Role of the Pulmonologist in Diagnosis and Treatment Selection for Lung Cancer
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Evolving Roles of the Pulmonologist
- From Phthisis-ist to Physiologist to the present
- From hand-holding (hopeless) to hand-wringing (helpless) to hand-waving (clueless) to...
- From compartmentalization (often left outside) to multi-discipline inclusion (ideally)
- Critical Partnerships with Imaging:
  1) Respirology & imaging
  2) Bronchoscopy & imaging
  3) Tissue and imaging
  4) Disease prevention and imaging
Slide 4

Phtisis

Definition (Gk): A Wasting Disorder; "Consumption" that claimed up to 25% of European population’s lives

Slide 5

The Pulmonologist

Slide 6

Annual Age Adjusted Cancer Death Rates 1930 - 2001

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Pulmonologists & Lung Cancer (1960s)
Late Diagnosis & Therapeutic Nihilism
• Pre-flexible bronchoscopy – pre-CT imaging
• Most LCs diagnosed by sputum cytology
  high specificity
  but
  poor sensitivity
• Limited role of rigid bronchoscopy
• Treatment – surgery & BSC

You’ve got Cancer
Lung Cancer!

Lung Cancer Stage Distribution
Lung Cancer Management in the 70s & 80s:
Reamo, Beamo & Chemo

? Role of the Pulmonologist?
Pulmonologists & Lung Cancer (1980-90s)

Initial Diagnosis & Late Management of often fatal complications: continued nihilism

- Advances in Chest Imaging
- Flexible bronchoscopy, percutaneous FNA – improved diagnostic sensitivity, poor tissue staging
- Treatment – slow incorporation of multi-modality therapy
- Complications - toxicities from chemotherapy (pre-growth factors), radiation pneumonitis
- Called to manage chronic worsening of COPD or acute exacerbations (pneumonia, sepsis)

Leading Causes of Death in US

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>Deaths [Number]</th>
<th>Deaths [Rate]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heart diseases</td>
<td>696,947</td>
<td>28.5</td>
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<tr>
<td>2</td>
<td>Cancer</td>
<td>557,271</td>
<td>22.8</td>
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<tr>
<td>3</td>
<td>Cerebrovascular diseases</td>
<td>162,672</td>
<td>6.7</td>
</tr>
<tr>
<td>4</td>
<td>Chronic lower respiratory diseases</td>
<td>124,816</td>
<td>5.1</td>
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<td>5</td>
<td>Accidents (unintentional injuries)</td>
<td>106,742</td>
<td>4.4</td>
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<tr>
<td>6</td>
<td>Diabetes mellitus</td>
<td>73,249</td>
<td>3.0</td>
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<tr>
<td>7</td>
<td>Influenza &amp; pneumonia</td>
<td>65,681</td>
<td>2.7</td>
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<tr>
<td>8</td>
<td>Alzheimer disease</td>
<td>58,866</td>
<td>2.4</td>
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<tr>
<td>9</td>
<td>Nephritis, nephrotic syndrome &amp; nephrosis</td>
<td>40,974</td>
<td>1.7</td>
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<tr>
<td>10</td>
<td>Septicemia</td>
<td>33,865</td>
<td>1.4</td>
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<tr>
<td>11</td>
<td>Intentional self-harm (suicide)</td>
<td>31,655</td>
<td>1.3</td>
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<tr>
<td>12</td>
<td>Chronic liver disease &amp; cirrhosis</td>
<td>27,257</td>
<td>1.1</td>
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<tr>
<td>13</td>
<td>Hypertension &amp; hypertensive renal disease</td>
<td>20,261</td>
<td>0.8</td>
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<tr>
<td>14</td>
<td>Assault (homicide)</td>
<td>17,638</td>
<td>0.7</td>
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<tr>
<td>15</td>
<td>Parkinson disease</td>
<td>16,959</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Note: Percentages may not total 100 due to rounding. Symptoms, signs, and abnormalities and pneumonitis due to solids and liquids were excluded from the cause of death ranking order.


Clinical N (nodal) Stage Vs Pathologic N Stage Survival
Slide 13

Perception of Lung Cancer Therapy

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Warning from our (pulmonary) elders regarding an interest in Lung Cancer

John Murray: “young Rex, don’t go to the Dark Side!”

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IASLC International Lung Cancer Staging Project

JTO 2007
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>109,000 Cases Submitted

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Treatment Modalities

Combined Chemo-radiation 1990 – 2000: 3% of all patients

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Pulmonologists and Lung Cancer: Entering the 21st Century

- Increasing emphasis on a comprehensive and integrated Multi-disciplinary Team approach, offering of Multi-modality LC therapies, emphasis on thorough pathologic staging
- Improvements of Imaging technology, incorporated into various Real-Time BIGI (Bronchoscopic Image-Guided Interventions)
- Molecular Biology advances - Overlapping development / interest in inflammatory lung & airways diseases (COPD, ILD) & dysplasia
An Example of Successful Multi-disciplinary disease management COPD: NETT for LVSR

- Thoracic Surgery
- Pulmonary
- Radiology
- Rehabilitation services
- Nutrition and other support services

Is this patient’s LUL tumor resectable

FEV1 0.87L (34% pred)
FEV1/FVC 45%
DLCO 43% predicted
Acceptable Physiologic Thresholds for Lung Cancer Resection (pre NETT)

• Traditional cut-offs for resection too strict: FEV1 > 1.0 - 1.2L
• Predicted Post-Operative (PPO) FEV1 of 800 ml - 1.0L. FEV1 and DLCO >= 40% predicted
• Exercise Testing: maximal VO2 consumption (12 to ) 15 ml/kg/min

Selective Quantitative Perfusion (Split Lung Function)

Selective Quantitative Perfusion Inhomogeneous COPD
Lessons Learned from LVRS which may be applicable to Lung CA Rx

- Expand the envelope of “Resectable” disease
- Aggressive & mandatory 6 wks rehabilitation
- Attention to nutrition, both pre and post operative
- O2 supplementation in hypoxemic patients
- Perioperative management: epidural catheters, PCA & NSAIDs to encourage early ambulation; bedside treadmill / aggressive chest physiotherapy; ? Minitrach - for feeble cough / heavy secretions

Increasing Appreciation and Incorporation of advanced Imaging to aid in LC Diagnosis & Staging

1. Metabolic Imaging to guide diagnosis and to monitor therapy
2. Multi-planar reconstruction of CT data
3. Software development to enhance image-guided bronchoscopic navigation & biopsies
4. Increasing role of Endoscopic Ultrasound

Aim for the Highest Staged Lesion, i.e. N2 = IIA node
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Fused PET-CT Image

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Fused PET-CT images of Liver Mets

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Radiology Report

INDICATION: Abnormal chest odograph. History of smoking.

TECHNIQUE: Axial CT images of the chest performed after uneventful administration of 100 cc of Omnipaque 350.

COMPARISON: Direct comparison to a prior study from 06/03/2013.

**FINDINGS:** There is a large airspace opacity or mass of irregular contour occupying the posterior segment of the right upper lobe, abuts the right major fissure with displacement inferiorly. Air bronchogram suggesting partial obstructive process. The mass obliterates the right hilar vessels, predominantly right upper lobe pulmonary artery. No apparent occlusion appreciated. The mass measures 5.4 cm in crescent-measure dimension, 0.1 cm in AP dimension and 7.8 cm in transverse dimension. Narrowing of the right upper lobe bronchus observed on the coronal and sagittal planes. Findings consistent with primary lung cancer.

There are small nodules in the mediastinum. No enlarged lymph nodes left hilar or mediastinal lymph nodes. No other local abnormalities. There is atelectasis, mild dilatation of the aorta. Generally satisfactory. Juxtaposition. There is small hiliar hernia.
BC: Large T3 (T2c) primary lesion, what about Nodal Staging?
Per CT: "Non pathologic LN"

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Long Vs Short Axis

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Craig Ben "non pathologic LN" viewed from coronal & Sagittal planes

Other Views of the LN using MPR
Case L.L.- 85 y/o W F with multiple lung nodules

- Multiple medical problems – h/o NSCLC s/p LUL resection 5 years prior, with finding of two foci of adenocarcinoma with BAC features in lobe
- Six months of progressive dyspnea on exertion
- Seizure (denies LOC); A-fib with pacemaker, hypertension, hypercholesterolemia
- Tobacco use 60 pack years, worked in shipyard with likely asbestos exposure
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Searching for ABS leading to lesions
Tsuboi Class I
With Tilt Planes, Class IV

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Target #2 RUL RB3 axillary segment
Tilt Plane view reveals Air Bronchus leading to the lesion
Coronal View Tilted Coronal View

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Target 3: RUL B1 apical lesions
Note Location of Pacemaker
Slide 40

Bronchoscopy Using Fluoroscopy, Radial EBUS, Guide Sheath system

Cytology Brushing up RR2 using a Guide Sheath as conduit

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Using Guide Sheath for passage of stiff instruments along bent airway segments

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Approach Target #2: RUL axillary segment

? How to make the lesion visible?
Use of the Rotatable C-arm
Should you rotate it RAO/LPO, or rotate the arm LAO/RPO?

Target #3 RUL Apical segment lesions
Invisible by planar Fluoroscopy
Using a thinner bronchoscope to steer additional two to three segmental divisions

Reliance of combination of EBUS & Fluoro
Results

C10-7943 Accessioned on 03/24/2010 at 10:28 am

FINAL DIAGNOSIS -----------
Pathologist: SYED Z. ALI, M.D.

1) BRONCHOSCOPIC BRUSH, RIGHT UPPER LOBE, RB2:
FINAL DIAGNOSIS: BENIGN RESPIRATORY EPITHELIUM.

2) LUNG, TRANSBRONCHIAL, FNA, RIGHT UPPER LOBE, RB2 MASS:
FINAL DIAGNOSIS: BENIGN RESPIRATORY EPITHELIUM. NO MALIGNANT NEOPLASM IDENTIFIED.

3) BRONCHOSCOPIC BRUSH, RIGHT UPPER LOBE, APICAL SEGMENT RB1:
FINAL DIAGNOSIS: RARE ATYPICAL CELLS IN A BACKGROUND OF BENIGN RESPIRATORY EPITHELIUM.

4) LUNG, TRANSBRONCHIAL, FNA, RIGHT UPPER LOBE, APICAL SEGMENT RB1 TOUCH PREP:
FINAL DIAGNOSIS: POORLY DIFFERENTIATED, NON-SMALL CELL CARCINOMA.

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Superdimension: Pre-op Planning
Generates a 3D CT "Road-Map" from standard CT
courtesy superDimension

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SuperDimension Bronchus EM Navigation System
"Bronchus" System
Electro-Magnetic Bronchoscopic Navigation System
SuperDimension: Steering

Alternative to Steering a Thin FOB:
A highly maneuverable catheter with accurate and guided steering superDimension™/Bronchus system
Electromagnetic Locator Guide
Inserted through an Extended Working Sheath

superDimension EMN
1) MC 2) RUL-carina 3) LUL-C 4) RML-C 5) LB6 6) RB7
superDimension “Bread-crumbs” to target

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Superdimension: CT to body Registration

**Slide 54**

superDimension example
Visicoil Gold Fiducial Markers to guide External Beam Radiation

Fluoro 1 courtesy Dr. Herran

Courtesy Dr. Herran, Bruce Taylor

Brachytherapy catheter H Becker
BF-UC160F-OL8

- Features
  - Safety
  - Approach to anterior LN’s
- Specifications
  - OD 6.9mm (Distal end)
  - 6.2mm (Insertion tube)
  - 2.0mm working channel
  - 22G needle
  - Scanning area 50° (7.5MHz)
  - Compatible with EU-C60
  - $44,800 list price

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EBUS TBNA with 22 ga Vizishot

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R.O.S.E (Rapid On-Site Evaluation)

Patient / Sampling / Results

- 63 nodal stations sampled in 39 cases, +1 extrathoracic node (groin), +7 lung nodules / masses:
  - Single node (17)
  - Two nodes (20)
  - Three (2)

<table>
<thead>
<tr>
<th>Patient / Sampling / Results</th>
<th>4R</th>
<th>4L</th>
<th>7</th>
<th>11R</th>
<th>11L</th>
<th>12R</th>
<th>Lung lesion</th>
<th>Extrathoracic</th>
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<td>LN Station</td>
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<td></td>
<td></td>
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<td>Cancer</td>
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<td></td>
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<tr>
<td>Dx</td>
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<tr>
<td>Lymphocytes</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Inadequate</td>
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<td></td>
</tr>
</tbody>
</table>

- 4R: 23:14:9:0
- 4L: 4:2:2:0
- 7: 11:8:3:0
- 11R: 18:6:10:2
- 11L: 4:2:2:0
- 12R: 2:0:1:1
- Lung lesion: 8:6:0:3
- Extrathoracic: 1:1:0:0
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71 y/o male, 45 pack yr smoker, quit 25 yrs prior, new persistent cough

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Muhammad Otis Squamous cell CA RML mass inhomogeneous station 7 and possible hilar LN

Next Imaging Step: 18 FDG PET scan

Sampling of single or multiple sites?

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Collection for Histology / Biomarkers
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**IHC tumor markers on clot**

- Cytokeratin markers: AE1/AE3, CAM 5.2, CK 7
- Lung Vs H & N: TTF-1; CK 5/6, p63 (SCCA);
- Lung (SCLC / mixed) / Neuroendocrine: synaptophysin, chromogranin, S100 (NSE)
- Colon: CDX-2, CK 20
- Adenocarcinoma: mucicarmine
- Pancreas: DPC4 loss
- Breast: ER, PR, Gross Cystic Disease Fluid Prot
- Uroepithelial: PSA
- Lymphoprolif. Disorders: CD34, CD117, flow

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**Cancer Dx & Molecular Biomarkers**

(WCLC 2011 poster presentation)

- Diagnosis: Cancer 61/80, 2 false-negative (NSCLC diagnosed by thoracotomies)
- Malignancies: 49 LCs in 47 patients: 38 new, 9 recurrences; Synchronous primaries in 2.
- In 30 patients with prior non-lung primaries: 15 thoracic metastases in other 15 new primary lung or granulomas
- KRAS 10+/33(30%); EGFR 8+/30(27%);
- EML4-ALK 2+/4(3.4%,3.5% fusion);
- BRAF ordered on 1 each lung, melanoma and colon 2+/3(66%); ERCC1/RRM1 high expression in 1 specimen sent for analysis. HPV16/18+ in two Head & Neck SCCA metastases in airways.
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Nakajima et al

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• Analysis of 38 patients with pN2 stage IIIA NSCLC, studied clot (core) for selected cell-cycle proteins that may be predictive of chemotherapy response
  • Rb pathway (pRb, cyclin D1, p16\(^{INK4A}\))
  • p53 pathway (p53, p21\(^{Waf1}\))
  • Ki67 proliferation index
Lung Cancer: A Preventable Epidemic

Worldwide Annual Mortality
>1 million and Increasing
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Perihemal Adenocarcinoma within field of Atypical Adenomatous Hyperplasia.

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**Temporal Sequence of Lung Cancer**

**Screening**
- US avg. million individuals at high risk of lung cancer

**Diagnosis & Staging**
- PET Scan
- MRI
- Surgery/Biopsy
- Re-scan

**Post Rx F/U**
- Symptoms
- Appear
- CT Scan
- Diagnosis & Staging
- Screening
- Surgical Resection
- Radiation
- Chemotherapy
- Palliation

**Disease Progression**
- Shortness of Breath
- Bloody Sputum
- Persistent Cough
- Recurring Pneumonia
- Chest Pain
- Weight Loss
- US 123 million individuals at high risk of lung cancer
- 2.4 million symptomatic individuals evaluated for lung cancer
- 2.1 million CT scan evaluations
- 750,000 surgical tissue lung biopsies
- 1.34 million not referred for biopsy
- 96 million current/former smokers
- 27 million industrial exposure/other
- 215,020 lung cancers

**Biopsy cost:** $8.1 bn
**Deaths:** ?
**Unnecessary biopsies:** 530,000

"If I have to have surgery, I want to know it’s cancer."

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**Lung Cancer Dx Methods, Cartoon**

**Comparison of Sensitivities of Early Detection Techniques**
- % chest x-ray
- % PET scan
- % CT Scan
- % Tissue biopsy

**Sensitivity**
- 10% chest x-ray
- 20% PET scan
- 80% CT scan
- 95% Tissue biopsy

**Specificity**
- 95% chest x-ray
- 85% PET scan
- 15% CT scan
- 5% Tissue biopsy

**Depiction of late stage vs early stage**
- Late stage: large tumor, multiple lesions
- Early stage: small tumor, single lesion

**Lesion size comparison**
- US 123 million individuals at high risk of lung cancer
- 2.4 million symptomatic individuals evaluated for lung cancer
- 2.1 million CT scan evaluations
- 750,000 surgical tissue lung biopsies
- 1.34 million not referred for biopsy
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"If I have to have surgery, I want to know it’s cancer."
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Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer

Aviram Spira, Elisha E. Broome, John G. McCall, Carolyn Reddick, Gang Li, I. Edwin Schuman, Jean Gahne, Yossi Hart, Richard H. Miller, Matthew Zeppetella, Ina Schultze, Carla Lamm, Danielle Anderson, Vincent Shearer, Joseph Frasci, Marc E. Leshner & Joseph R. Saxby

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Patients suspected of having lung cancer undergoing bronchoscopy

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Airway Epithelium Gene Expression: Clinicogenomics

Acknowledge its role as identifying “Field Effect”, not actual cancer.
Thus far establish role as an adjunctive study during bronchoscopy (cancer negative, whether to proceed to next more invasive test).
Now with preliminary work on Nasal epithelium to Stratify Risk.

Serum Blood Test

“Auto-antibodies” made against Tumor Associated Antigen (TAA) that would be found in circulation.
Tumors (even of the same organ site / cell type) will have different antigens, hence no single “Lung Cancer – autoantibody”, and the same antibody e.g. vs p53 may be found in cancers from different organ sites.

Identification of an autoantibody panel to separate lung cancer from smokers and nonsmokers.
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Slide 99:
Role of the Pulmonologist in LC Diagnosis & Management
- Part of a Multi-disciplinary Team of interested and committed clinicians and scientists
- Key partners – radiologists and pathologists
- Aggressive tissue staging, and tissue harvest for predictive and prognostic biomarkers to allow for promote personalized therapies
- Retain role in primary prevention, & managing COPD and pulmonary complications of therapy
- Promising potential in secondary prevention (screening/ early detection) studies

I am so depressed, doctor that I feel like taking my own life...,
Dear Friend, Leave that to Me!

Combined Modality Therapy for Lung Cancer