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Lung Cancer

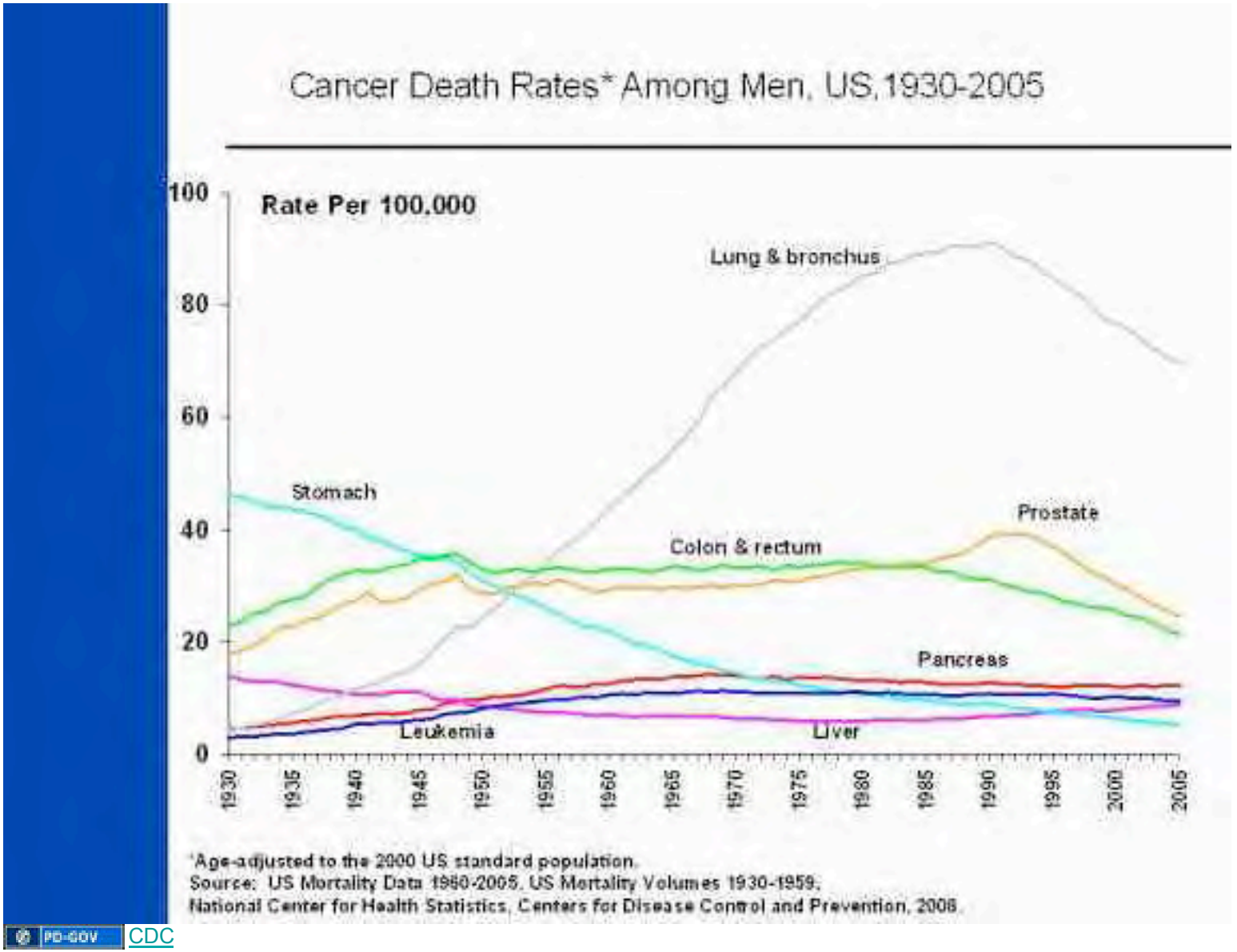
M2 – Respiratory Sequence

Douglas Arenberg, M.D.

Fall, 2009

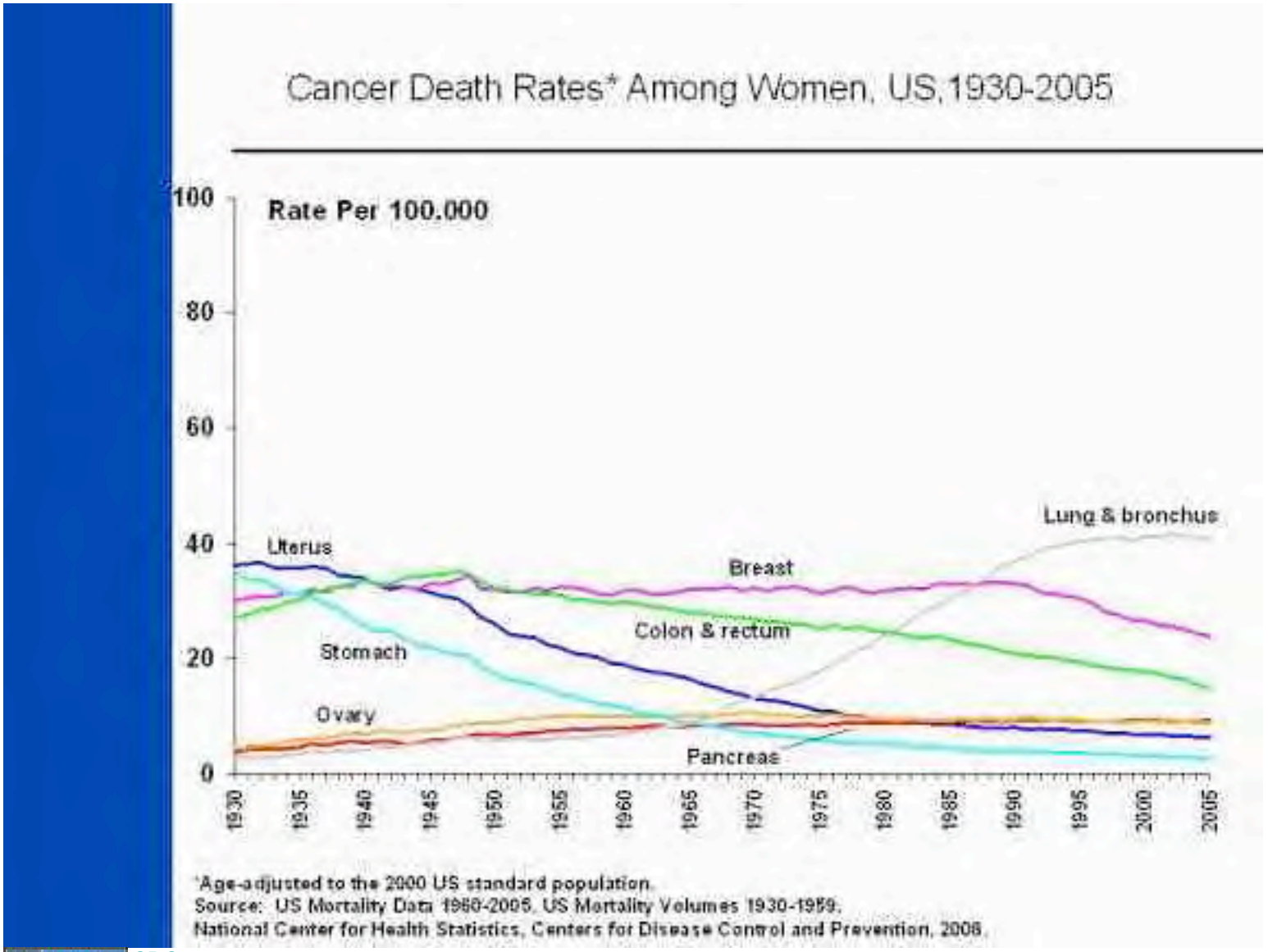
University of Michigan
Medical School

Cancer Mortality Rates - Male



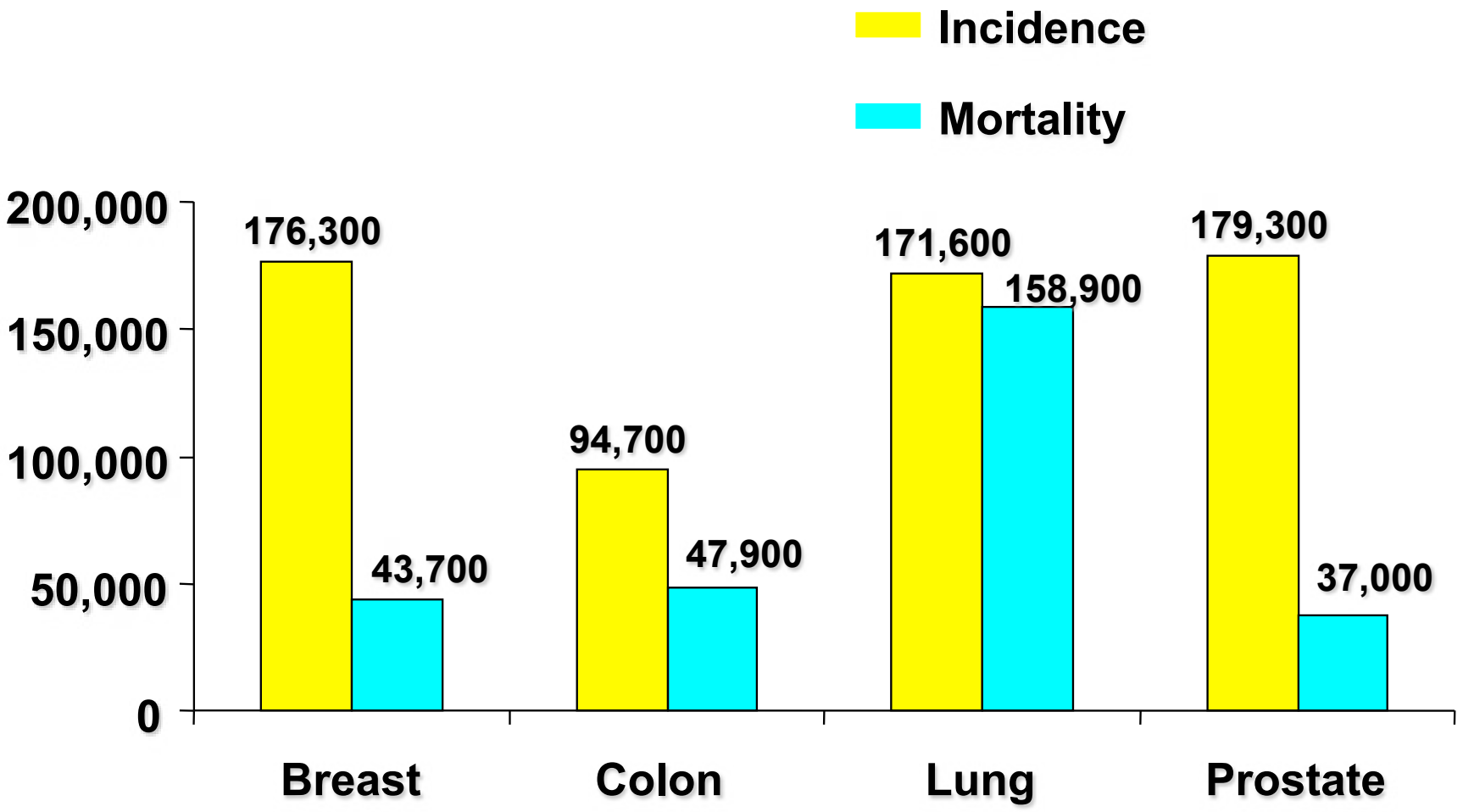
PD-GOV CDC

Cancer Mortality Rates - Female



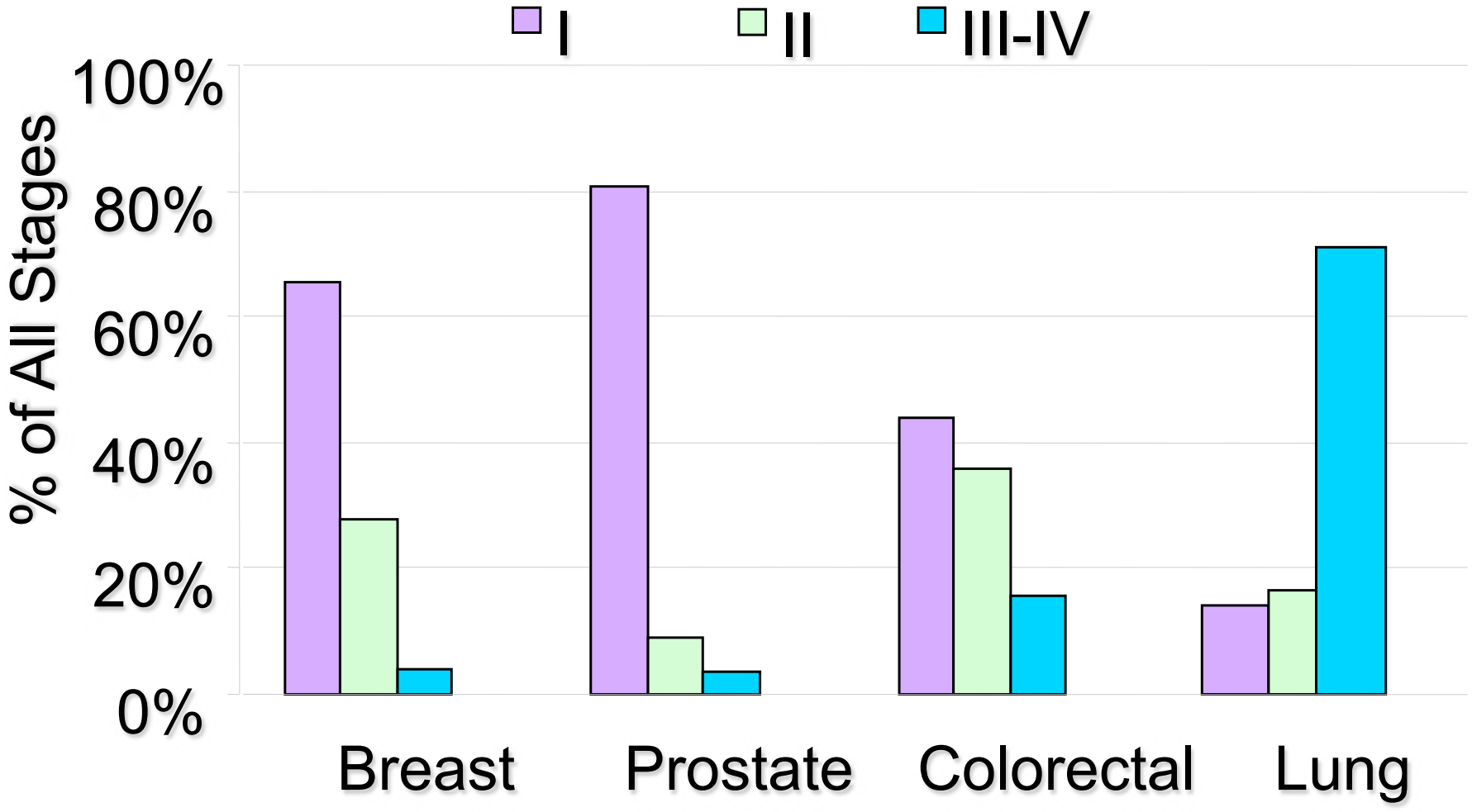
PD-GOV CDC

One of these things is not like the others



D. Arenberg, American Cancer Society. *Cancer Facts & Figures–1999.*

Approximate Cancer Stage at Diagnosis



With respect to lung cancer, which of the following is true?

- Surgery offers the only chance for a cure in lung cancer
- Below a certain absolute level of lung function, surgery is absolutely contraindicated
- Thoracoscopic lobectomy is less painful but results in inadequate staging of mediastinal lymph nodes
- Post-operative chemotherapy prolongs survival and offers a greater chance of long term cure

- **How do lung cancer patients differ from other cancer patients?**
  - **Many co-morbid diseases**
  - **Surgery implies part removal of a vital organ**
  - **Surgery for locally advanced disease is not usually standard of care**
  - **Role(s) of adjuvant and neoadjuvant therapy is less well defined (until recently)**

Patients with lung nodules should be assumed to have cancer until proven otherwise

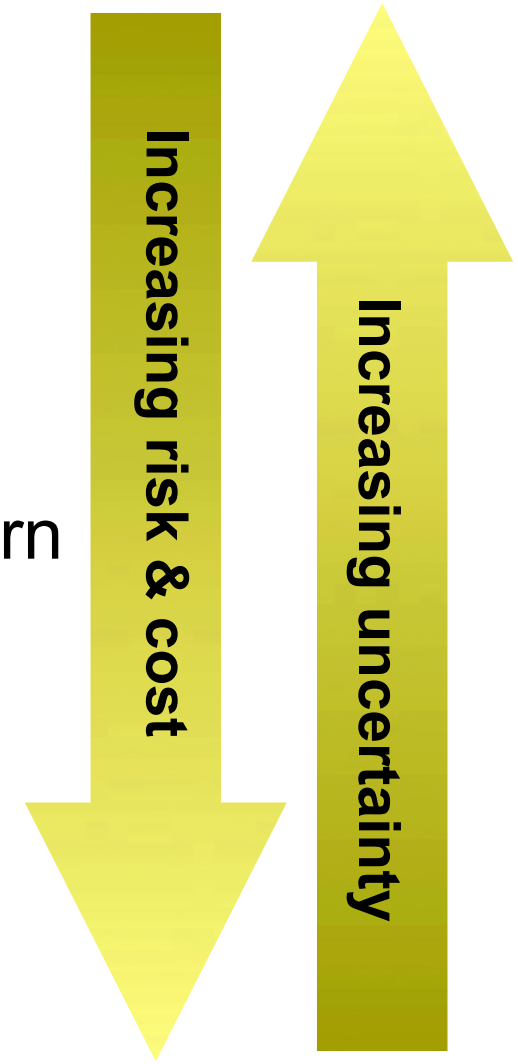
Dr. Arenberg, have you taken leave of your senses?

Principles guiding the evaluation of patients with lung nodules

- #1 Do you or do you not have lung cancer
  - Lung nodules are cancer until ***proven*** otherwise
  - Certainty/urgency of proof differs for each patient
- Over *98%* of lung nodules detected by CT scan are benign

Cancer until proven otherwise?

- Clinical history
  - Recent febrile illness
- Radiologic
  - Size stability?
  - CT evidence of benign calcification pattern
- PET scanning
- Biopsy
  - Bronchoscopic or FNA
  - Surgical



FDG-PET

Diagnostic Performance of PET in Assessment of Mediastinal Lymph Nodes of Lung Cancer. 2007 J Nuc Med 48 (11)

Index	Visual interpretation (%)	SUV Cutoff of 2.5 (%)
Sensitivity	91 (85–98)	89 (81–96)
Specificity	85 (81–90)	84 (79–88)
Accuracy	87 (82–91)	85 (81–89)
Positive predictive value	64 (55–73)	61 (52–71)

Principles guiding the evaluation of patients with lung nodules

- *#2 If you have lung cancer, is it resectable*
  - *For now*, surgery offers the greatest possibility of cure (assume a cancer is resectable until ***proven*** otherwise)
  - Risk of morbidity & mortality
  - No benefit in locally advanced disease (IIIa or worse)
  - Accurate staging is a must
- A surgeon must be involved in the determination of whether a patient has “resectable” cancer

Factors which predict a higher likelihood of cancer

- Size of the nodule
- Border (spiculated versus smooth)
- Age of the patient
- History of tobacco use
- Location of the nodule (upper lobe higher risk than lower lobe)
- Prior history of cancer
  - http://www.chestx-ray.com/SPN/SPNProb.html

Causes of lung cancer

- Tobacco smoking
- Tobacco smoking
- Tobacco smoking
  - Some types of lung cancer more closely associated with tobacco than others
  - Small cell > squamous > adeno
  - *All* are more common in smokers
- Asbestos
- Radon
- Genetic susceptibility?
  - Common risk factors for both lung cancer and tobacco addiction/dependence

Causes of lung cancer

- Tobacco
  - Fewer than 10% of smokers get lung cancer
- Tobacco
  - Smokers with COPD are at much greater risk than smokers without COPD
- Over 50% of newly diagnosed lung cancer patients are former or never smokers

Lung cancer signs and symptoms at presentation*

Finding	% of Pts (n=214)
Cough	54
Dyspnea	36
Weight loss	33
Chest pain	32
Fatigue	20
Anorexia	16
Hemoptysis	15
Hoarseness	9

- **Most people with these symptoms DO NOT have lung cancer**
- **Early stage lung cancer causes NO symptoms!!**

Squamous Cell Carcinoma

- Used to be the most common type
- More common in the proximal of the tracheobronchial (60 to 80%)
- Squamous cancers are more likely to be cavitated than other types
- A subset occur as endobronchial lesions in patients with a normal CXR.
  - Patients present with persistent cough, recurrent hemoptysis, or relapsing pulmonary infections due to airway obstruction.
- 5 year survival 65% (combined stages)

Adenocarcinoma

The most common type of lung cancer

Most frequent histologic type in women and nonsmokers of either sex.
Most adenocarcinomas are located peripherally (75%).
Bronchoalveolar carcinoma —subtype of adenocarcinoma, probably more indolent

- **An origin distal to grossly recognizable bronchi**
- **Well-differentiated cytology**
- **A propensity for aerogenous and lymphatic spread**
- **Growth along intact alveolar septa**
  ("lepidic" growth pattern; Air-bronchograms)

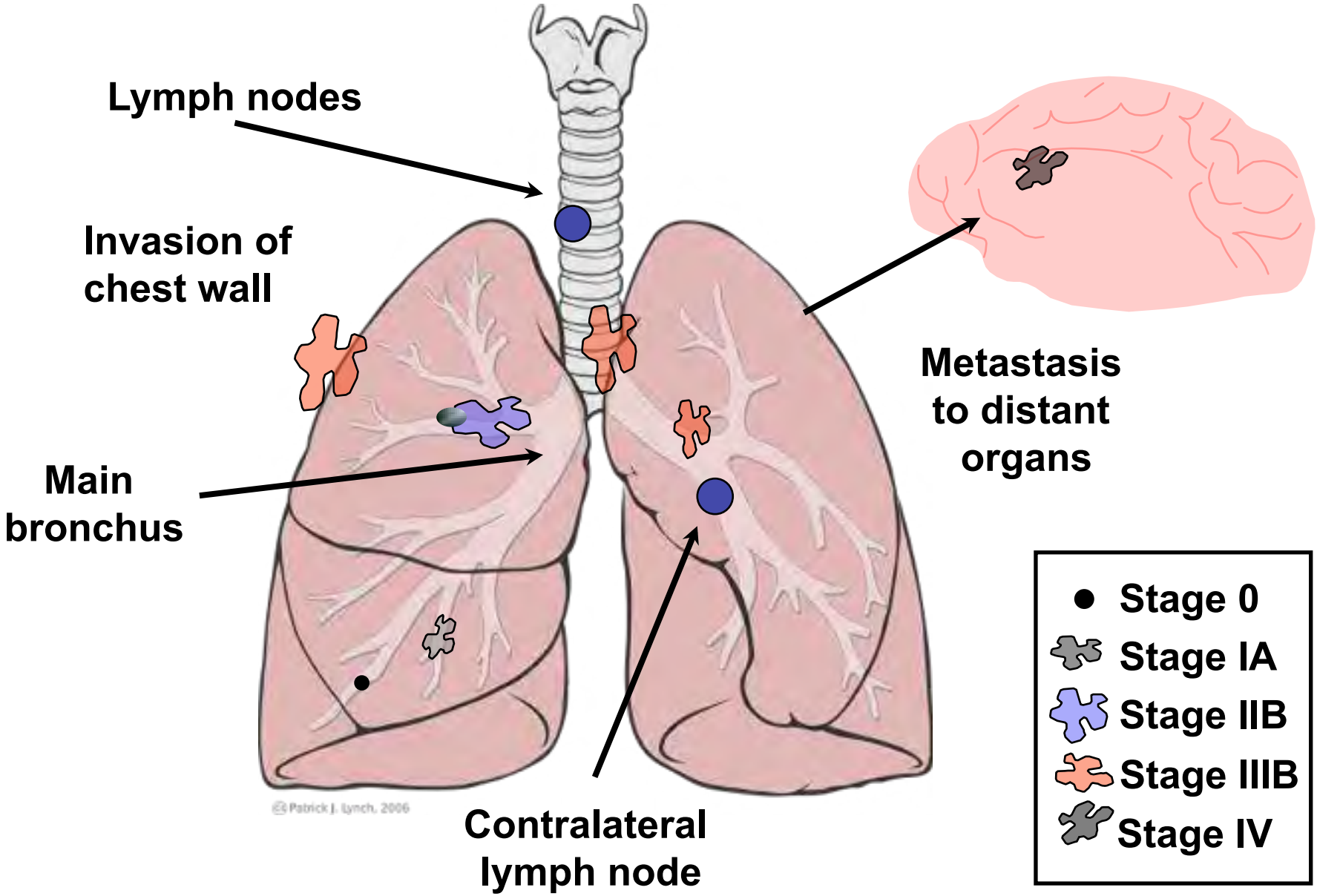
Small Cell Carcinoma

- 15 to 20%. Smokers (nearly only)
- Are neuroendocrine lung tumors
- *Rapid* doubling time, early development of widespread metastases.
- Highly sensitive to chemo- and radiotherapy
  - Almost always relapses in < 2 years. Only 3-8% survive beyond 5 years. Not a surgical disease.
- Typically a large hilar mass with massive mediastinal adenopathy
  - Cough, dyspnea, weight loss, debility, post-obstructive pneumonia.
- 70% present with metastatic disease

Goals in work-up of patients with suspected lung cancer

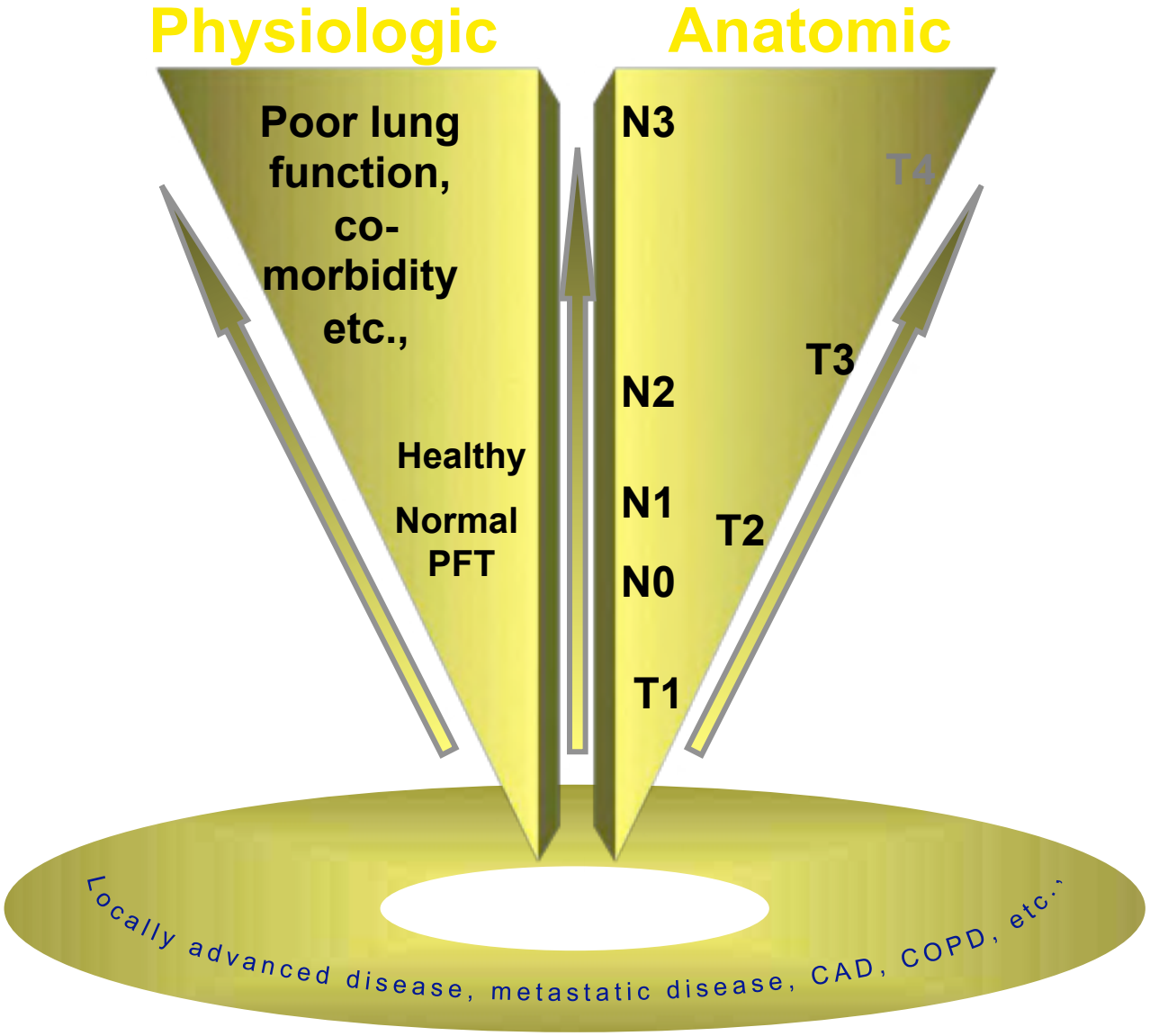
- Find *every patient* who can tolerate surgery
- Find *every patient* whose disease is anatomically amenable to surgery
- For patients who meet both criteria, introduce them to a surgeon, quickly
  - Do not pass go, do not collect $200 and DO NOT biopsy!!
- Minimal work-up
  - Spirometry, liver/renal/coagulation
  - Assessment of exercise tolerance (usually clinical)
  - CT scan with IV contrast
  - Consider PET scanning if available

NSCLC stages



 D. Arenberg, Adapted from Lungs Diagram Simple, Patrick J. Lynch, Wikipedia

Staging in practice



Barriers to surgical resection

Therapy of non-small cell lung cancer

- **Stage I-II (disease confined to lungs and/or peribronchial lymph nodes)**
  - **Surgery for patients with adequate pulmonary reserve**
  - **Limited resection (less than lobectomy) for patients with borderline lung function**
- **Stage III (disease which has spread to mediastinal lymph nodes)**
  - **Chemoradiation therapy (concurrent is better than sequential, but at a greater cost in toxicity)**
  - ***Partial resection (leaving tumor behind) is of no value***

Chemotherapy for Non-small cell lung cancer (NSCLC)

- Cell type (squamous vs adeno vs large cell) does not matter
- Response rates generally better in phase I-II trials than in phase III RCTs
- Until recently survival difference measured in weeks

Advanced NSCLC: chemotherapy agents

- **Platinum-based combination therapy gives better response rates than monotherapy and remains the 'gold standard' for first-line therapy for advanced disease**
- **Paclitaxel, vinorelbine, docetaxel, gemcitabine**
- **In the past 3 decades, median survival in NSCLC patients has only improved by approximately 2 months**

Source: Corey Langer 2000; Breathnach et al 2001; Schiller et al 2002

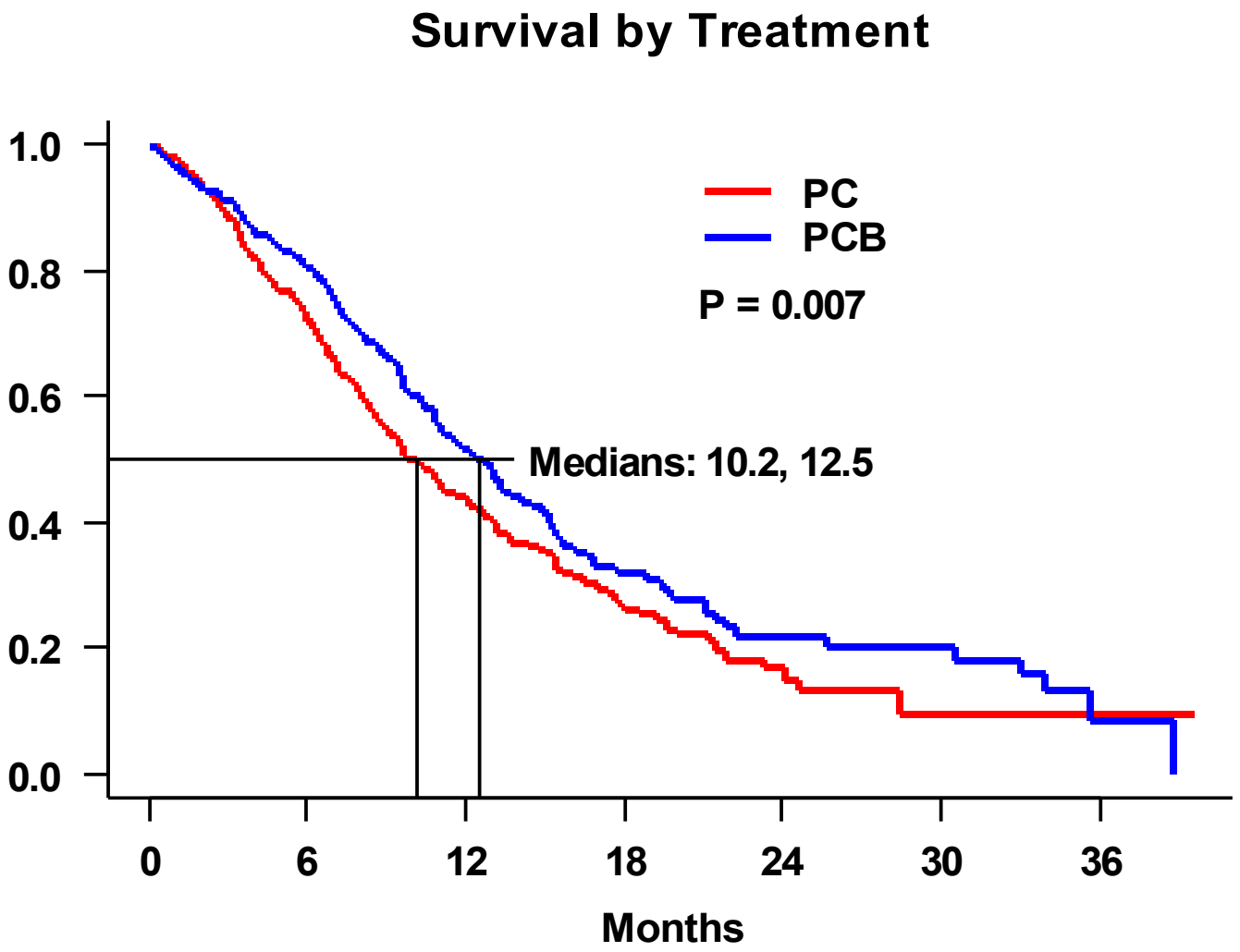
Clinical Characteristics Predictive of Response to EGFR inhibitors

- Female
- Adenocarcinoma, especially Bronchioloalveolar (BAC)
- Non-Smoker
- Asian (Japan, Taiwan, Singapore)
- Development of Rash

anti-VEGF (Bevacizumab) in Advanced Stage Lung Cancer

Response Category (Patients)	PC (383)	PCB (391)
CR	0.3%	1.4%
PR	10%	26%
CR/PR	10%	27%*

*p<0.0001



Novel biological approaches

- Anti-angiogenic agents
  - monoclonal antibodies, eg bevacizumab (rhuMab-VEGF)
  - VEGF receptor TKIs, eg ZD6474, PTK787
  - matrix metalloproteinase inhibitors
  - thalidomide
- Vascular targeting agents, eg combretastatin A4 phosphate, ZD6126

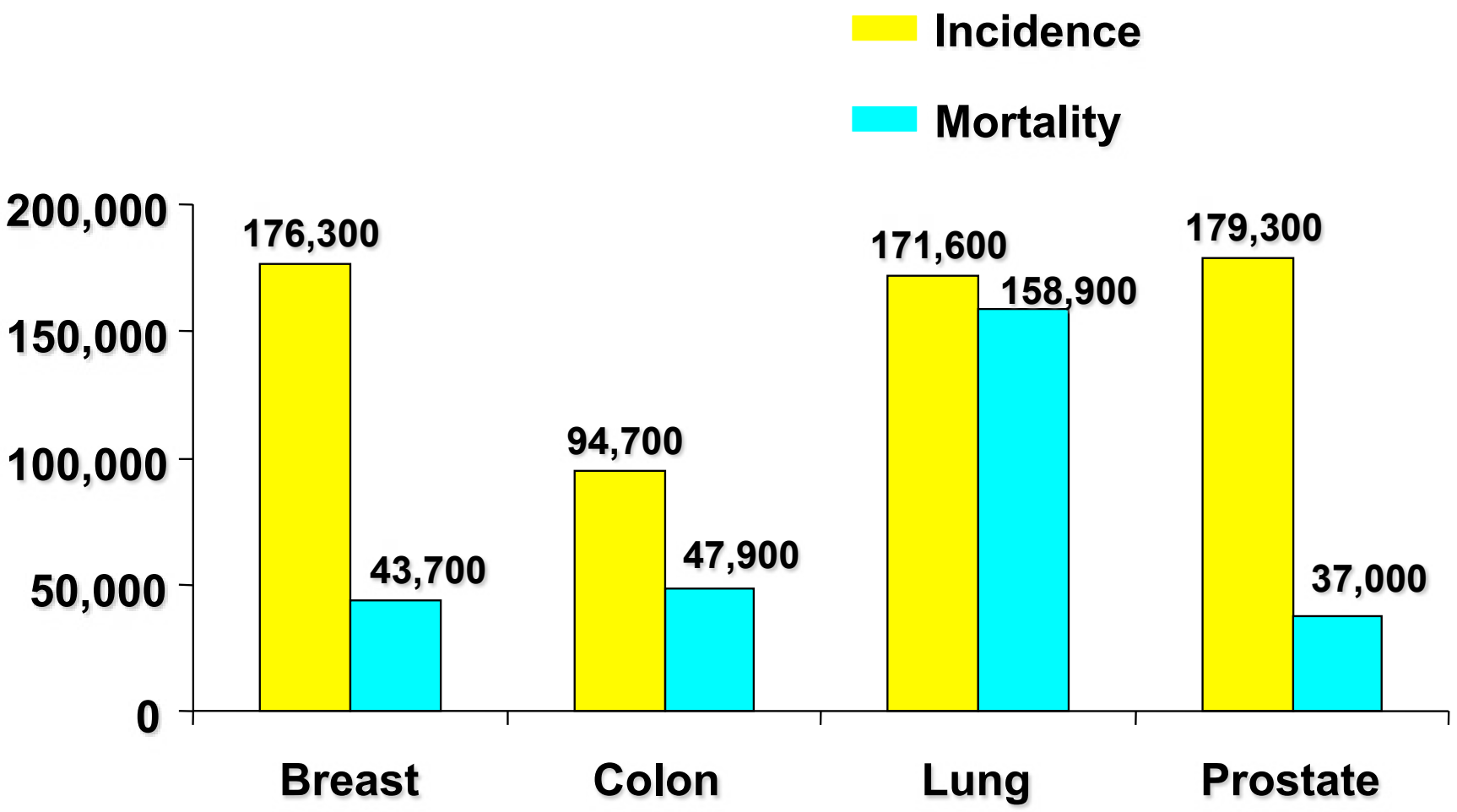
Radiation therapy in non-small cell lung cancer

- Curative intent for early stage medically unresectable lung cancer
  - Cure rates approaching surgery when high doses can be delivered
- Excellent Palliation of bony pain, endobronchial obstruction, bleeding
- Post-operative radiotherapy yields no survival advantage for completely resected lung cancer
  - Eliminates local recurrences, but patients die of metastases
- Symptomatic radiation-pneumonitis in 4-15%

Treatment of lung cancer requires multi-modality cooperation

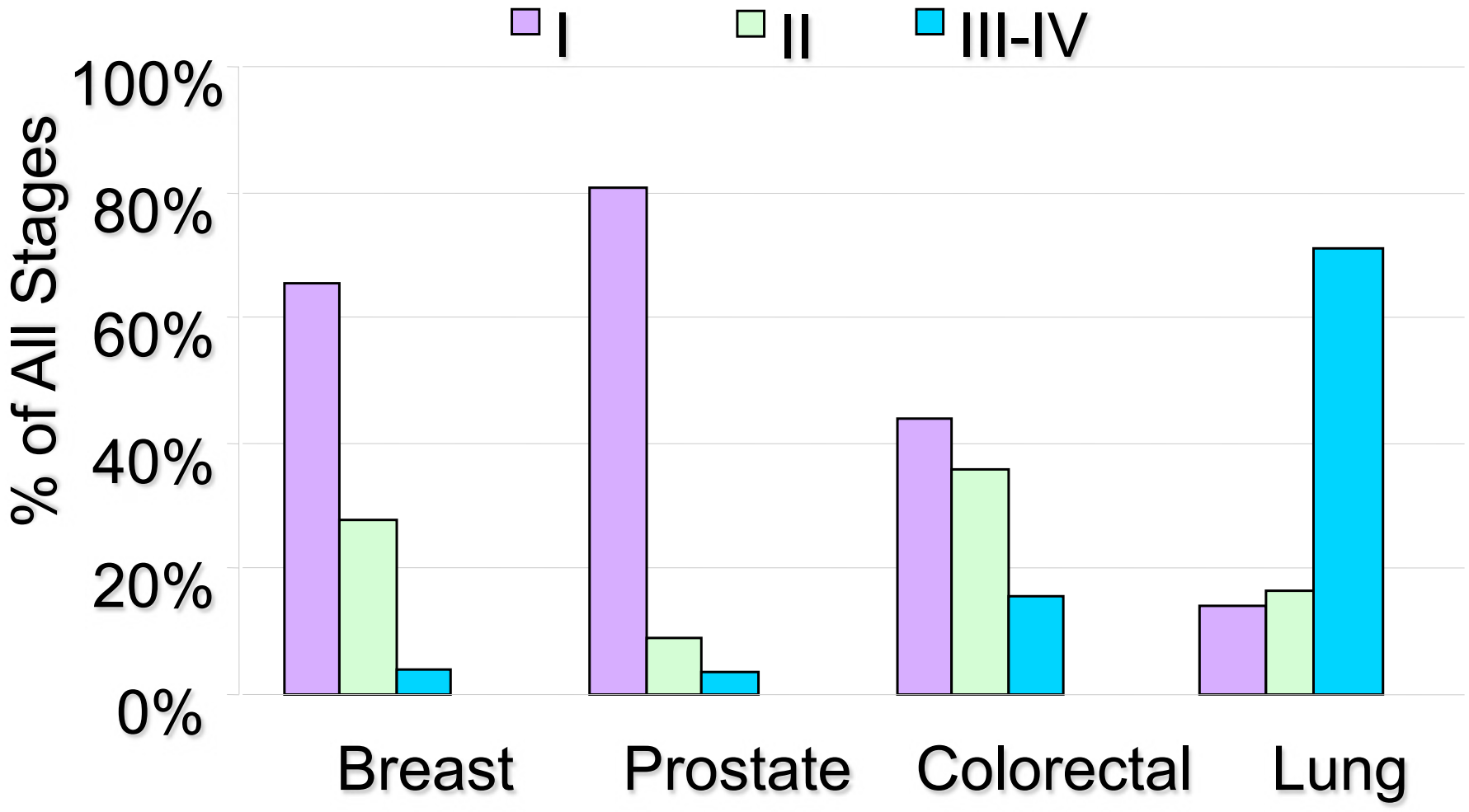
- Primary Provider
- Pulmonologist
- Diagnostic radiologist, Interventional radiologist, Nuclear Medicine
- Pathologist
- Thoracic Surgeon
- Medical and radiation oncologists

Why?



D. Arenberg, American Cancer Society. *Cancer Facts & Figures–1999.*

…why?


I
II
III-IV
100%
80%
60%
40%
20%
0%
% of All Stages
Breast
Prostate
Colorectal
Lung

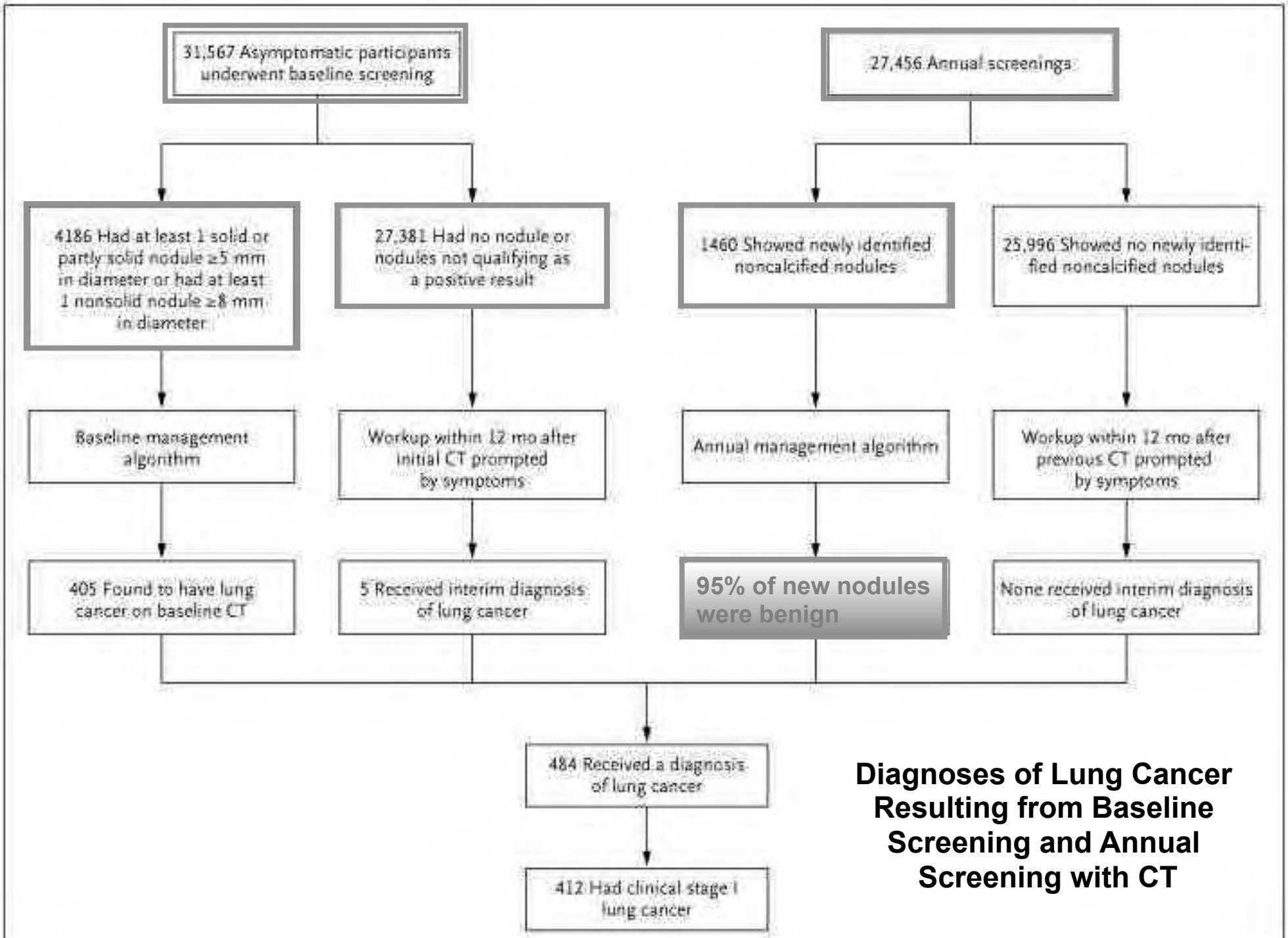
Summary of screening vs "controls"

- Mayo, Johns Hopkins, Memorial Sloan-Kettering, and Czeck Lung projects (Over 35,000 patients)
  - –More cases detected
  - –More early stage disease
  - –Improved survival in the screened group
  - –*No difference* in one's likelihood of dying from lung cancer

ELCAP & Mayo data

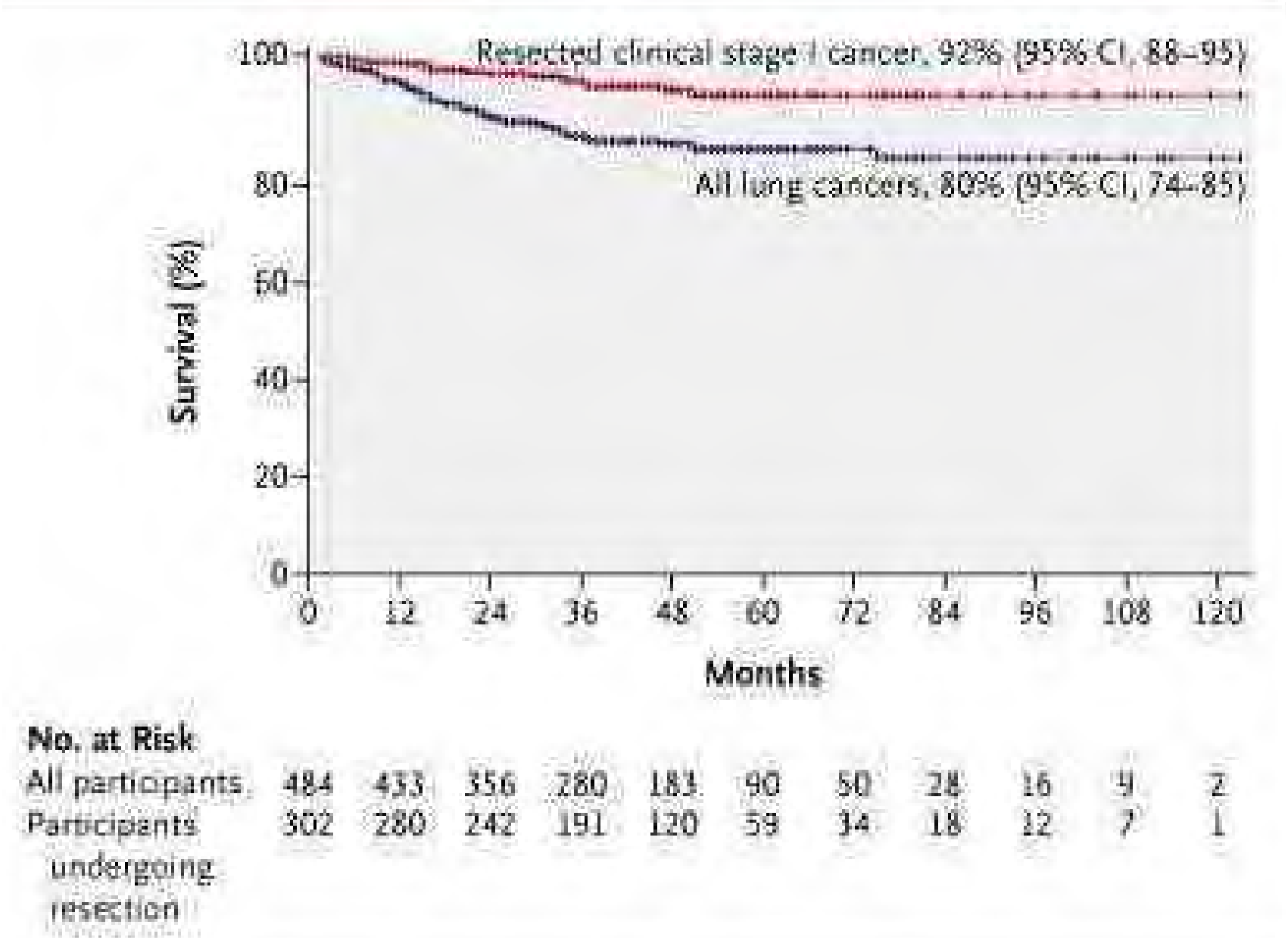
- ELCAP: 1000 smokers over age 60
  - 233 patients had non-calcified nodules by CT
  - 28 cancers, 27 stage I
  - One patient with a benign nodule had surgery
- Mayo: 1520 smokers over 50 (prevalence and two annual follow up scans)
  - 1,049 (69%) patients had >2,000 nodules
  - 40 cancers detected after 3 years (26 prevalence)
  - IA (22), IB (3), IIA (4), IIB (1), IIIA (5), IV (1), and limited small cell (4)
  - 7 patients had benign nodules resected

Source: Swensen. *Radiology* 2003 Henscke. *LANCET* 1999



Diagnoses of Lung Cancer Resulting from Baseline Screening and Annual Screening with CT

 The International Early Lung Cancer Action Program Investigators. N Engl J Med 2006;355:1763-1771



The NEW ENGLAND JOURNAL of MEDICINE

The International Early Lung Cancer Action Program Investigators. N Engl J Med 2006;355:1763-1771

NLST

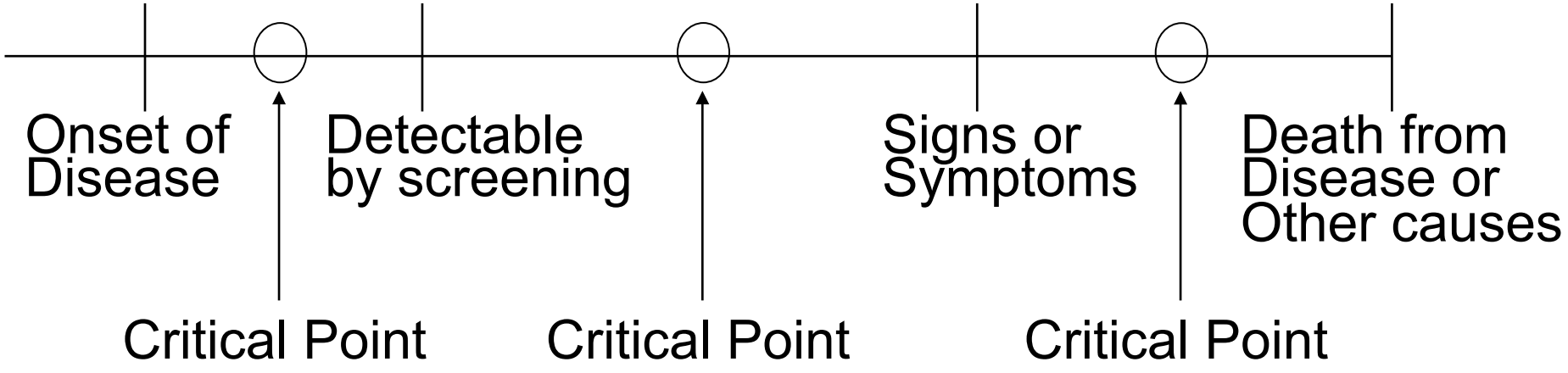
- 50,000 current or former smokers
- 30 study sites
- Closed to enrollment in February 2004
- Slated to collect data for 8 yr
- Powered to detect a 20 percent or greater drop in lung cancer mortality from using spiral CT compared to chest X-ray

“Critical Point”

Screening is ineffective

Screening is effective

Screening is unnecessary



Prevention

- **Education and primary prevention**
  - **avoidance of environmental carcinogens, eg tobacco smoke**
- **Chemoprevention**
  - **retinoids**
  - **EGFR inhibitors**
  - **selenium**
  - **COX-2 inhibitors**
  - **green tea**

Phase III chemoprevention:
trials in progress, July 2003

- Gefitinib vs placebo (SPORE trial)
  - former/current smokers with previous history of smoking-related cancer
  - 6 months of treatment
  - efficacy endpoints: histological response, biomarkers including the Ki-67 labelling index
  - expected accrual: 2 years to recruit 150 patients
- Selenium study E5597
  - patients following surgery for stage I NSCLC
  - 4 years of treatment
  - evaluation of effectiveness of selenium in reducing incidence of new lung tumours, and of toxicity and effects on survival compared with placebo
  - expected accrual: 1960 (980 per arm) participants within 4 years

Lung cancer: Summary

- Deadliest of all common solid tumors
- Screening not yet proven effective
- Treatment
  - Surgery for early stage patients with adequate pulmonary reserve
  - Radiation therapy for medically unresectable, early stage disease
  - *Adjuvant* chemotherapy for stage II or more

Lung cancer: Summary

Treatment

- Concurrent chemoradiation therapy for stage III disease (~15% five year survival)
- Unresectable does not mean incurable
- Stage IV, only chemotherapy, long term cures rare

- Future predictions
  - Enhanced screening based upon better risk prediction
  - Chemoprevention strategies
  - Improved treatment and prevention of tobacco dependence
  - Individualized therapy

Additional Source Information

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Slide 4: Source Undetermined

Slide 5: Source Undetermined

Slide 6: D. Arenberg, American Cancer Society. *Cancer Facts & Figures–1999.*

Slide 7: D. Arenberg

Slide 23:D. Arenberg, Adapted from Lungs Diagram Simple, Patrick J. Lynch, Wikipedia, http://commons.wikimedia.org/wiki/File:Lungs_diagram_simple.svg, CC BY: http://creativecommons.org/licenses/by/2.5/

Slide 34: D. Arenberg

Slide 27: Corey Langer 2000; Breathnach et al 2001; Schiller et al 2002

Slide 29: D. Arenberg, Sandler; ASCO 2005

Slide 33: D. Arenberg, American Cancer Society. *Cancer Facts & Figures–1999.*

Slide 34: D. Arenberg

Slide 36: Swensen. *Radiology* 2003 Henscke. *LANCET* 1999

Slide 37: The International Early Lung Cancer Action Program Investigators. N Engl J Med 2006;355:1763-1771

Slide 38: The International Early Lung Cancer Action Program Investigators. N Engl J Med 2006;355:1763-1771

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