyle factors that may contribute to increased risk of colorectal cancer include:
    - Low fiber intake
    - High-fat diet
    - Smoking
    - Alcohol consumption

- In 2008
  - 142,950 people in the United States were diagnosed with colorectal cancer, including 73,183 men and 69,767 women.
  - 52,857 people in the United States died from colorectal cancer, including 26,933 men and 25,924 women.

Colon Cancer
Incidence Rates by Race/Ethnicity and Sex,

Colon Cancer
Survival by Stage

<table>
<thead>
<tr>
<th>Stage subcategory</th>
<th>Stage distribution (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (confined to primary site)</td>
<td>20%</td>
<td>80.9</td>
</tr>
<tr>
<td>Regional (spread to regional lymph nodes)</td>
<td>26%</td>
<td>49.9</td>
</tr>
<tr>
<td>Distant (cancer has metastasized)</td>
<td>20%</td>
<td>11.9</td>
</tr>
</tbody>
</table>
Colon cancer: okay
Lung cancer: bad

- Overall five year survival rates:
  - Colon: 65.3%
  - Lung: 16.8%

Types of Colon Cancer

- Adenocarcinoma (~95%)
- Gastrointestinal stromal tumor
- Lymphoma
- Other carcinomas
  - Adenosquamous carcinoma
  - Spindle cell carcinoma
  - Undifferentiated carcinoma
- Neuroendocrine tumors
  - Most are carcinoid tumors
- Melanoma
- Leiomyosarcoma

Types of Colon Adenocarcinoma

- “Conventional”
- Mucinous
- Signet-ring
- Medullary
- Cribriform comedo-type adenocarcinoma, micropapillary carcinoma, serrated adenocarcinoma
Colonic Adenocarcinoma
Sites of Metastasis
- Liver
- Lungs
- Peritoneum
- Bone and bone marrow
- Brain

Microsatellite Instability (MSI)
- Microsatellite instability is a symptom
  - In fact, one doesn’t even need to demonstrate MSI to conclude a patient has MSI
  - The causes of MSI can be tested for directly
- What’s the disease?

Mismatch repair defect
Mismatch Repair Genes

- Mismatch repair proteins correct errors in DNA
  - Most of these errors occur during DNA replication
  - DNA polymerase makes an error once per 10,000 to once per 1,000,000 bases
  - The human genome contains 3 billion base pairs
    - Per cell division, DNA polymerase working alone would produce 3,000 to 300,000 mutations!
  - Safeguards exist to improve fidelity
    - One of these is the mismatch repair proteins

Mismatch Repair Genes

- Mismatch repair (MMR) proteins scan DNA after replication
  - Compare parent strand to daughter strand
  - Correct errors in daughter strand
  - Improve error rate to once per 1 billion to once per 10 billion bases
    - Per cell division, we’re down to zero to three mutations
    - Keep in mind most mutations are harmless

Mismatch Repair Genes

- Most errors occur in areas of DNA which are difficult to replicate
- Microsatellites are an example of such areas
- As microsatellites are preferentially affected, these areas tend to accumulate mutations (i.e. they are unstable)
Immunoperoxidase stains:
- MLH1, MSH2, PMS2, and MSH6
- Absence of one of these proteins is a “positive” result
- A “negative” test does not rule out MMR mutations

PCR testing
- PCR for microsatellite instability
  - MSI-H = microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers in tumors
  - MSI-L = microsatellite instability–low in tumors refers to changes in only one of the five NCI-recommended panels of microsatellite markers in tumors.
  - MSS = microsatellite stable if no changes are present

**So How Do We Test?**

**What does a positive test mean?**

- Can be found in two situations:
  - Sporadically (~12% of colon cancers)
    - MSI-H tumors have a better prognosis
    - MSI-L and MSS tumors behave in similar fashion
  - In patients with Lynch syndrome (~3% of colon cancers)

Lynch syndrome
- Also known as hereditary nonpolyposis colon cancer (HNPCC)
  - Patients have germline mutations in mismatch repair proteins
  - Syndromes of hereditary cancers including:
    - Colon (60-80% lifetime risk)
    - Endometrium (40-60% lifetime risk)
    - Ovarian, urinary tract, stomach, small intestine, bile ducts, brain, and others

- If any of these tests are “positive,” and the patient fits the clinical picture for Lynch (i.e., development of cancer at young age, family history, etc.), the patient can be referred for genetic sequencing to confirm diagnosis of Lynch

**“Conventional” adenocarcinoma Grading**

- **Well-differentiated**: greater than 95% gland formation
- **Moderately-differentiated**: between 50% and 95% gland formation
- **Poorly-differentiated**: between 0% and 49% gland formation
- **Undifferentiated**: no gland formation, mucin production, or neuroendocrine, squamous, or sarcomatoid differentiation

- Well-differentiated, moderately-differentiated, and MSI-H tumors fall into the low-grade category
- Poorly-differentiated tumors are high-grade
Mucinous adenocarcinoma

- Definition: greater than 50% of lesion is composed of pools of extracellular mucin
- Many mucinous adenocarcinomas are MSI-H (microsatellite unstable), and thus have a good prognosis

Mucinous adenocarcinoma
Signet-ring adenocarcinoma

- Definition: greater than 50% of lesion is composed of signet-ring cells
- Usually an aggressive subtype, but can behave more indolently if MSI-H
Medullary adenocarcinoma

- Definition: sheets of malignant cells with abundant eosinophilic cytoplasm exhibiting prominent infiltration by intraepithelial lymphocytes
- Essentially all medullary adenocarcinomas are MSI-H and thus have a good prognosis
Colon Cancer

Immunohistochemistry

- Colonic adenocarcinoma:
  - CK7: Negative
  - CK20: Positive (membrane)
  - CDX2: Positive (nucleus)
  - Villin: Positive (membrane)

Other Colon Tumors

Gastrointestinal Stromal Tumor (GIST)

- Rare in the colon, more common in the stomach and small intestine
- More likely to be malignant
  - Mitotic rate and size are the most important features which predict malignancy
- Differential diagnosis includes:
  - Leiomyosarcoma
  - Peripheral nerve sheath tumor
  - Spindle-cell variety of some other malignancy (such as carcinoma or melanoma)
Gastrointestinal Stromal Tumor (GIST)

- Characteristic immunohistochemical features:
  - C-kit (CD117)
    - CD117 is the molecular target for Gleevec®
  - CD34
  - DOG-1
Gastrointestinal Stromal Tumor

Lymphomas of the Colon
- Comprise ~1% of all colonic malignancies
  - Most lymphomas involve colon secondarily
  - Most common in the cecum
- Common types:
  - Diffuse large B-cell lymphoma
  - Mantle-cell lymphoma
  - Follicular lymphoma
  - Marginal zone/MALT lymphoma

Normal Lymphoid Aggregate
Diffuse Large B-cell Lymphoma

Colon Cancer
Molecular Studies
- Epidermal growth factor receptor (EGFR)
- K-ras and B-raf are part of EGFR signaling pathway

Colon Cancer
Molecular Studies
- Avastin® (bevacizumab)
- Erbitux® (cetuximab)
- Vectibix® (panitumumab)
  - All are FDA approved to treat colon cancer, and all act on EGFR receptor
  - They may, however, be ineffective if K-ras or B-raf are mutated
Lung Cancer

The Carcinomas

- **Non-small cell carcinoma**
  - Adenocarcinoma (30-40% of lung carcinomas)
    - In-situ (formerly known as bronchoalveolar carcinoma)
      - Non-mucinous
      - Mucinous
      - Acinar
      - Papillary
      - Solid
  - Squamous cell carcinoma (25-30% of lung carcinomas)
  - Neuroendocrine tumors (other than small cell)
  - Others
  - Small cell carcinoma (10-15% of lung carcinomas)
    - Some may include large cell neuroendocrine carcinoma in this category

Immunohistochemistry

- **Lung adenocarcinoma**:
  - **CK7** Positive (membrane)
  - **CK20** Negative
  - **TTF-1** Positive (nucleus)
  - **Napsin-A** Positive (cytoplasm)
- **Lung squamous cell carcinoma**:
  - **CK7** Negative
  - **CK20** Negative
  - **TTF-1** Negative
  - **Napsin-A** Negative
  - **p63** Positive (nucleus)
  - **CK5/6** Positive (membrane)
- **Lung neuroendocrine (including small cell carcinoma)**:
  - **Chromogranin** Positive (cytoplasm)
  - **Synaptophysin** Positive (may be weak)
  - **CD56** Positive
Lung Cancer
Sites of Metastasis

- Brain (particularly common for small cell carcinoma)
- Bone
- Adrenal gland
- Liver
- Small intestine

Pulmonary Adenocarcinoma

- Makes up 30-40% of lung cancer cases
- Most cases are seen in smokers
  - But! it's the most common type of cancer in non-smokers
- Usually peripheral
- More likely than other lung cancers to have pleural or chest wall involvement

Pulmonary Adenocarcinoma
In-situ (bronchoalveolar) carcinoma

- No stromal, vascular, or pleural invasion
- 100% cure rate if completely resected
- Tumors with small foci of invasion also have very favorable prognosis
- May have aerogenous dissemination within lung
  - Therefore, often multifocal
- Often show ground-glass opacities on CT
Normal Lung

Lung Adenocarcinoma
In-situ (bronchoalveolar) subtype

Lung Adenocarcinoma
In-situ (bronchoalveolar) subtype
Lung Adenocarcinoma
Papillary subtype

Lung Adenocarcinoma
Solid subtype

Lung Squamous Cell Carcinoma

- Makes up 25-30% of lung cancers
- Over 90% associated with smoking
  - Arsenic also strongly associated with SCC
- Most arise centrally
- May cavitate
- Stage for stage survival better than for adenocarcinoma
Normal Skin and Squamous Mucosa

Intercellular bridges

Squamous Cell Carcinoma
Cytology
Squamous Cell Carcinoma

- Almost all cases due to smoking
- Most arise centrally and often have mediastinal lymphadenopathy at presentation
- Usually metastatic at presentation
  - It's the symptoms of metastatic disease that often bring patients to the doctor
    - Weight loss, abdominal pain (liver mets), bone pain (bone mets), neurological symptoms (brain mets), etc.
- Very sensitive to chemotherapy, but almost all tumors eventually recur
  - Very high mortality
- Does not use TNM staging system
- Staged as either limited or extensive disease

Lung Small Cell Carcinoma
Small Cell Carcinoma

- Cell nuclei crowded together, giving appearance of small cells
- Salt and pepper chromatin
- Nuclear molding

Pankeratin
Small Cell Carcinoma

The Spectrum of Pulmonary Neuroendocrine Tumors

- Carcinoid tumor
  - Often discovered incidentally
  - May occur anywhere in lung
  - Low mitotic rate, indolent behavior (90-98% 5-year survival)
- Atypical carcinoid
  - More often peripheral
  - Slightly higher mitotic rate, more aggressive (61-73% 5-year survival)
- Large cell neuroendocrine carcinoma
  - Aggressive, high mortality (21% 5-year survival)
- Small cell carcinoma
  - Very aggressive, very high mortality
    - Limited disease: 20% 5-year survival
    - Extensive disease: 0% 5-year survival
Neuroendocrine Tumors

- Carcinoid
- Atypical carcinoid
- Large cell
- Small cell

Non-Small Cell Carcinoma

- So-called when the pathologist believes the lung tumor is a carcinoma and is pretty sure it isn’t small cell carcinoma, but is otherwise fairly clueless.
  - Adenocarcinoma? Could be. Nice weather we’ve been having, don’t you think?
  - Squamous cell carcinoma? Your guess is as good as mine. Falcons sure are playing well, aren’t they?

Clinicians *hate* this diagnosis

Non Small Cell Carcinoma
### Lung Cancer Immunohistochemistry

- **Lung adenocarcinoma**
  - CK7: Positive (membrane)
  - CK20: Negative
  - TTF-1: Positive (nucleus)
  - Napsin-A: Positive (cytoplasm)

- **Lung squamous cell carcinoma**
  - CK7: Negative
  - CK20: Negative
  - Napsin-A: Negative
  - P63: Positive (nucleus)
  - CK5/6: Positive (membrane)

- **Lung neuroendocrine (including small cell carcinoma)**
  - Chromogranin: Positive (may be weak)
  - Synaptophysin: Positive (may be weak)
  - CD56: Positive

### Squamous Cell Carcinoma

![Squamous Cell Carcinoma](image)

### Other Lung Tumors

- **Lymphoma**
- **Sarcoma**
  - Most sarcomas in the lung are metastatic
- **Mesothelioma**
  - Technically, a tumor of the pleura (not the lung)
Lung Cancer
Molecular Studies

- EGFR Mutational Analysis
  - EGFR receptors with certain mutations respond BETTER to some therapies
    - Iressa® (gefitinib) and Tarceva® (erlotinib)
- K-ras mutated tumors
  - Do not respond to Iressa® or Tarceva®
- ALK translocation
  - More common in younger patients who have never smoked
    - Xalkori® (crizotinib)
  - Do not respond to Iressa® or Tarceva®

These mutations are relevant for adenocarcinoma.

Quiz!!!

What kind of lung cancer is this?

A. Squamous cell carcinoma
B. Adenocarcinoma
C. Small cell carcinoma
What type of cancer is this?

- A patient presents with abdominal pain. An abdominal CT scan shows multiple liver masses. A core biopsy reveals a poorly-differentiated carcinoma. The following immunoperoxidase stains were obtained:
  - CK7: Negative
  - CK20: Positive
  - TTF-1: Negative
  - Napsin-A: Negative
  - p63: Negative
  - CK5/6: Negative
  - Chromogranin: Negative
  - Synaptophysin: Negative

A. Pulmonary adenocarcinoma
B. Squamous cell carcinoma
C. Small cell carcinoma
D. Colonic adenocarcinoma

Of each pair, which has the worst prognosis?

- A. Stage 1 colonic mucinous adenocarcinoma
- B. Stage 1 pulmonary acinar-type adenocarcinoma
Of each pair, which has the worst prognosis?

- A. Stage 1 colonic mucinous adenocarcinoma
- B. Stage 1 pulmonary acinar-type adenocarcinoma
- A. Stage 2 colonic “conventional” adenocarcinoma
- B. Stage 1 pulmonary squamous cell carcinoma
- A. Limited extent pulmonary small cell carcinoma
- B. Stage 4 colonic signet-ring adenocarcinoma

What type of colon cancer is this?

- A. Signet-ring cell adenocarcinoma
- B. Medullary adenocarcinoma
- C. Mucinous adenocarcinoma
- D. Conventional adenocarcinoma

Which of the following statements is true?

- A. MSI-H (microsatellite unstable) colon tumors have a worse prognosis when compared to tumors without microsatellite instability
- B. Colon adenocarcinomas with K-ras mutations do not respond to therapy with Erbitux®
- C. EGFR mutational analysis in lung adenocarcinoma is obtained to determine which tumors will not respond to therapy with Tarceva®
- D. Squamous cell carcinomas of the lung are the primary tumor investigated for ALK translocations
The End