OBJECTIVES

- Introduce Interventional Pulmonology
- Review advances in diagnostic techniques
- Discuss ablative technologies
- Clinical applicability of Interventional Pulmonology in the management of obstructive lung disease
- Future applications of technology
THE HUMAN LUNG

- 22-24 generations
- >100,000 bronchi, bronchioles
- 2400 km (1500 miles) of airways
- 300-500 million alveoli
- 0.3mm in diameter
- Surface area 70m²
- Capillaries 992 km (616 miles) end to end

Detroit to Key West

Michael J. Simoff, M.D.
LUNG CANCER MORTALITY: WOMEN
INTERVENTIONAL PULMONOLOGY AND LUNG CANCER

- Diagnosis
- Staging
- Airways obstruction
- Stump dehiscence
- Malignant pleural effusions
- Tracheoesophageal fistulas
- Therapy of early endobronchial disease
The purpose of staging is to define homogenous groups of patients that are distinct from one another.

- Recommend therapy
- Compare treatment results
- Assess outcomes
- Staging changes 2009

Rusch. J Thor Onc 2009
• Autofluorescence
• Endobronchial Ultrasound
• EBUS - TBNA
• Transthoracic Needle Aspiration
• Electromagnetic Navigation
• CT Fluoroscopy Guided Bronchoscopic Biopsies
• Confocal Microendoscopy
• Endocytoscopy
Superficial airway evaluation
AUTOFLUORESCENCE

Submucosal evaluation
• Blue light stimulates ground state energy level
• Excited state decay releases energy
  – 500 nm - Green (majority)
  – 650 nm - Red
• Released light energy can be visualized = Autofluorescence
MICROINVASIVE CARCINOMA

White Light

Auto fluorescence
ENDOBRONCHIAL ULTRASOUND

Beyond the airway
CROSS SECTIONAL ANATOMY
EBUS - ANATOMY
EBUS - ANATOMY

Michael J. Simoff, M.D.
EBUS – CLINICAL USES

- Airway invasion
- Mediastinal structure invasion
- Transbronchial biopsy
- Ultrasound guided TBNA
- EBUS-TBNA
ENDOBRONCHIAL ULTRASOUND

• Evaluate up to 6 cm from airway
• Identify LN to 5mm
• Improve diagnostic accuracy of TBNA
• Assist in assessing T-stage of disease
  – Vessel invasion
  – Mediastinal invasion

F Herth, MD. Heidelberg, Germany
AIRWAY ANATOMY

Epithelium/Submucosa (0.05mm)
Outer Submucosa (0.68mm)
Inner bronchial cartilage
Bronchial cartilage (0.9mm)
Outer bronchial cartilage/Adventitia

CIBA Collection Vol 7, 1980
Michael J. Simoff, M.D.
TRANSBRONCHIAL NEEDLE ASPIRATION

- Simple and safe
- Lung cancer staging
- Diagnostic tool:
  - Lymph nodes / Masses
  - Submucosa
  - Peripheral nodules
CURRENT USE OF TBNA

• 11.8% routine use
  – 1991

• 10% routine use
  by fellows
  – 1997

• 28% routine use
  – 1999
EBUS GUIDED TBNA

• Incorporate a directional ultrasound probe into a bronchoscope
• Allow real-time visualization of sampling
EBUS GUIDED TBNA
Vessel involvement
EBUS-TBNA at HFH

- Last 30 EBUS-TBNA cases
  - 76 samples taken
  - Target size 0.6-4.5cm
  - Locations
    - 2L, 4R, 4L, 7, 11L, 11R, 12R
    - Left hilar mass, R lung mass
- Diagnosis achieved in 93.8% of cases (28/30)
- Clinically relevant sample 92.9% (71/76)
SOLITARY PULMONARY NODULES
THE SOLITARY PULMONARY NODULE

Adenocarcinoma

12mm

X-ray and Fluoro Invisible

Adenocarcinoma
BRONCHOSCOPY FOR SOLITARY PULMONARY NODULES

- Transbronchial biopsies with fluoroscopic guidance
  - > 2 cm: Yield 60%
  - < 2 cm: Yield <20%

Unchanged for previous 20 years
• Peripheral lesions are beyond bronchoscopic visualization

• Sampling techniques are guided using fluoroscopy

• Lesions that are \( \leq 2 \) cm not visible with fluoroscopy
FLUOROSCOPIC GUIDED TRANSBRONCIAL BIOPSY
Invasive Poorly Differentiated Adenocarcinoma
EBUS AND PERIPHERAL LESIONS
PERIPHERAL
LOCATABLE GUIDE
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>True Positive</th>
<th>Diagnostic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inner 2/3</strong></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>4</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>6</td>
<td>66.7%</td>
<td>83.3%</td>
</tr>
<tr>
<td><strong>Outer 1/3</strong></td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>4</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>17</td>
<td>77.0%</td>
<td>76.9%</td>
</tr>
</tbody>
</table>

**HFH EXPERIENCE: 6 MONTHS**
BRONCHOSCOPY FOR SOLITARY PULMONARY NODULES

- Transbronchial biopsies with fluoroscopic guidance
  - > 2 cm
    - Yield 60%
  - < 2 cm
    - Yield <20%

Now 77%-83% with electromagnetic navigation
THERAPEUTIC INTERVENTIONAL PULMONOLOGY

Malignant Disease

Benign Conditions

Stenosis
THERAPEUTICS – BENIGN DISEASE

- Tracheal Stenosis
- Bronchostenosis
- Tracheobronchomalacia
- Broncholiths
- Asthma
- Emphysema
- Radiation airway injury
- Foreign body removal
- Stump Dehiscence

- Rare Diseases
  - Amyloidosis
  - Wegener’s Granulomatosis
  - Relapsing Polychondritis
  - Fibrosing Mediastinitis

- Vascular, Bony, or thyroid airway obstruction
THERAPEUTICS – MALIGNANT DISEASE

• Endobronchial airway obstruction
• External compression
• Tracheoesophageal fistula
• Massive Hemoptysis
• Metastatic airways disease
AIRWAY OBSTRUCTION

INTRINSIC  EXTRINSIC  MIXED
THERAPEUTIC TECHNIQUES

- Rigid Bronchoscopy
- Laser
- Electrocautery
- Argon Plasma Coagulation
- Cryotherapy
- Photodynamic therapy
- Microdebridement
THERAPEUTIC TECHNIQUES

- Silastic Stents
- Metallic Stents
- Hybrid Stents
- Brachytherapy
- Balloon Dilatation
- Fibrin Glue
RIGID BRONCHOSCOPY

- Airway control:
  - Ventilation
  - Bleeding
- Faster
- Applecoring
- 8% of pulmonologists

Chest 1991;100:1660
LASER

- Light amplification by stimulated emission of radiation
  - Nd:YAG
  - KTP
- Tissue effects:
  - Thermal necrosis
  - Photocoagulation
LASER

- 84-92% symptom palliation
- Improved survival:
  - Control (n=25) Mortality
    - 4 month 76%
    - 7 month 100%
  - Laser treated (n=71)
    - 7 month 40%
    - 1 year 72%

Brutinel et al. Chest 1987;91:159
IMPACT ON PATIENT ASSESSED QOL

EORTC QLQ-C30 Survey

- Monopolar high frequency alternating current
- Tissue resistance is high
- Energy converted to heat
Rigid or flexible bronchoscope
  - Forceps
  - Cautery tip
  - Wire snare
  - Electrosurgical scalpel
ARGON PLASMA COAGULATION

- Ionized argon gas
- Conducts electrical field from electrode to tissue
- Coagulative necrosis
- Superficial tissue destruction
• Appropriate eye protection
• FiO2 less than .40
• Equipment ignition
• Airway rupture
  – Pneumothorax
  – TEF
  – Aortic or pulmonary artery perforation
CRYOTHERAPY

- Tissue destruction at -20° to –40° C
- Liquid nitrogen –196° C
- 1cm radius destruction
- Cryonecrosis occurs over 48 to 72 hours
MICRODEBRIDMENT

- Newer technique
- Precise resection of endobronchial tumor / granulation tissue
- 1200 rpm
- Active suctioning with cutting to maintain a clear field

Lunn et al. Chest 2004:126;706-707s
PHOTODYNAMIC THERAPY
- Silastic stents
- Metal stents
- Hybrid Stents
- Balloon dilatation
STENTING

- Exchange one chronic condition for another
- No perfect stent:
  - Migration
  - Erosion / rupture
  - Stent fracture
  - Bacterial overgrowth
SILASTIC STENTS

- Dumon Stent
- Hood Stent
- Montgomery T-Tube
• Removable
• No growth through stent
• Cost
• Requires rigid bronchoscopy
METALLIC STENTS

- Ultraflex
- Guidant
- Aero
METALLIC STENTS

- Favorable wall/inner diameter ratio
- Airway diameter adaptability
- Absence of kinking
- Flexible bronchoscopic insertion
METAL STENTS: LIMITATIONS

- Granulation tissue
- Wall erosion
- Migration
- Fracture
- Epithelialization
- Stiff walls
- Impaired mucous clearance
• Hybrid
  – Silicone
  – Stainless steel struts
• Thin posterior silicone membrane
• Dynamic design
• Rigid bronchoscopy
• 3 Sizes

Michael J. Simoff, M.D.
RUSCH-Y STENT

Pre-stent  Proximal stent  Distal stent
• Rigid bronchoscopy
• Insert and insufflate balloon
• Hold dilatation for 1-2 minutes
• Sequentially increase balloon size
BRACHYTHERAPY

- Localized radiation therapy
- Iridium-192
- Low, intermediate, and high dose
- HDR most effective for palliation (71-100%)

Lo et al. Radiother Oncol 1995;35:193
Seagren et al. Chest 1985;88:810
FIBRIN GLUE

- Endobronchial adhesive
- Used for “plugging”
  - Tracheo-esophageal fistula
  - Stump dehiscence
  - Broncho-pleural fistula
- Temporary
PLEURAL DISEASE

- Pleural effusion: 7-15% patients
- Medical thoracoscopy
  - Diagnostic
  - Therapeutic
- Indwelling catheters
  - PleurX catheters
MEDICAL THORACOSCOPY

• 67 Year old white male
• Increasing shortness of breath
• Pleural effusion diagnosed
• Thoracentesis performed twice
  - Exudative lymphocytic effusion
  - Cytology negative
INDWELLING CATHETERS

- Malignant effusion management
- Implantation with subcutaneous tubing for home management
- Effective non-irritant pleurodesis

Pleur-X Catheter
Most disorders require several complimentary procedures
MULTIMODALITY THERAPY: ENDOBRONCHIAL TUMOR
MULTIMODALITY THERAPY: ENDOBRONCHIAL TUMOR

1.9 mm
MULTIMODALITY THERAPY: TRACHEAL-ESOPHAGEAL FISTULA
THE FUTURE

Lost in Space

A Thrill Ride of a Movie... Exciting, Adventurous Eye-Popping Fun!
SOLITARY PULMONARY NODULES
THE FUTURE: ULTRASOUND
THE FUTURE:
THE WAY WE SEE THINGS

- Narrow Band Imaging
- Confocal microendoscopy
- Optical coherence tomography (OCT)
- Endocytoscopy
- Raman spectroscopy
- X-ray photoelectron spectroscopy
NARROW BAND IMAGING

• White light bronchoscopy with filters to only allow imaging of:
  - Blue 400-430 nm
  - Green 420-470 nm
  - Red 560-590 nm

• Significant emphasis on vascular changes
• Blue light excitation laser (480nm)
• Allows dynamic imaging
  – 0-250µm depth
  – 5µm resolution
  – 600µm field of view
• In-focus imaging of biological tissue
- Broadband near-infrared coherent light
- Reflected light combined into interference pattern
- Computer signal acquisition and processing
  - Penetration 2-4mm
  - Resolution 10-20μm
- Need 1-2μm to assess cellular structures (malignant vs. benign)

Normal Retina
Cross-section of Chicken Trachea
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OBJECTIVES

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Bronchoscopy

Autofluorescence

EBUS
OBJECTIVES

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  - Nd:YAG
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- Tissue effects:
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Michael Unger, MD
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BRONCHOSCOPIC TREATMENTS FOR EMPHYSEMA

• Plugs or Blockers
• Bronchial Valves
• Airway bypass procedures (Stents through airway wall)
• Sealants and biologics
• Thermal Injury (Steam)
• Mechanical collapse (Wire on spring)
OBJECTIVES

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NAVIGATION
EBUS AND THE DIAGNOSIS OF CANCER

Can we diagnose cancer?

Adenocarcinoma  VS.  Atelectasis

Courtesy of Felix Herth
EBUS AND THE DIAGNOSIS OF CANCER

Distribution of greyscale signals

Tuberculoma

Courtesy of Felix Herth
Distribution of greyscale signals

Squamous cell Carcinoma

Courtesy of Felix Herth
GENE THERAPY

Dan Sterman, MD
GENE THERAPY AT HFH: A Novel Three-Pronged Approach

Oncolytic Viral Therapy

Replication-Competent Adenovirus containing Two Therapeutic Genes

Radiotherapy

Tumor eradication

Double Suicide Gene Therapy

5-FC + GCV

Phase I Study of Replication-competent Adenovirus-mediated Double Suicide Gene Therapy for the Treatment of Locally Recurrent Prostate Cancer

Svend O. Freytag, Mark Khil, Hans Stricker, James Peabody, Mani Menon, Mariza DePeralta-Venturina, Daniel Nafziger, Jan Pegg, Dell Paielli, Steve Brown, Ken Barton, Mei Lu, Estuardo Aguilar-Cordova, and Jae Ho Kim

Departments of Radiation Oncology [S. O. F., M. K., J. Peg., D. P., S. B., K. B., J. H. K.], Urology [H. S., J. Pea., M. M.], Pathology [M. D-Y.], Infectious Disease [D. N.], and Biostatistics [M. L.], Henry Ford Health System, Detroit, Michigan 48202, and Department of Cell and Gene Therapies, Baylor College of Medicine, Houston, Texas 77030 [E. A-C.]
**STAGING - TNM**

Primary Tumor (T)
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ
- **T1**: Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus)
- **T2**: Tumor with any of the following features of size or extent:
  - More than 3 cm in greatest dimension
  - Involves main bronchus, 2 cm or more distal to the carina
  - Invades the visceral pleura
  - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- **T3**: Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
- **T4**: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural or pericardial effusion,** or with satellite tumor nodule(s) within the ipsilateral primary tumor lobe of the lung

Regional Lymph Nodes (N)
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor
- **N2**: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- **N3**: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)
- **M0**: No distant metastasis
- **M1**: Distant metastasis present

Mountain, Dresler. Chest 1997;111:1718
Carcinogenesis

Mutagenesis
3-4 Years

Dysplasia

Carcinoma in situ
6 Months

Saccomano et al.
Cancer 1974
ANATOMIC CHANGES IN PREINVASIVE LUNG CANCER

Epithelium

Upper Submucosa

Abnormal epithelium

70-116 μm

Lower Submucosa

Cartilage

1.2 mm

Abnormal epithelium
LASER ABLATION IMPACT ON QOL AND ECOG SCORES

- 133 Laser Ablations
- 89 patients
- Standard Techniques:
  - Low power Photocoagulation (<30 W)
  - Endoluminal Resection
  - High power (50 W) vaporization
  - Base of lesion treated low power (20-30 W to 1000-2000 J)

BRACHYTHERAPY

- 20-40 Gy delivered 0.5-2 cm from beads
- 2-3 treatments 1 week apart
- Complications:
  - Massive hemoptysis
  - Fistula formation
THE FUTURE: TO BIOPSY OR JUST LOOK

Optical biopsies:
- Optical coherence tomography
- Confocal microendoscopy
- Endocytoscopy
COPD

- Emphysema, chronic bronchitis, obstructive bronchiolitis, asthma
- Forth ranked cause of death in the United States
- >100,000 deaths per year
- Substantial debility, physical impairment, reduced quality of life

Courtesy Bronchus Tech
THE PROBLEM

Normal Lung

Emphysema
ENDOBRONCHIAL LUNG VOLUME REDUCTION

- Reduce lung volume by endoscopically occluding bronchi and anatomically / physiologically collapsing the lung
- Multiple techniques have been attempted
BRONCHOSCOPIC TREATMENTS FOR EMPHYSEMA

• Plugs or Blockers
• Bronchial Valves
• Airway bypass procedures (Stents through airway wall)
• Sealants and biologics
• Thermal Injury (Steam)
• Mechanical collapse (Wire on spring)
DOES IT WORK?

**FEV₁**

- Before: 0.7
- After 7 days: 1.28
- After 1 month: 1.16
- After 4 months: 1.08
- After 6 months: 0.98

**Residual volume**

- Before: 7.71
- After 7 days: 5.27
- After 1 month: 5.39
- After 4 months: 5.16
- After 6 months: 5.51

**Shuttle distance**

- Before: 330
- After 7 days: 490
- After 1 month: 520
- After 4 months: 510
- After 6 months: 570
Unilateral Total Lobar Occlusion RUL
CLINICAL TRIALS

- **Emphysus / PulmonX**
  - Study completed
  - Denied FDA approval
  - Purchased by PulmonX

- **Bronchus**
  - Study complete
  - FDA review underway

- **Spiration**
  - Recruitment began in mid 2007

- **Pneumonx**
  - European preliminary trials ongoing

- **Aeri Seal**
  - Phase 2 trial ongoing in Europe
• 20 million asthma sufferers in US
  ~14 million are adults
• Lack of control is an enormous problem
  – Not optimally responsive or non-compliant
  – 10.4 million unscheduled physician office visits
  – 1.8 million ER visits
  – 0.5 million hospitalizations
  – 5,000 deaths
  – Asthma-related healthcare costs = $14 billion/yr
Release of IgE

Plasma cell

B lymphocyte

\(\Rightarrow\)-switch

Release of IgE

Allergic mediators

Allergens

Mast cells

Basophils

Asthma Exacerbation

Allergic Inflammation: eosinophils and lymphocytes
Bronchial thermoplasty reduces airway smooth muscle through controlled thermal treatment to the airway wall.

- Requires 3 bronchoscopies
- Bronchioles to 2 mm in size to be treated
Altered Airway Smooth Muscle
12 Weeks Post-Treatment

UNTREATED

TREATED

BRONCHIAL THERMOPLASTY

• Methacholine stimulates bronchoconstriction in most patients with asthma
• Post treatment minimal response to methacholine

Cox et al. Eur Respir Journal; 24: 659-663, 2004
The Alair® System

- The Alair Catheter is a flexible tube with an expandable wire basket at the tip

- The Alair Radiofrequency Controller supplies energy via the Alair Catheter to heat the airway wall
AIR2 Trial

Objective
- To demonstrate the safety and effectiveness of the Alair System in a population of subjects with severe asthma

Study Design
- Randomized, double blind, sham-controlled
- Minimum of 225 subjects; Maximum of 600 (Bayesian Adaptive Statistics)
- Multi-center, international study involving up to 40 centers
Health Care Utilization for Respiratory Symptoms Post-Treatment Period (Events / Subject / Year^1)

- **Severe Exacerbations**: 32% Decrease Over Sham
- **Unsched. Office Visits**: 23% Decrease Over Sham
- **ER Visits**: 84% Decrease Over Sham
- **Hospitalizations**: 73% Decrease Over Sham

Michael J. Simoff, M.D.
CURRENT STATUS OF BRONCHIAL THERMOPLASTY IN THE USA

- Bronchial thermoplasty has been approved by the FDA (Federal Drug Administration) for clinical use in the USA
- Many insurance carriers are not covering the cost of this procedure
- Henry Ford Hospital is currently recruiting patients for the AIR3 trial