Lung Cancer-a primer

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CLINICAL CATEGORIES

- THE SOLITARY PULMONARY NODULE
- MULTIPLE PULMONARY NODULES

Differential Diagnosis

- Malignant tumors
  - Bronchogenic carcinoma, lymphoma, sarcoma, plasmacytoma, solitary metastases
- Benign tumors
  - Harmatoma, adenoma, lipoma
- Infectious Granulomas
  - Tuberculosis, histoplasmosis, coccidioidomycosis, mycetoma, ascaris, echinococcal cyst, dirofilariasis (dog heartworm)

Differential Diagnosis

- Noninfectious Granulomas
  - Rheumatoid arthritis, Wegener's granulomatosis, sarcoidosis, paraffinoma
- Miscellaneous
  - BOOP, abscess, silicosis, fibrosis/scar, hematoma, spherical pneumonia, pulmonary infarction, A-V malformation, bronchogenic cyst, amyloidoma

Etiology

- Benign
  - Infectious granulomas (80%)
  - Hamartomas (10%)
- Malignant
  - Primary lung cancer
  - Metastatic nodules

RULE OUT PRIMARY LUNG CANCER

Epidemiology of Lung Cancer

- Leading cause of cancer death
- Risk Factors
  - Age
  - Tobacco
  - Occupational agents
    - Asbestos, Radon, Arsenic, Chromium, etc
  - Genetic factors

Epidemiology of Lung Cancer

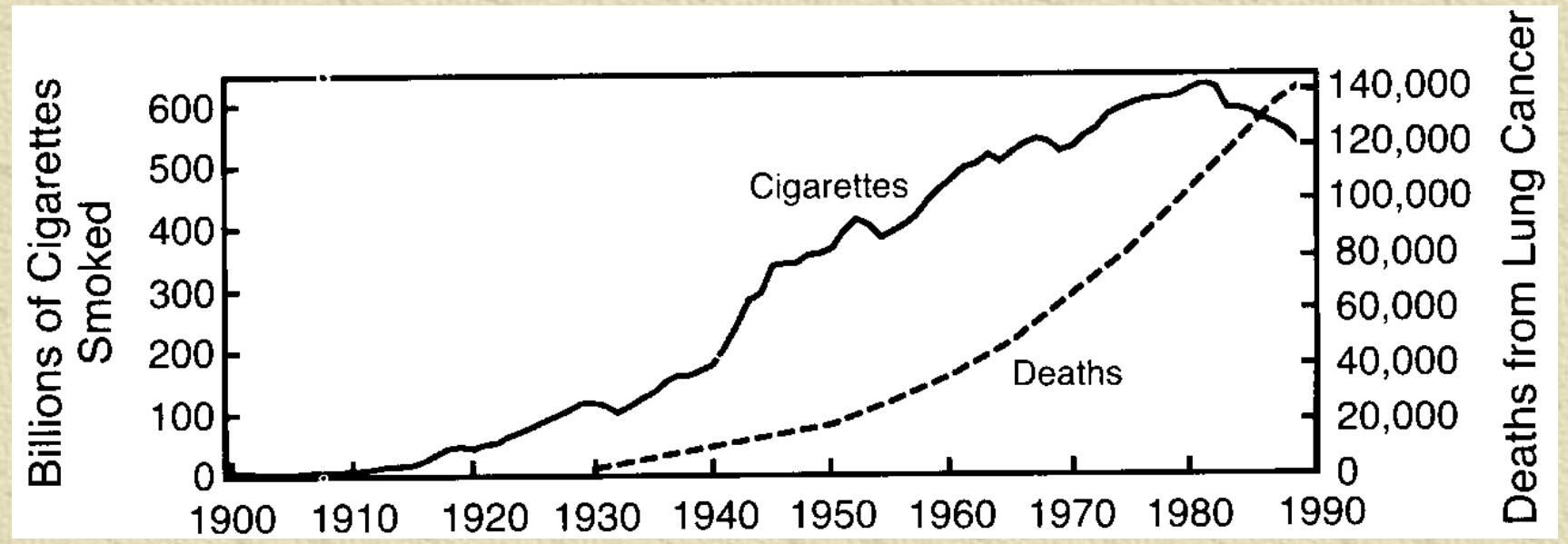
- Risk Factors
  - ? Gender
    - Conflicting results
  - Diet
    - Vitamins A & E, fruits & vegetables intake lower the risk
  - COPD/Pulmonary fibrosis

Pulmonary Nodule Risk

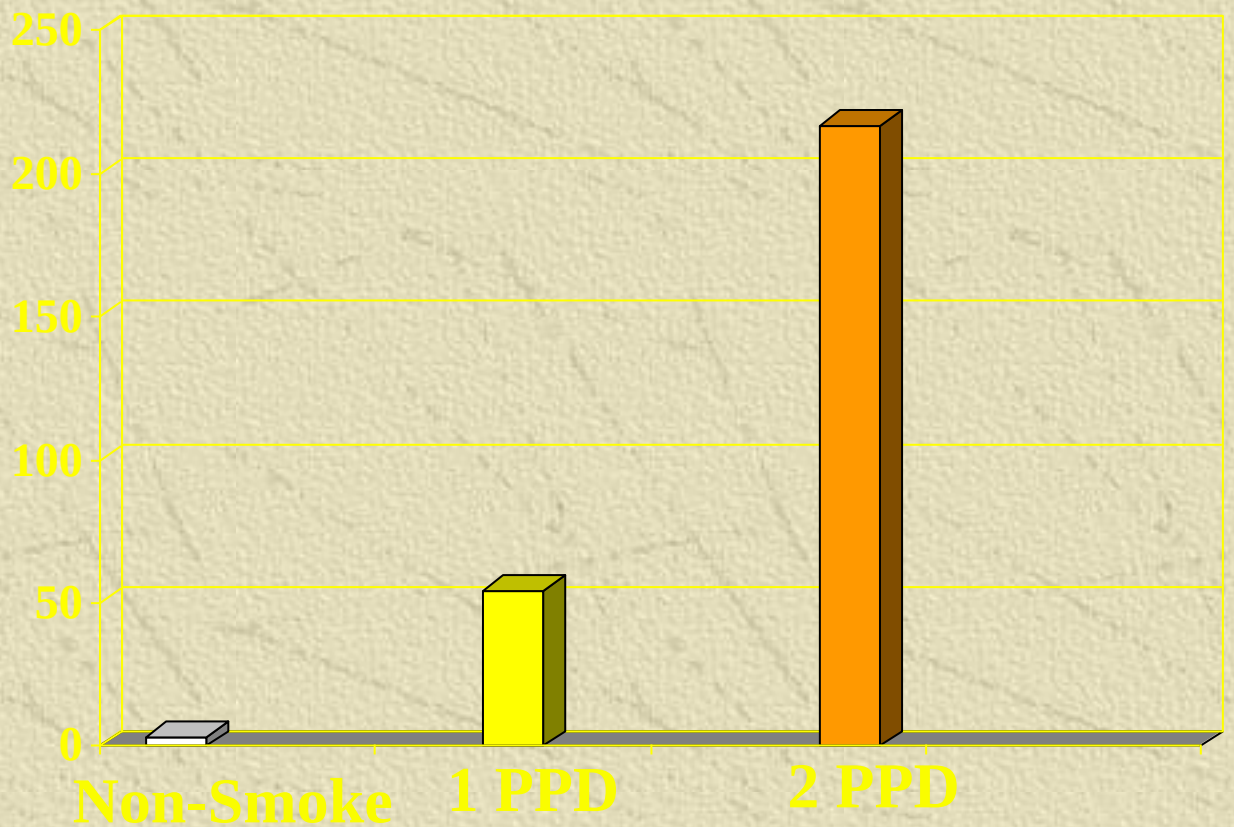
Table 19–5. INCIDENCE OF MALIGNANCY IN SOLITARY PULMONARY NODULES RELATED TO AGE

Age (yr)	Malignant (%)
35–44	15
45–49	26
50–59	41
60–69	50
70–79	70

Smoking and Lung CA



Incidence (per 100,000)



Evaluation

- Clinical
- Laboratory
- Radiographic
- Physiologic
- Diagnostic

Clinical Manifestations

- Factors which Affect Symptoms
  - Location
  - Extension
  - Mets
  - Hormonal syndromes

Symptoms-Pulmonary

- Pulmonary
  - Cough
  - Hemoptysis
  - Dyspnea
  - Fever
  - Chest pain

Symptoms-Extrapulmonary

- Extra Pulmonary
  - Pleural effusion - dyspnea
  - Recurrent Nerve - Hoarseness
  - SVC Syndrome
  - Dysphagia

Symptoms-Extrathoracic

- **Extra Thoracic**
  - **Hypertrophic pulmonary osteoarthropathy**
  - **Cervical Lymph Node Mets**
  - **Bone Pain**
  - **CNS Symptoms**

Symptoms-General

- **Non-specific**
  - **Weight loss**
  - **Weakness**
- **Hormonal**
  - **Cushing's Small Cell**
  - **SIADH Adeno or poorly diff**
  - **Parathormone, Hypercalcemia SCCA**

Symptoms-General

- Asymptomatic - 5 to 15%
- Others
  - Neuromyopathies (Eaton-Lambert)
  - Dermatoses
  - Vascular
  - Hematologic

Physical Findings

- Will depend on extent of disease
- Cachexia
- Lymphadenopathy
- Clubbing
- Pulmonary findings
- Manifestations of metastases

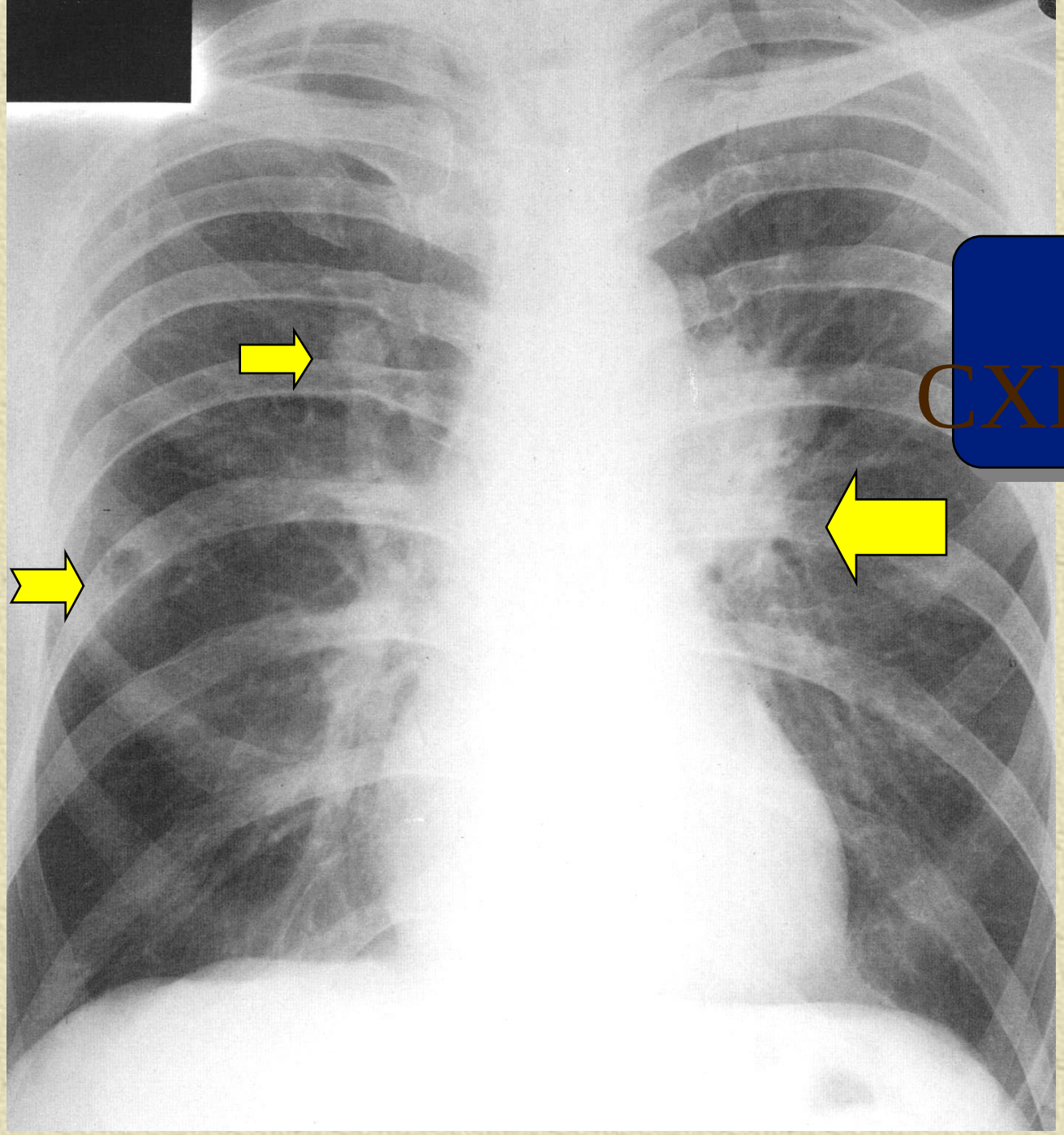
Physical Exam

Laboratory

- Non-specific findings
- Anemia
- Hypercalcemia
- Elevated CEA level
- Abnormal LFTs
- Elevated ALP

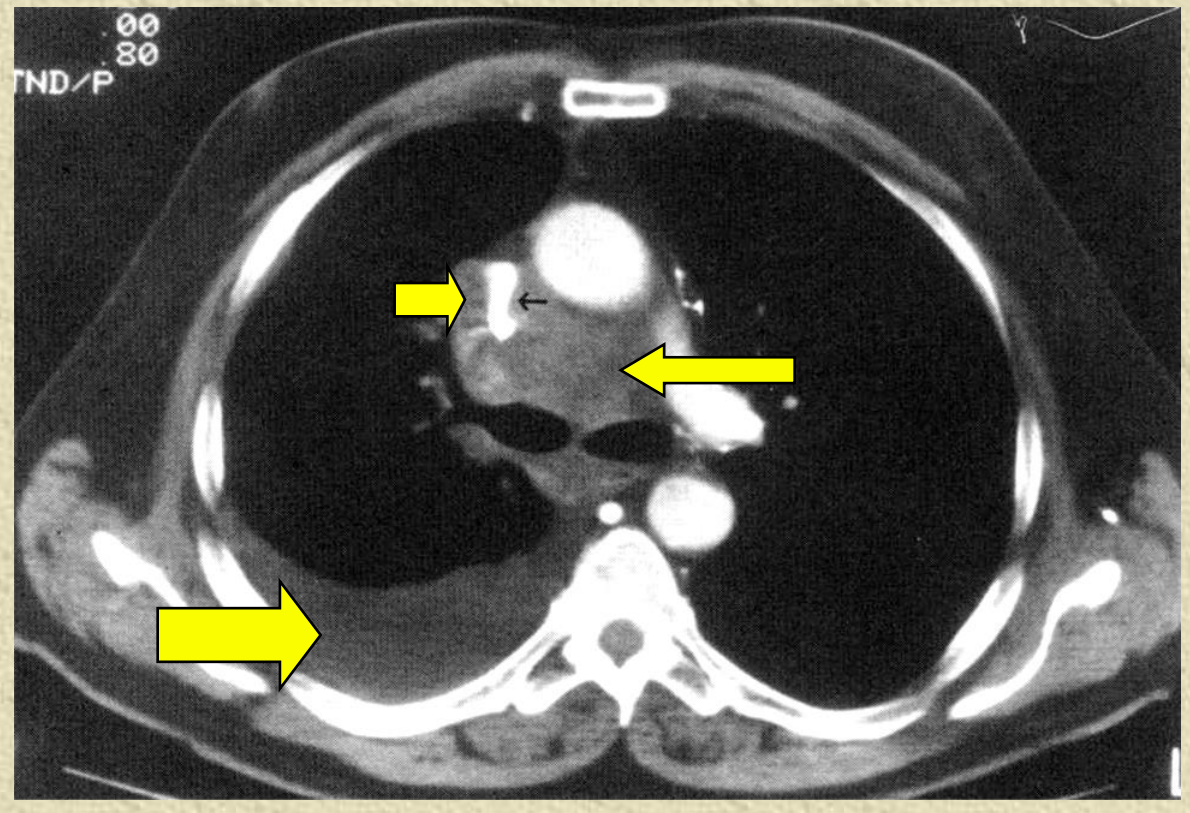
Imaging

- **CXR (OLD FILMS!)**
- **CT Scan**
- **MRI**
- **Bone Scan**
- **PET Scan**



CXR

CT Scan



Sites of Metastases

- Lymph nodes
- Other Lung lobes
- Brain
- Liver
- Adrenal glands
- Bone

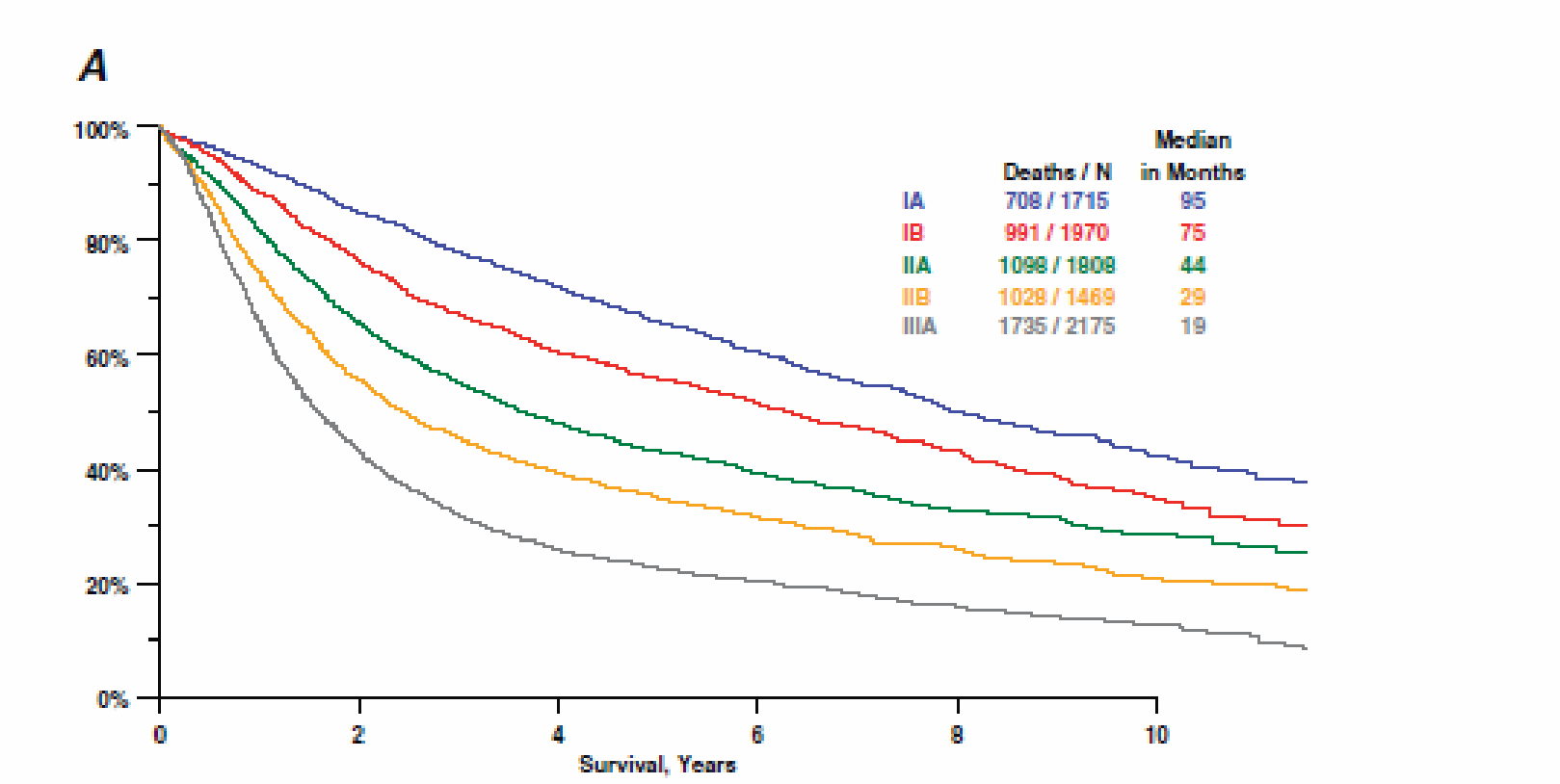
PET Scan

- Based on FDG Uptake
- Sensitivity > 95%
- Specificity 78%
- False negatives
  - Carcinoids, bronchioloalveolar Ca
- False positives – Inflamm lesions
- Expensive

Physiologic Evaluation

- Pulmonary Assessment
  - Spirometry
    - FVC, FEV1, DLCO
  - Arterial Blood Gases
    - pCo2, pO2
  - Pulmonary Perfusion Scan
  - Exercise Pulmonary Testing
    - Max oxygen consumption (MVO2)

Bronch Findings

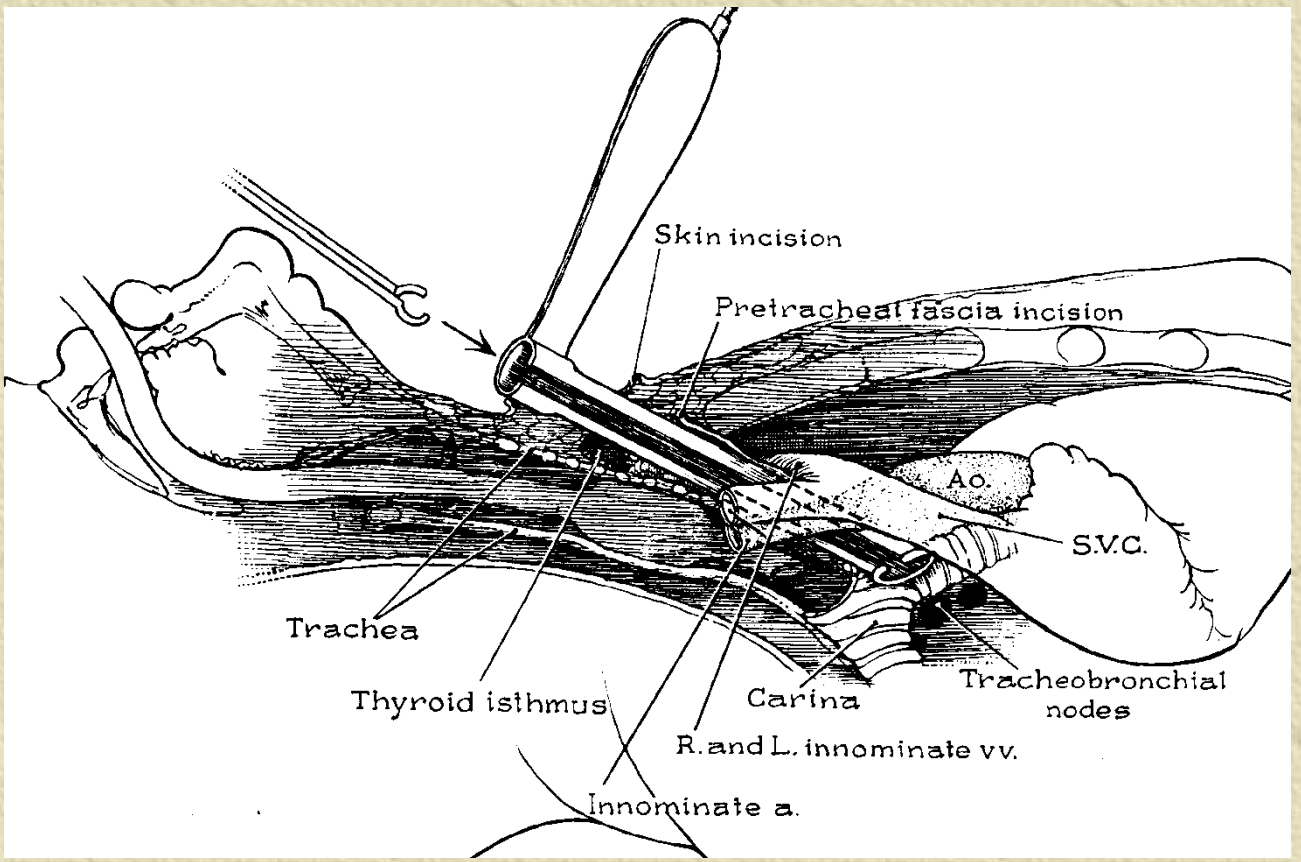


Survival of non-small cell lung cancer by stage – Journal of Thoracic Oncology

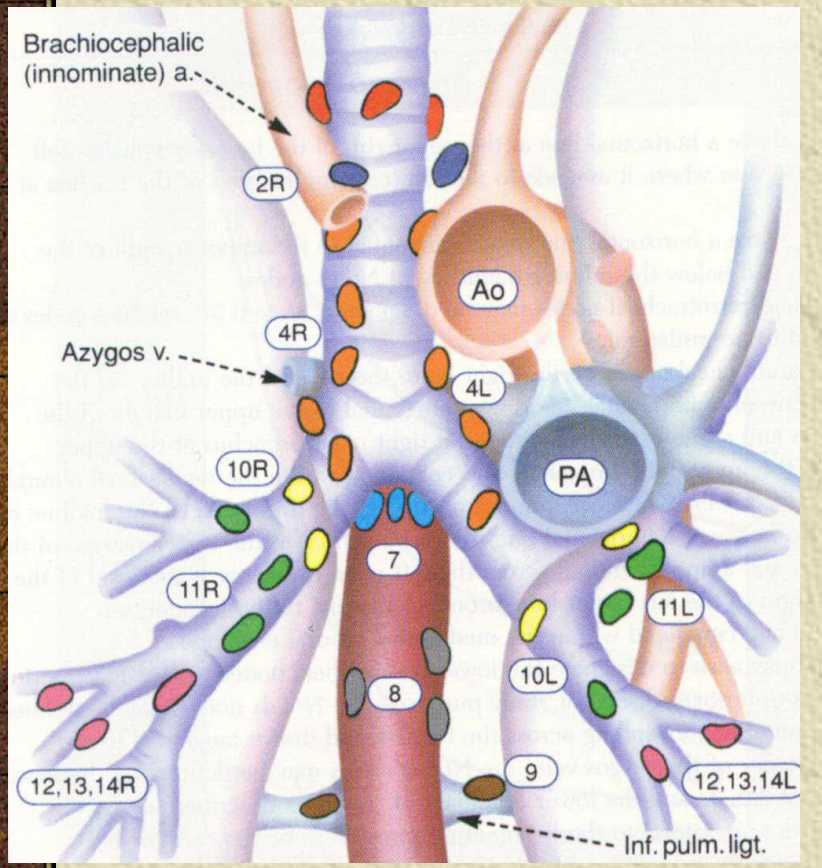
Surgical Staging

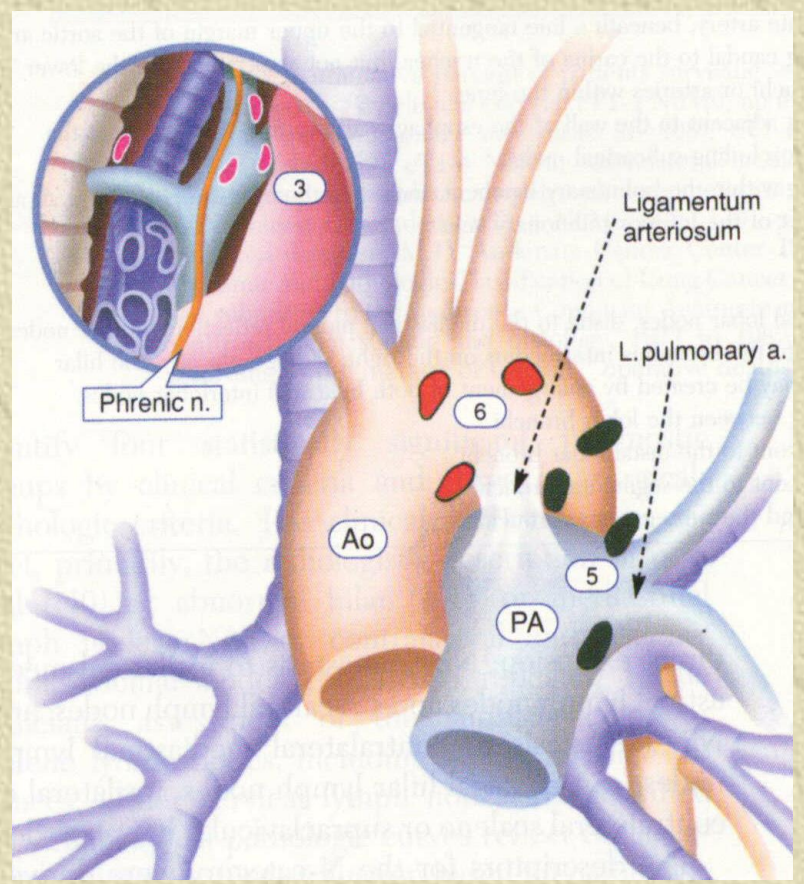
- Mediastinoscopy
- Mediastinotomy (Chamberlain procedure)
- Thoracoscopy (VATS)

Mediastinoscopy



Mediastinal Lymph Nodes





Surgical Management

- Surgically Curable
  - 50% present with distant mets
  - 25% Incurable intrathoracic spread
  - 25% Possibly curable

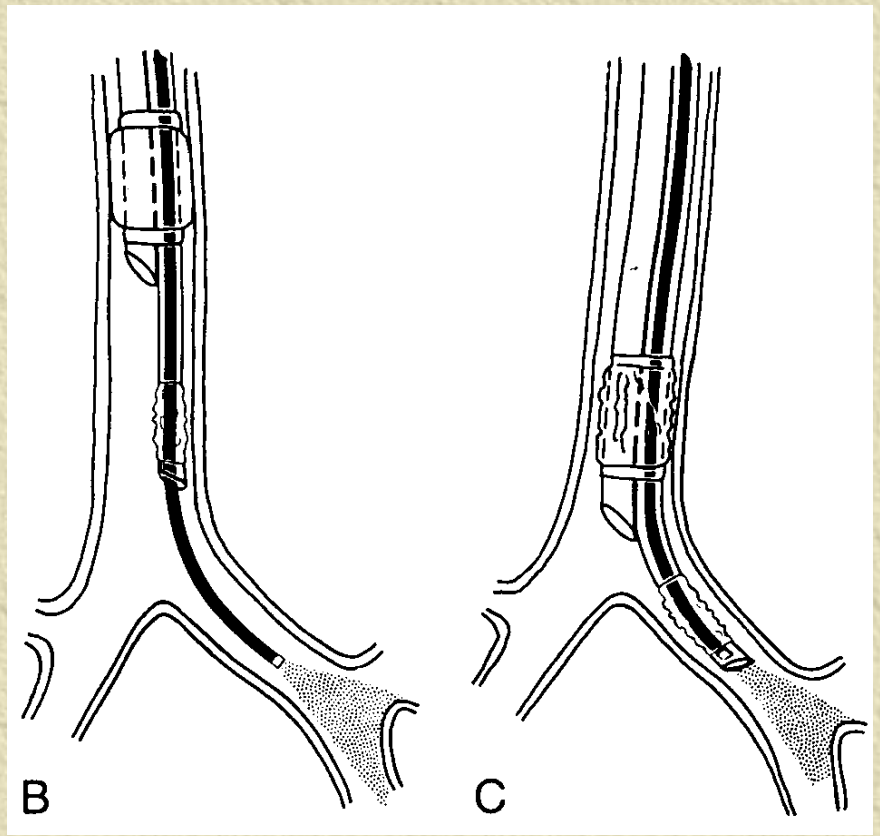
Surgical Management

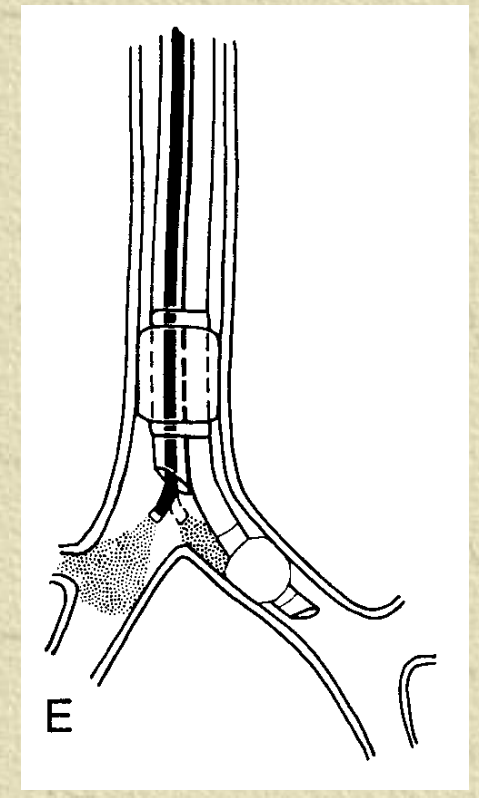
- Approach
- Video Assisted Thoracic Surgery (VATS)
- Thoracotomy
  - Posterolateral
  - Anterior
- Median Sternotomy

Surgical Management

- Lobectomy (+ lymphadenectomy)
- Larger resections
  - Bilobectomy, Pneumonectomy
- Lesser resections
  - Segmentectomy, wedge resection

Airway control





Non-Surgical Therapies

- Chemotherapy
- Radiotherapy
- Combination therapy
  - Neoadjuvant (prior to surgery)
  - Palliative
  - Definitive
  - Adjuvant (after surgery)

National Lung Screening Trial

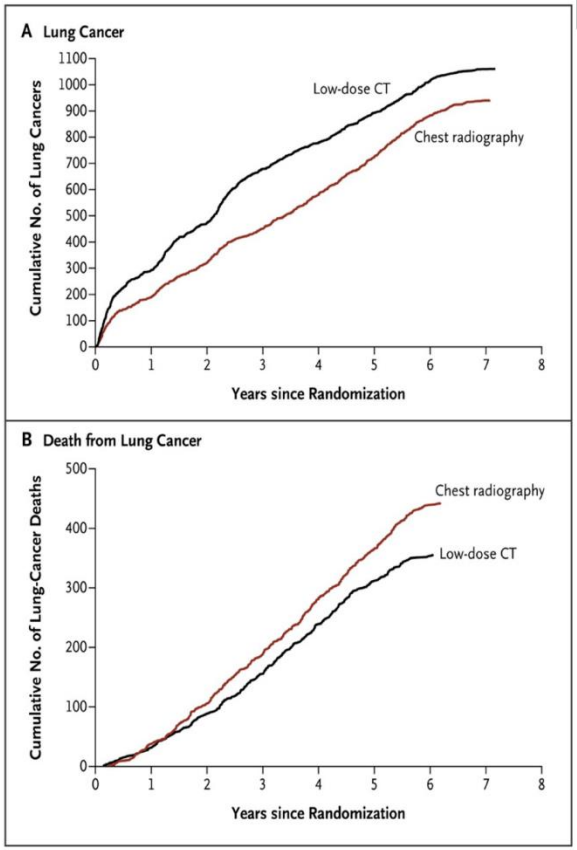
- Largest lung cancer screening trial to date.
- NCI sponsored
- Compared low-dose CT (LDCT) scan to chest X-Ray. Randomized patients to either arm with standard of care follow up.
- Patients had 3 annual LDCTs
- Over 30 institutions in the United States

	Low-dose CT Arm				CXR Arm		
	Screen 1 (%)	Screen 2 (%)	Screen 3 (%)		Screen 1 (%)	Screen 2 (%)	Screen 3 (%)
Total positives	7 193	6 902	4 054	Total positives	2 387	1 482	1 175
Lung cancer	270 (**4**)	168 (**2**)	211 (**5**)	Lung cancer	136 (6)	65 (4)	78 (7)
No lung cancer	6 923	6 734	3 843	No lung cancer	2 251	1 417	1 097

True and False Positive Screens

Final interpretation data, including benefit of historical comparison exams

Geralda DS , RSNA 2010



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

In other words...

- 354 of pts who had CT screening died, compared to 442 with CXR.
- 88 did not die who would have otherwise so there was a 20% reduction in lung cancer mortality.

The National Lung Screening Trial Research Team, NEJM, Vol. 365, Figure 1, 2011

Ref : Cancergrace.org

Screening

- Screening for lung cancer has been demonstrated to be successful
- However, many screening tests are false positive – testing for this has risks
- How can we separate benign nodules from malignant ones?

Attempts to separate benign from malignant nodules

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer

Gerard A. Silvestri, M.D., Anil Vachani, M.D., Duncan Whitney, Ph.D., Michael Elashoff, Ph.D., Kate Porta Smith, M.P.H., J. Scott Ferguson, M.D., Ed Parsons, Ph.D., Nandita Mitra, Ph.D., Jerome Brody, M.D., Marc E. Lenburg, Ph.D., and Avrum Spira, M.D., for the AEGIS Study Team*

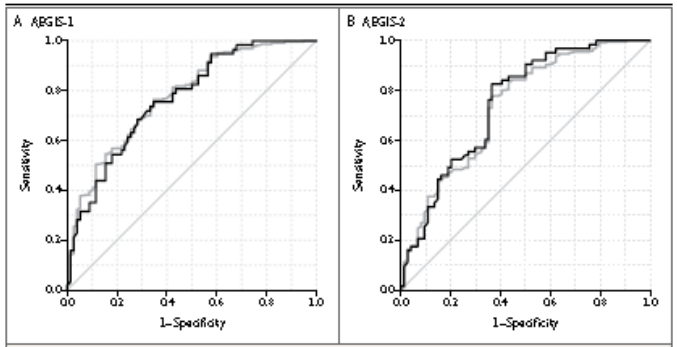


Figure 1. Classifier Performance in the AEGIS-1 and AEGIS-2 Studies.

Shown are receiver-operating-characteristic curves for all patients (gray) and the subset of patients with a nondiagnostic bronchoscopic examination (black) in the AEGIS-1 and AEGIS-2 cohorts. In AEGIS-1, the area under the curve (AUC) was 0.78 (95% CI, 0.73 to 0.83) for all patients and 0.76 (95% CI, 0.68 to 0.83) for patients with a nondiagnostic examination ($P=0.31$). In AEGIS-2, the AUC was 0.74 (95% CI, 0.68 to 0.80) and 0.75 (95% CI, 0.68 to 0.82), respectively ($P=0.85$). The AUC was also not significantly different for patients with a nondiagnostic examination in the comparison between AEGIS-1 and AEGIS-2 ($P=0.61$).

Attempts to separate benign from malignant nodules

Blood based biomarkers

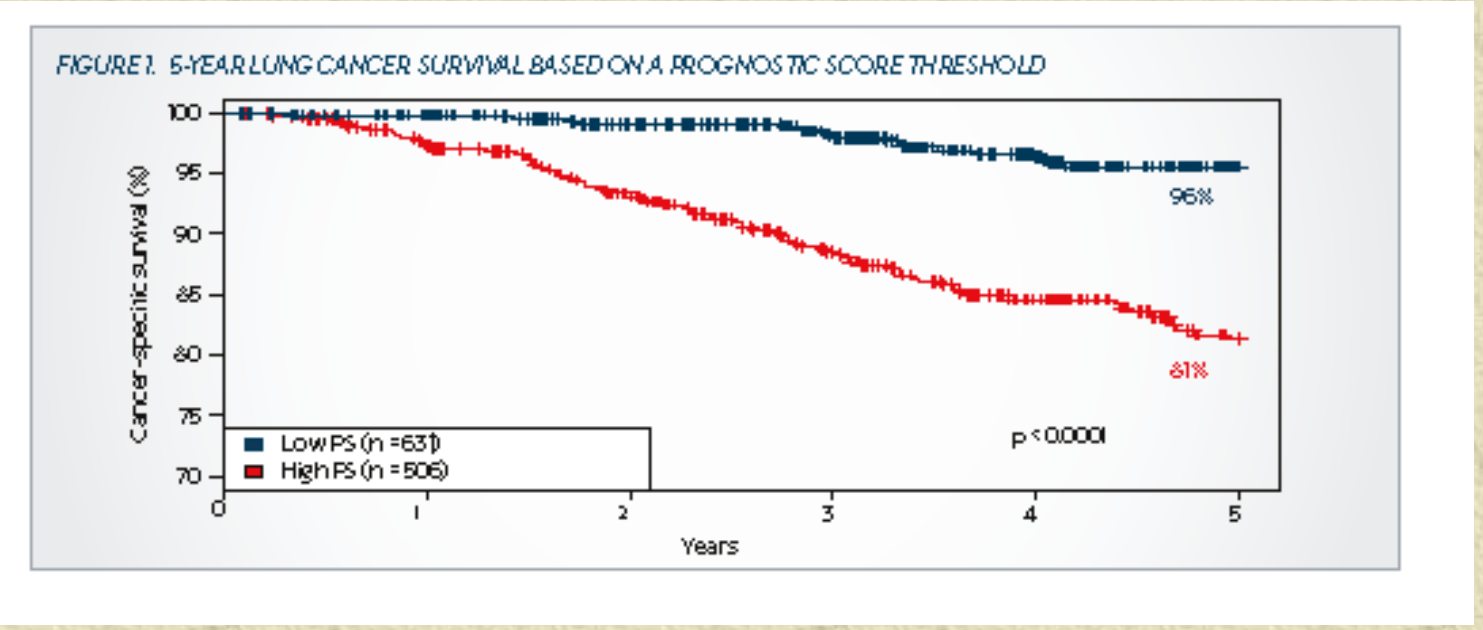
Serum microRNAs

Circulating tumor cells

Early stage lung cancer

- Most patients undergo resection
- However, there is a high recurrence rate
- Prognostic biomarkers may help with deciding if any patients should be treated with adjuvant chemotherapy

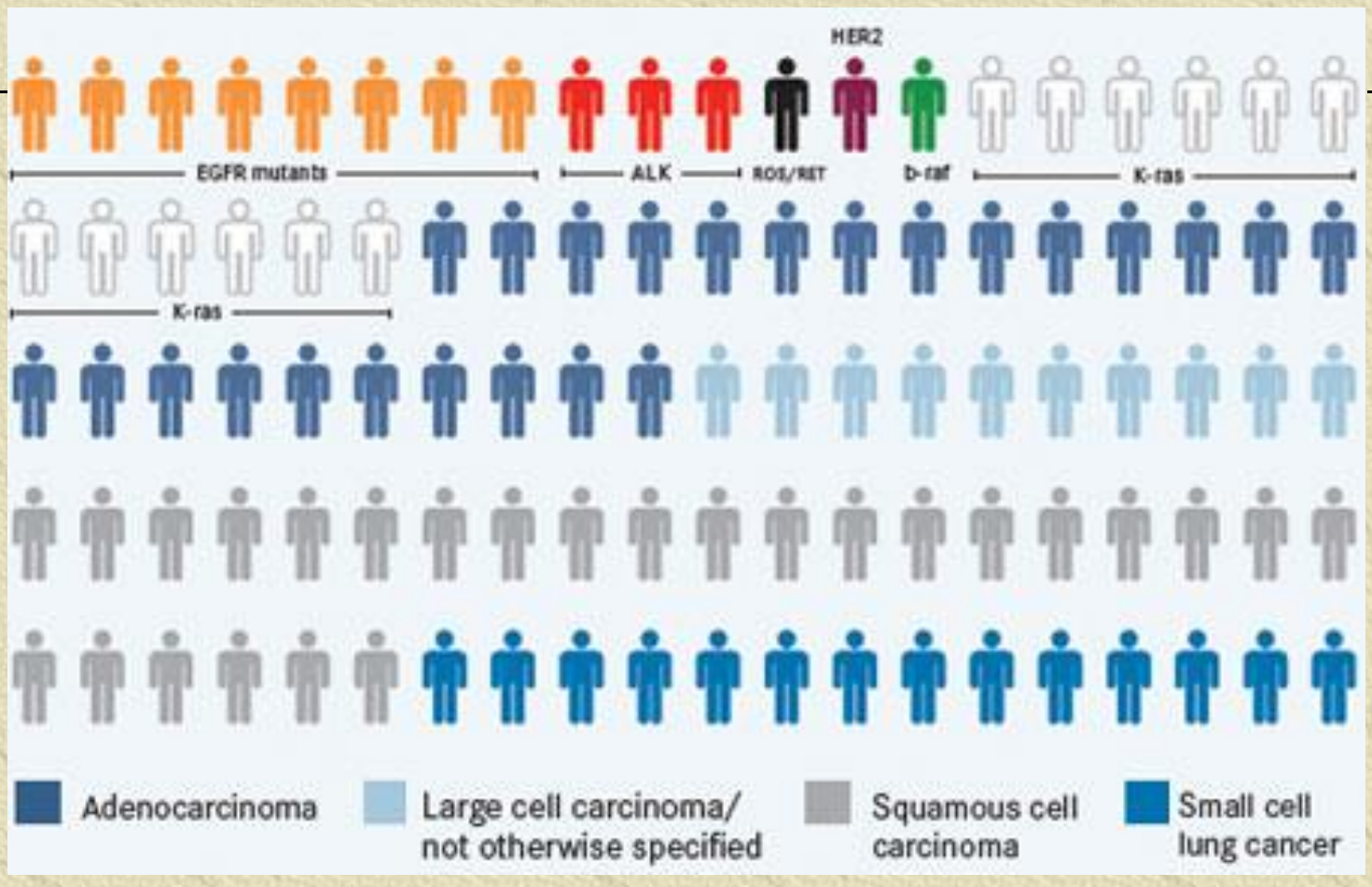
Prognostic signatures

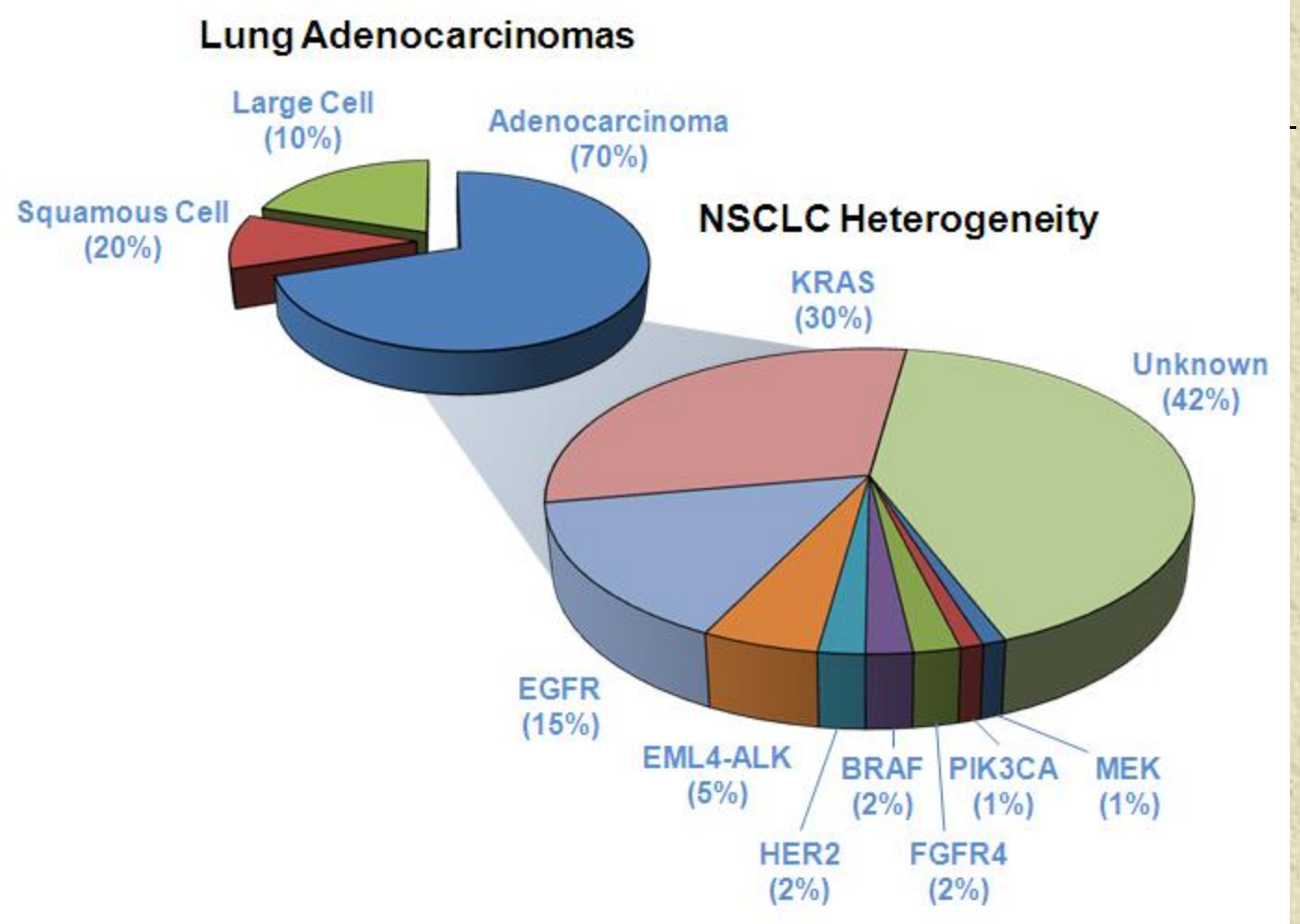


46 gene signature - adenocarcinoma

RT-PCR based

Validated in many cohorts


HER2
EGFR mutants
ALK
ROS/RET
b-raf
K-ras
K-ras
Adenocarcinoma
Large cell carcinoma/ not otherwise specified
Squamous cell carcinoma
Small cell lung cancer


Lung Adenocarcinomas
Large Cell (10%)
Adenocarcinoma (70%)
Squamous Cell (20%)
NSCLC Heterogeneity
KRAS (30%)
Unknown (42%)
EGFR (15%)
EML4-ALK (5%)
BRAF (2%)
PIK3CA (1%)
MEK (1%)
HER2 (2%)
FGFR4 (2%)

Immunotherapy

- Checkpoint inhibitors
- Monoclonal antibodies against tumor antigens
- Therapeutic vaccines against tumor antigens to generate a durable immune response
- Adoptive T cell therapy

Mutations and response

Corrected 11 February 2016; see full text.

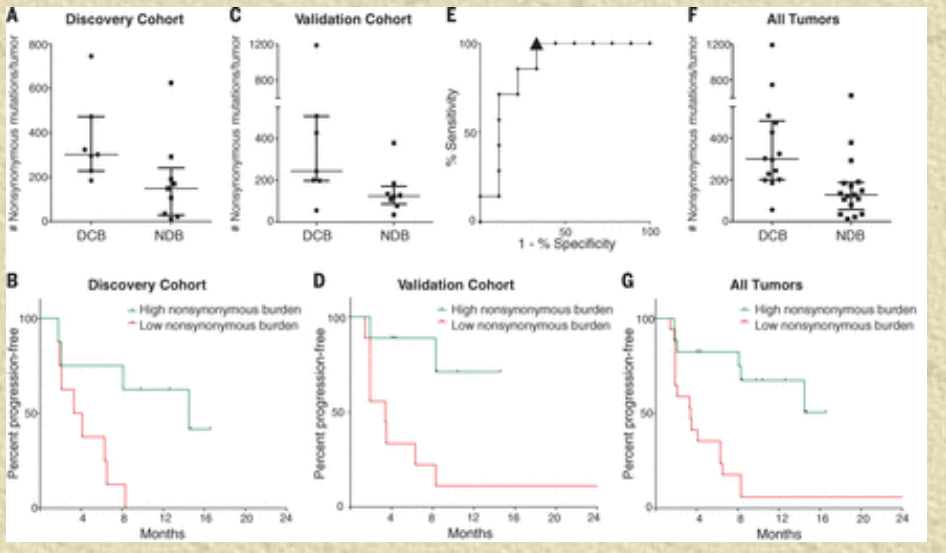
RESEARCH | REPORTS

CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Naiyer A. Rizvi,[1,2]† Matthew D. Hellmann,[1,2] Alexandra Snyder,[1,2,3] Pia Kvistborg,[4] Vladimir Makarov,[5] Jonathan J. Havel,[5] William Lee,[5] Jianda Yuan,[5] Phillip Wong,[5] Teresa S. Ho,[5] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[3,8,2]†

Immune checkpoint inhibitors, which unleash a patient's own T cells to kill tumors, are revolutionizing cancer treatment. To unravel the genomic determinants of response to this therapy, we used whole-exome sequencing of non–small cell lung cancers treated with pembrolizumab, an antibody targeting programmed cell death-1 (PD-1). In two independent cohorts, higher nonsynonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit, and progression-free survival. Efficacy also correlated with the molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations; each factor was also associated with mutation burden. In one responder, neoantigen-specific CD8+ T cell responses paralleled tumor regression, suggesting that anti–PD-1 therapy enhances neoantigen-specific T cell reactivity. Our results suggest that the genomic landscape of lung cancers shapes response to anti–PD-1 therapy.



Conclusions

- Lung cancer has a low cure rate
- The scope of research in this malignancy is increasing exponentially