Role of the Pulmonologist in Diagnosis and Treatment Selection for Lung Cancer

Rex C. Yung, MD
Dir of Bronchology
Johns Hopkins Hospital
Disclosures

• Research Funding from & Consultant for Philips Imaging, North America
• Research Funding & Consultant for FreshMedx
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
Phtisis

Definition (Gk): A Wasting Disorder; “Consumption” that claimed up to 25% of European population’s lives
Pulmonologists & Lung Cancer (1960s)
Late Diagnosis & Therapeutic Nihilism

- Pre-flexible bronchoscopy – pre-CT imaging
- Most LCs diagnosed by sputum cytology
  - high specificity
  - 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

#### The pulmonologists’ & critical care specialists’ focus

<table>
<thead>
<tr>
<th>All causes</th>
<th>2,443,387</th>
<th>843.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Heart diseases</td>
<td>696,947</td>
<td>28.5</td>
</tr>
<tr>
<td>2 Cancer</td>
<td>557,271</td>
<td>22.8</td>
</tr>
<tr>
<td>3 Cerebrovascular diseases</td>
<td>162,672</td>
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<tr>
<td>4 Chronic lower respiratory diseases</td>
<td>124,816</td>
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<td>106,742</td>
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<td>6 Diabetes mellitus</td>
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<td>7 Influenza &amp; pneumonia</td>
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<tr>
<td>8 Alzheimer disease</td>
<td>58,866</td>
<td>2.4</td>
</tr>
<tr>
<td>9 Nephritis, nephrotic syndrome, &amp; nephrosis</td>
<td>40,974</td>
<td>1.7</td>
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<td>33,865</td>
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<tr>
<td>11 Intentional self-harm (suicide)</td>
<td>31,655</td>
<td>1.3</td>
</tr>
<tr>
<td>12 Chronic liver disease &amp; cirrhosis</td>
<td>27,257</td>
<td>1.1</td>
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<td>20,261</td>
<td>0.8</td>
</tr>
<tr>
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<td>17,638</td>
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*Lung Cancer 163,000*

<table>
<thead>
<tr>
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<th>Causes</th>
<th>Rate per 100,000</th>
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*Rates are per 100,000 population and age-adjusted to the 2000 US standard population.

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

- **Cumulative Percent Surviving**
  - **Months After Treatment**

Left:
- CN0
- CN1
- CN2
- CN3

Right:
- pN0
- pN1
- pN2
Perception of Lung Cancer Therapy
Warning from our (pulmonary) elders regarding an interest in Lung Cancer

John Murray: “young Rex, don’t go to the Dark Side!”
IASLC International Lung Cancer Staging Project

JTO 2007
>109,000 Cases Submitted

Asia
National Data From Japan 7,393
Korea Cancer Center Hospital 1,119
Guangdong Provincial People’s Hospital 2,011

Europe
Amsterdam Cancer Registry 14,869
European Lung Cancer Working Party 2,068
Leuven Lung Cancer Group 6,760
Medical University of Gdansk 1,380
CHU – Grenoble 974
Thoraxclinic Heidelberg 5,498
Institut Jules Bordet 746
Policlinic of Perugia 111
BCCG-Spain 2993
Universita’Degli Studi di Torino 1006

North America
National Cancer Institute of Canada 255
Southwest Oncology Group/BLOT 2,919
Radiation Therapy Oncology Group 239
North Central Cancer Treatment Group 3,293

Australia
Peter MacCallum Cancer Institute 203
University of Sydney 1,750
Western Hospital, Melbourne 765
Queensland Radium Institute 5,487

www.theodora.com/maps
Combined Chemo-radiation 1990 – 2000: 3% of all patients
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
A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

National Emphysema Treatment Trial Research Group

ABSTRACT

BACKGROUND
Lung-volume–reduction surgery has been proposed as a palliative treatment for severe emphysema. Effects on mortality, the magnitude and durability of benefits, and criteria for the selection of patients have not been established.

METHODS
A total of 1218 patients with severe emphysema underwent pulmonary rehabilitation and were randomly assigned to undergo lung-volume–reduction surgery or to receive continued medical treatment.

RESULTS
Overall mortality was 0.11 death per person-year in both treatment groups (risk ratio for death in the surgery group, 1.01; P=0.90). After 24 months, exercise capacity had improved by more than 10 W in 15 percent of the patients in the surgery group, as compared with 3 percent of patients in the medical-therapy group (P<0.001). With the exclusion of a subgroup of 140 patients at high risk for death from surgery according to an interim analysis, overall mortality in the surgery group was 0.09 death per person-year, as compared with 0.10 death per person-year in the medical-therapy group (risk ratio, 0.89; P=0.31); exercise capacity after 24 months had improved by more than 10 W in 16 percent of patients in the surgery group, as compared with 3 percent of patients in the medical-therapy group (P<0.001). Among patients with predominantly upper-lobe emphysema and low exercise capacity, mortality was lower in the surgery group than in the medical-therapy group (risk ratio for death, 0.47; P=0.005). Among patients with non–upper-lobe emphysema and high exercise capacity, mortality was higher in the surgery group than in the medical-therapy group (risk ratio, 2.06; P=0.02).

CONCLUSIONS
Overall, lung-volume–reduction surgery increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy. It does yield a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity. Patients previously reported to be at high risk and those with non–upper-lobe emphysema and high base-line exercise capacity are poor candidates for lung-volume–reduction surgery, because of increased mortality and negligible functional gain.
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 = IIIA node
PET-CT Fused liver mets

Fused PET-CT images of Liver Mets
INDICATION: Abnormal chest radiograph. 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 06/09/2003.

FINDINGS: There is a large airspace opacity or mass of lobular 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 abuts the right hilar vessels, predominantly right upper lobe pulmonary artery. No apparent occlusion appreciated. The mass measures 5.4 cm in craniocaudal dimension, 8.4 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 worrisome for primary lung cancer.

There are small right hilar lymph nodes. No enlarged pathologic left hilar or mediastinal lymph nodes. No axillary lymph nodes identified. There is atherosclerosis, mild dilatation of the aorta. Coronary calcification identified. There is small hiatal hernia.
BC: Large T3 (T2c) primary lesion, what about Nodal Staging?
Per CT: "Non pathologic LN"
BC: Large T3 (T2c) primary lesion, what about Nodal Staging?

Per CT: “Non pathologic LN”

Long Vs Short Axis
Other Views of the LN using MPR
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
3-23-2010 CT of chest

Multiple GGO with cavitations RB1

Lesion in RB3 axillary segment

Densest most PET+ RB2 lesion
Searching for ABS leading to lesions

Tsuboi Class I

With Tilt Planes, Class IV
Tilt Plane view reveals Air Bronchus leading to the lesion.

Coronal View

Tilted Coronal View
Target 3: RUL B1 apical lesions

Note Location of Pacemaker
Bronchoscopy Using Fluoroscopy, Radial EBUS, Guide Sheath system

Cytology Brushing up RB2 using a Guide Sheath as conduit
Using Guide Sheath for passage of stiff instruments along bent airway segments
Approach Target #2: RUL axillary segment

How to make the lesion visible?

Rotate Image Horizontally into Bronchoscopic View
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.
superDimension
“Bronchus” System
Electro-Magnetic Bronchoscopy Navigation System
SuperDimension: Pre

Generates a 3D CT "Road Map" from standard CT
superDimension™ / Bronchus system

Electromagnetic Locator Guide
Inserted through an
Extended Working Sheath
1) MC  2) RUL-carina  3) LUL-C  4) RML-C  5) LB6  6) RB7
superDimension “Bread-crumbs” to target
Place the tip of the Locatable Guide at the actual body location of the selected Registration Point, as marked in the Virtual Image, and press the "Acquire" button.
Electromagnetic Navigation Bronchoscopy: confirming Location Guide by fluoroscopy
superDimension steering to target

Multiple targets in the same patient

TAR2RLL: 0.7 cm
Electromagnetic Navigation Diagnostic Bronchoscopy in Peripheral Lung Lesions*

Ralf Eberhardt, MD; Devanand Anantham, MD; Felix Herth, MD; David Feller-Kopman, MD, FCCP; and Armin Ernst, MD, FCCP

Table 1—Yield, Registration/Navigation Accuracy, Procedure Duration, and Pneumothorax Incidence in Studies of ENB Diagnosis of Peripheral Lung Lesions*

<table>
<thead>
<tr>
<th>Study</th>
<th>Technique</th>
<th>No.</th>
<th>Size, mm</th>
<th>Diagnostic Yield, %</th>
<th>Error, mm</th>
<th>Duration, min</th>
<th>Pneumothorax</th>
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</thead>
<tbody>
<tr>
<td>Becker et al⁴</td>
<td>ENB and fluoroscopy-forceps biopsy and brush</td>
<td>29</td>
<td>All</td>
<td>69</td>
<td>Registration, 6.1 ± 1.7</td>
<td>Registration, 2 (1–3.3); navigation, 7.3 (1.3–14.1)</td>
<td>1 patient treated with chest tube</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 30</td>
<td></td>
<td>Navigation, 5.8 ± 3.7</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 30</td>
<td></td>
<td>Navigation, 10.4 ± 7.8</td>
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<tr>
<td>Schwarz et al⁴</td>
<td>ENB and fluoroscopy-forceps biopsy and brush</td>
<td>13</td>
<td>All</td>
<td>69</td>
<td>Navigation, 5.7</td>
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<tr>
<td>Gildea et al⁵</td>
<td>ENB and fluoroscopy-forceps biopsy and brush</td>
<td>54</td>
<td>All</td>
<td>74</td>
<td>Registration, 6.6 ± 2.1; navigation, 9.0 ± 5.0</td>
<td>Registration, 3 ± 2; navigation, 7 ± 6; total, 51 ± 13</td>
<td>2 patients treated with chest tubes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>&lt; 20</td>
<td>74</td>
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<td>11</td>
<td>&gt; 30</td>
<td>82</td>
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*Values are given as the mean ± or No. (range), unless otherwise indicated.
Visicoil Gold Fiducial Markers to guide External Beam Radiation
Visicoil Gold Fiducial Markers to guide External Beam Radiation Fluoro 1 courtesy Dr. Herran

Courtesy Dr. Herran, Bruce Taylor
Electromagnetically Navigated Brachytherapy as a New Treatment Option for Peripheral Pulmonary Tumors

Wolfgang Harms, Robert Krempien, Christian Grehn, Frank Hensley, Jürgen Debus, Heinrich D. 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
EBUS TBNA with 22 ga Vizishot
R.O.S.E (Rapid On-Site Evaluation)

Stewart CJ, Stewart IS. J Clin Pathol 1996;49:839-
PET + N2 node plus contralateral nodule

EBUS-TBNA

Preparing the clot for histology

Histology of clot Vs smear
Patient / Sampling / Results

- 63 nodal stations sampled in 39 cases, +1 extra-thoracic node (groin), +7 lung nodules / masses: Single node (17); two nodes (20); three (2)

<table>
<thead>
<tr>
<th>LN Station</th>
<th># sampled</th>
<th>Cancer Dx</th>
<th>Lymphocytes</th>
<th>Inadequate</th>
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<td>4R</td>
<td>23</td>
<td>14</td>
<td>9</td>
<td>0</td>
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<td>4L</td>
<td>4</td>
<td>2</td>
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<td>0</td>
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<td>7</td>
<td>11</td>
<td>8</td>
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<td>11R</td>
<td>18</td>
<td>6</td>
<td>10</td>
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<td>4</td>
<td>2</td>
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<td>0</td>
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<tr>
<td>12R</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Extrathoracic</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung lesion</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>3</td>
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71 y/o male, 45 pack yr smoker, quit 25 yrs prior, new persistent cough
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?
Collection for Histology / Biomarkers

RML Tumor
STN 7 subarachnoid

SPECIMEN SPECIMEN

0 1 2 3 4
Diff – Quik Vs Cell Block
EBUS Tissue-clot Histology
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
**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.
Standard (?) Rx for NSCLC (2011)
Distinguishing Squam from non-Squam

Squamous
- Platinum
- Doublet
- Cetuximab?

Non-squamous
- Bevacizumab
- (Cetuximab?)
- Platinum
- Doublet

- Docetaxel
- Erlotinib
- Pemetrexed
Targeted Therapy

“Bummer of a Birthmark, Hal!”
Gary Larson
Assessment of Epidermal Growth Factor Receptor Mutation by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Takahiro Nakajima, Kazuhiro Yasufuku, Makoto Suzuki, Kenzo Hiroshima, Rieko Kubo, Sherif Mohammed, Yohei Miyagi, Shoichi Matsukuma, Yasuo Sekine and Takehiko Fujisawa

Chest 2007;132;597-602; Prepublished online June 15, 2007; DOI 10.1378/chest.07-0095
Figure 3. Chest CT scan findings in a patient successfully treated with gefitinib. A 67-year-old woman with multiple mediastinal lymph node metastases along with malignant pericardial effusion was treated with gefitinib. Top, A: CT scan shows enlarged stations 2R, 6, 4L, and 5 before the administration of gefitinib. Middle, B: two weeks after the administration of gefitinib, all of the enlarged mediastinal lymph nodes decreased in size dramatically. Bottom, C: the patient has been in stable condition for 17 months after the administration of gefitinib.
Discussion

Analysis of cell cycle-related proteins in mediastinal lymph nodes of patients with N2-NSCLC obtained by EBUS-TBNA: relevance to chemotherapy response

S Mohamed, K Yasufuku, T Nakaiima, K Hiroshima, R Kubo, A Iwoda, S Yoshida, M Suzuki, Y Sekine, K Shibuya

Results: Immunostaining was feasible in all studied specimens. Univariate analysis revealed that p53 and p21^{Waf1} expressions were significantly related to the response to chemotherapy (p = 0.002 and p = 0.011, respectively). Multivariate logistic regression analysis revealed that only p53 overexpression was associated with a poor response to chemotherapy (p = 0.021).

Conclusions: These results suggest that EBUS-TBNA is a feasible tool for obtaining mediastinal nodal tissue samples amenable for immunohistochemical analysis. Immunostaining of p53 in EBUS-TBNA-guided specimens may be useful in predicting the response to chemotherapy in patients with N2-NSCLC and helping in the selection of patients who might benefit from certain chemotherapeutic strategies.

Figure 1 Representative example of mediastinal lymph node tissue sample obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a patient with pN2 non-small cell lung cancer (NSCLC) adenocarcinoma (original magnification ×20).
(A) Note that the main constituents are tumour cells, blood constituents and a small amount of lymphocytes and histiocytes (H&E).
(B) Immunohistochemical staining for DO-7 showing overexpression of p53 protein.
Analysis of cell cycle-related proteins in mediastinal lymph nodes of patients with N2-NSCLC obtained by EBUS-TBNA: relevance to chemotherapy response

S Mohamed, K Yasufuku, T Nakajima, K Hiroshima, R Kubo, A Iyoda, S Yoshida, M Suzuki, Y Sekine, K Shibuya, A Farouk and T Fujisawa

Thorax 2008;63;642-647; originally published online 4 Apr 2008; doi:10.1136/thx.2007.090324

• 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\textsuperscript{INK4A})
  • p53 pathway (p53, p21\textsuperscript{Waf1})
  • Ki67 proliferation index
## Analysis of cell cycle-related proteins in mediastinal lymph nodes of patients with N2-NSCLC obtained by EBUS-TBNA: relevance to chemotherapy response

**Table 3** Relationships between the response to chemotherapy and immunohistochemical parameters (univariate analysis)

<table>
<thead>
<tr>
<th>IHC parameters</th>
<th>Responders (CR+PR)</th>
<th>Non-responders (SD+PD)</th>
<th>Response rate (%)</th>
<th>Risk value (95% CI)</th>
<th>p Value*</th>
<th>PD rate (%)</th>
<th>p Value*</th>
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<tbody>
<tr>
<td>pRb Negative</td>
<td>3</td>
<td>5</td>
<td>37.5</td>
<td>0.692 (0.204 to 2.353)</td>
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<td>37.5</td>
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<td>pRb Positive</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclin D1 Negative</td>
<td>10</td>
<td>11</td>
<td>47.6</td>
<td>0.865 (0.236 to 3.174)</td>
<td>1.000</td>
<td>14.3</td>
<td>0.574</td>
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<td>Cyclin D1 Positive</td>
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<td>4</td>
<td>42.9</td>
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<td>28.6</td>
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<tr>
<td>P16 Negative</td>
<td>4</td>
<td>10</td>
<td>28.6</td>
<td>0.222 (0.045 to 1.094)</td>
<td><strong>0.061</strong></td>
<td>21.4</td>
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<td></td>
<td>14.3</td>
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<tr>
<td>P53 Negative</td>
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<td>3</td>
<td>76.9</td>
<td>0.288 (0.104 to 0.803)</td>
<td>0.002</td>
<td>0.0</td>
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<td>P53 Positive</td>
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<tr>
<td>P21 Negative</td>
<td>6</td>
<td>14</td>
<td>30.0</td>
<td>0.061 (0.006 to 0.613)</td>
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<tr>
<td>Ki-67 LI &lt;20%</td>
<td>5</td>
<td>6</td>
<td>45.5</td>
<td>1.026 (0.565 to 1.862)</td>
<td>0.937</td>
<td>18.2</td>
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<td>Ki-67 LI &gt;20%</td>
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<td></td>
<td>17.6</td>
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<tr>
<td>Total</td>
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</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response; IHC, immunohistochemical; LI, labelling index; PD, progressive disease; PR, partial response; SD, stable disease. *χ² test or Fisher exact test.
Lung Cancer: A Preventable Epidemic

Worldwide Annual Mortality
>1 million and Increasing
My chief diagnostic tool is a CAT SCAN. You run across in front of a cat—if you get away, you're probably pretty healthy. If you get caught, you were probably sick.
National Lung Screening Trial

Enrolling healthy men and women in research to detect lung cancer

http://cancer.gov/nlst

Copyright © 2002
NIH Publication No. 02-5131
August 2002
P025
National Institutes of Health
Peripheral Adenocarcinoma within field of Atypical Adenomatous Hyperplasia
Temporal Sequence of Lung Cancer

**Screening**

- Disease Progression

- US 123 million individuals at high risk of lung cancer

- 96 million current/former smokers + 27 million industrial exposure/other

**Diagnosis & Staging**

- Symptoms Appear

  - Shortness of Breath
  - Bloody Sputum
  - Persistent Cough
  - Recurring Pneumonia
  - Chest Pain
  - Weight Loss

- 2.4 million symptomatic individuals evaluated for lung cancer

- 2.1 million CT Scan evaluation

- 1.34 million not referred for biopsy

- 750,000 surgical tissue lung biopsies

**Post Rx F/U**

- Surgical Resection
- Radiation
- Chemotherapy
- Palliation
- Re-scan For recurrence of SPLC

- 215,020 lung cancers

- 530,000 unnecessary biopsies

- Biopsy cost: $8.1 bn
- Deaths: ?

"If I have to have surgery, I want to know it's cancer."
Comparison of Sensitivity of Early Detection Techniques

Sputum Immunocytochemistry

Volume of Distribution
10-15 cell/10⁶ cell/5L

Serum Radioimmunoassay

ng/Intravascular/Interstitial Volume/Space
Figure 4. Detection of PLC with the breath test: receiver operating characteristic curve. The BMACs in patients with PLC were compared to the BMACs of age-matched healthy control subjects. Using discriminant analysis, the probability of lung cancer based on each subject's breath test result was determined as a value between 0 and 1. This ROC curve shows the results obtained with a model using nine VOCs to discriminate between patients with PLC (n = 67) and healthy volunteers (n = 41). Using a cutoff point of p = 0.5, the sensitivity was 89.6% (60 of 67 patients) and the specificity was 82.9% (34 of 41 patients). The contour of a receiver operating characteristic curve indicates the overall accuracy of a diagnostic test.

Figure 5. Predictions of the discriminant model in patients with PLC and healthy volunteers. The scatter diagram indicates the probability of lung cancer according to the cross-validation of the discriminant model employing the nine breath VOCs. Left, A: the probability for each of the patients with PLC and the healthy volunteers is shown. Right, B: the PLC data were stratified according to TNM staging in the 59 patients for whom staging data were available.
Using Protein Microarray as a Diagnostic Assay for Non-Small Cell Lung Cancer

Li Zhong, Giovanna E. Hidalgo, Arnold J. Stromberg, Nada H. Khattar, James R. Jett, and Edward A. Hirschowitz

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, and Department of Statistics, University of Kentucky; Lexington Veteran’s Administration Medical Center, Lexington, Kentucky; and Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota

Rationale: Phenotypic and genotypic heterogeneity of lung cancer likely precludes the identification of a single predictive marker and suggests the importance of identifying and measuring multiple markers.

Objectives: We describe the use of a fluorescent protein microarray to identify and measure multiple non-small cell lung cancer-associated antibodies and show how simultaneous measurements can be combined into a single diagnostic assay.

Methods: T7 phage cDNA libraries of non-small cell lung cancer were first biopanned with plasma samples from normal subjects and patients with non-small cell lung cancer to enrich the component of tumor-associated proteins, and then applied to microarray slides. Two hundred twelve immunogenic phage-expressed proteins were identified from roughly 4,000 done, using high-throughput screening with patient plasmas and assayed with 40 cancer and 41 normal plasma samples. Twenty patient and 21 normal plasma samples were randomly chosen and used for statistical determination of the predictive value of each putative marker. Statistical analysis identified antibody reactivity to seven unique phage-expressed proteins that were significantly different (p < 0.01) between patient and normal groups. The remaining 20 patient and 20 normal plasma samples were used as an independent test of the predictive ability of the selected markers.

Main Results: Measurements of the 5 most predictive phage proteins were combined in a logistic regression model that achieved 90% sensitivity and 95% specificity in prediction of patient samples, whereas leave-one-out statistical analysis achieved 88.9% diagnostic accuracy among all 81 samples.

Conclusion: Our data indicate that antibody profiling is a promising approach that could achieve high diagnostic accuracy for non-small cell lung cancer.

METHODS

Human Subjects

After informed consent was obtained, 50 plasma samples (10 used for selection and 40 for analysis) were obtained from individuals with histologically confirmed NSCLC. (Table 1). Notably, the inclusion of multiple markers has been shown to increase diagnostic accuracy. Tumor-associated antibodies may expand the number of available markers (10–16). Our previous work clearly shows that some proteins from T7 phage display NSCLC libraries are recognized by antibodies in cancer patient plasma but not in normal plasma (17). Although additional investigation may identify a single highly predictive marker of NSCLC, heterogeneity of this disease will likely require a panel of markers to achieve the sensitivity and specificity required for clinical application.

In the context of developing a diagnostic assay for NSCLC, we have adapted fluorescent microarray technology to the task of identifying immunogenic phage-expressed proteins and assessing the presence of their corresponding antibodies. Robotic microarray spotters that allow grouping of thousands of proteins, in replicate, onto a single glass slide make this feasible, efficient, and reproducible. Automated spotting of the array also allows production of hundreds of identical chips, thus making this technology a logical tool for this application. To develop an assay for detecting NSCLC, we employed a high-throughput method of isolating immunogenic phage-expressed proteins from T7 phage NSCLC tumor libraries, using antibodies in NSCLC patient plasmas. We then combined multiple phage-expressed proteins onto a single protein “diagnostic chip” and evaluated our ability to predict disease.
Clinical Genomics

Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer

Avrum Spira\textsuperscript{1}, Jennifer E Beane\textsuperscript{2,8}, Vishal Shah\textsuperscript{2,8}, Katrina Steiling\textsuperscript{1}, Gang Liu\textsuperscript{1}, Frank Schembri\textsuperscript{1}, Sean Gilman\textsuperscript{3}, Yves-Martine Dumas\textsuperscript{1}, Paul Calner\textsuperscript{4}, Paola Sebastiani\textsuperscript{5}, Sriram Sridhar\textsuperscript{1}, John Beamis\textsuperscript{3}, Carla Lamb\textsuperscript{3}, Timothy Anderson\textsuperscript{6}, Norman Gerry\textsuperscript{7}, Joseph Keane\textsuperscript{4}, Marc E Lennburg\textsuperscript{7} & Jerome S Brody\textsuperscript{1}

Lung cancer is the leading cause of death from cancer in the US and the world\textsuperscript{1}. The high mortality rate (80–85\% within 5 years) results, in part, from a lack of effective tools to diagnose the disease at an early stage\textsuperscript{2–4}. Given that cigarette smoke creates a field of injury throughout the airway\textsuperscript{5–11}, we sought to determine if gene expression in histologically normal large-airway epithelial cells obtained at bronchoscopy from smokers with suspicion of lung cancer could be used as a lung cancer biomarker. Using a training set (\(n = 77\)) and gene-expression profiles from Affymetrix HG-U133A microarrays, we identified an 80-gene biomarker that distinguishes smokers with and without lung cancer. We tested the biomarker on an independent test set (\(n = 52\)), with an accuracy of 83\% (80\% sensitive, 84\% specific), and on an additional validation set independently obtained from five medical centers (\(n = 35\)). Our biomarker had \(\sim 90\%\) sensitivity for stage 1 cancer across all subjects. Combining cytopathology of lower airway cells obtained at bronchoscopy with the biomarker yielded 95\% sensitivity and a 95\% negative predictive value. These findings indicate that gene expression in cytologically normal large-airway epithelial cells can serve as a lung cancer biomarker, potentially owing to a cancer-specific airway-wide response to cigarette smoke.
Patients suspected of having lung cancer undergoing bronchoscopy

1) Patient screened
2) Patient consented
3) Appropriate CRFs filled out

Bronchoscopy Procedure

- 2 Bronchial brushings
- Blood sample
- Nasal sample

STUDY SCHEME:

Patients followed up for diagnosis and clinical outcomes

Samples stored in the refrigerator until packed and shipped to Affymetrix

Site faxes Sample Tracking List to Allegro & Affymetrix

CRFs continuously filled out as appropriate and faxed to the data management center as soon as appropriate

CELL files delivered to Allegro from Affymetrix and data set files delivered to Allegro from the data management center

Allegro produces test report
Figure 2 Hierarchical clustering of biomarker probeset expression in two independent test sets.
(a, b) Expression levels of the biomarker probesets in the 52 test set samples and the 35 prospective validation set samples were normalized by z-score and are organized from top to bottom by hierarchical clustering. The Affymetrix HG-U133A probeset ID and HUGO symbol are given to the right of each gene along with functional annotation of select genes (cross-hatched boxes). The samples are organized from left to right by diagnosis (that is, whether the patient had a clinical diagnosis of cancer). Within these two groups, the samples are organized by the accuracy of the class prediction (samples classified incorrectly are on the right for each group of patients, shown in light green). Classification was correct for 43 of 52 (83%) test samples and 27 of 35 (80%) prospective validation set samples.

Samples from 129 individuals

Training set (n = 77)  Test set (n = 52)

Gene filter

Gene selection (signal to noise)

Gene committee (genes chosen by internal cross-validation)

Predict class of test set (weighted-voted algorithm)

Assess accuracy

Patient diagnosis
- No cancer
- Small cell
- Non-small cell
- Adeno
- Squamous
- Unknown cancer

Prediction accuracy
- Correct
- Incorrect

Gene function
- Inflammation
- Cell cycle
- Antioxidant
Airway Epithelium Gene Expression: Clinicogenomics

Figure 3  Principal component analysis (PCA) of airway biomarker gene expression in lung tissue samples. The 80 biomarker probesets were mapped to 64 probesets in a HG-U95Av2 microarray dataset of lung cancer and normal lung tissue. The normal lung samples separate from lung cancer samples along the first principal component (t-test, P-value = 0.026), indicating that cancer status is a major source of variation in the expression of biomarker probesets.
Serum Blood Test

• “Auto-antibodies” made again 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

William N Rom*1, Judith D Goldberg1, Doreen Addrizzo-Harris1, Heather N Watson1, Michael Khilkin1, Alissa K Greenberg1, David P Naidich1, Bernard Crawford1, Ellen Eylers1, Daorong Liu2 and Eng M Tan2

Abstract
Background: Sera from lung cancer patients contain autoantibodies that react with tumor associated antigens (TAAs) that reflect genetic over-expression, mutation, or other anomalies of cell cycle, growth, signaling, and metabolism pathways.

Methods: We performed immunoassays to detect autoantibodies to ten tumor associated antigens (TAAs) selected on the basis of previous studies showing that they had preferential specificity for certain cancers. Sera examined were from lung cancer patients (22); smokers with ground-glass opacities (GGOs) (46), benign solid nodules (55), or normal CTs (35); and normal non-smokers (36). Logistic regression models based on the antibody biomarker levels among the high risk and lung cancer groups were developed to identify the combinations of biomarkers that predict lung cancer in these cohorts.

Results: Statistically significant differences in the distributions of each of the biomarkers were identified among all five groups. Using Receiver Operating Characteristic (ROC) curves based on age c-myc, Cyclin A, Cyclin B1, Cyclin D1, CDK2, and survivin, we obtained a sensitivity = 81% and specificity = 97% for the classification of cancer vs smokers (no nodules, solid nodules, or GGO) and correctly predicted 31/36 healthy controls as noncancer.

Conclusion: A pattern of autoantibody reactivity to TAAs may distinguish patients with lung cancer versus smokers with normal CTs, stable solid nodules, ground glass opacities, or normal healthy never smokers.
Figure 2 ROC Curve Based on Stepwise Multiple Logistic Regression and Log Transformed Biomarkers to Classify Cancer/No Cancer (no nodules, solid nodules, and ground glass opacities groups).
original article

**Technical validation of an autoantibody test for lung cancer**

A. Murray¹, C. J. Chapman², G. Healey¹, L. J. Peek³, G. Parsons⁴, D. Baldwin⁵, A. Barnes³, H. F. Sewell⁶, H. A. Fritsche⁷ & J. F. R. Robertson²

<table>
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<tr>
<td></td>
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<td>CVₑ (%)</td>
<td>CVᵣ (%)</td>
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<td>26</td>
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ASCO 2010: claim detection of 40% lung ca, 35% “early NSCLC” Poster 7032 with overall specificity 88% (total # “high risk” 1029)
Positioning of Adjunctive studies

First Step: Adjunctive non-invasive non-ionizing radiation Diagnostic studies; choose “set-point(s)” to select a “enhanced high-risk group for biopsies

Chest CT Scan: all referred for surgical biopsy
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
Questions?
End
AND BY DEVELOPING A HYBRID OF TOBACCO AND BROCCOLI, WE CAN CREATE A PRODUCT THAT PREVENTS THE CANCER IT CAUSES.

The tobacco industry's misguided attempt at making a "safe" cigarette