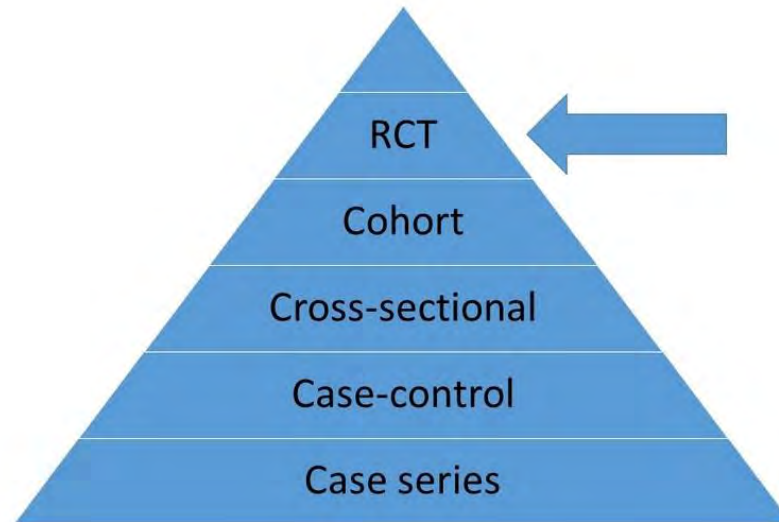


Do RCTs Really Change Practice?

A Cautionary Tale



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K. Craig Kent Chair in Strategic Leadership
Professor of Surgery and Medicine**

University of Wisconsin School of Medicine and Public Health



Financial Disclosures

- **Consultant: PulmonX (DSMB Convert Trial)**
- **SAB: Pleural Dynamics (Device start-up)**
- **Director: American Board of Thoracic Surgery**
- **Director: American Lung Association UMW**

What is needed for an RCT?

- A new treatment, procedure or device
- Disagreement in the medical community regarding effectiveness aka

‘Equipoise’

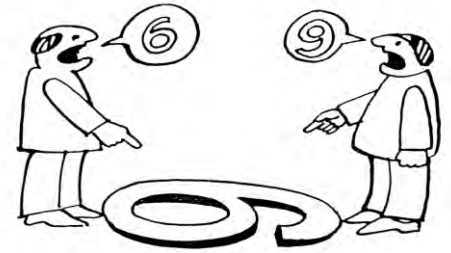
**What is Equipoise
and
Who Has It?**



EQUIPOISE

ALPHA[®] PHARMACEUTICALS NDC 6327-9810 Injection
EQUIPOISE
300 mg/mL
Net contents: 3000mg Boldenone Undecylate, 1.8g Benzyl Alcohol, USP, Other contents: Benzyl Benzoate, USP 1.8g, Alcohol, USP 0.2mL; in sterile Grape seed oil, USP
Intramuscular use only
Injection Solution • 10 mL Multiple Dose Vial

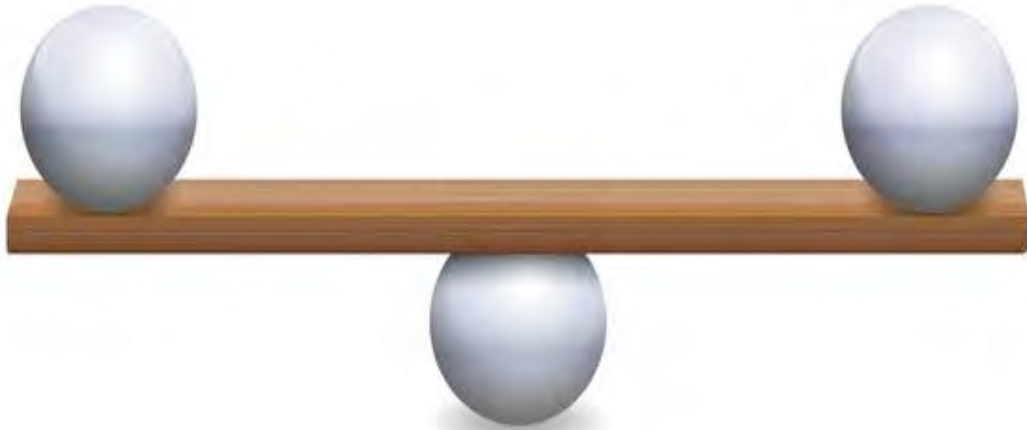
Ethics of an RCT?



Benjamin Freedman, 'Equipoise and the Ethics of Clinical Research' *NEJM*, 1987

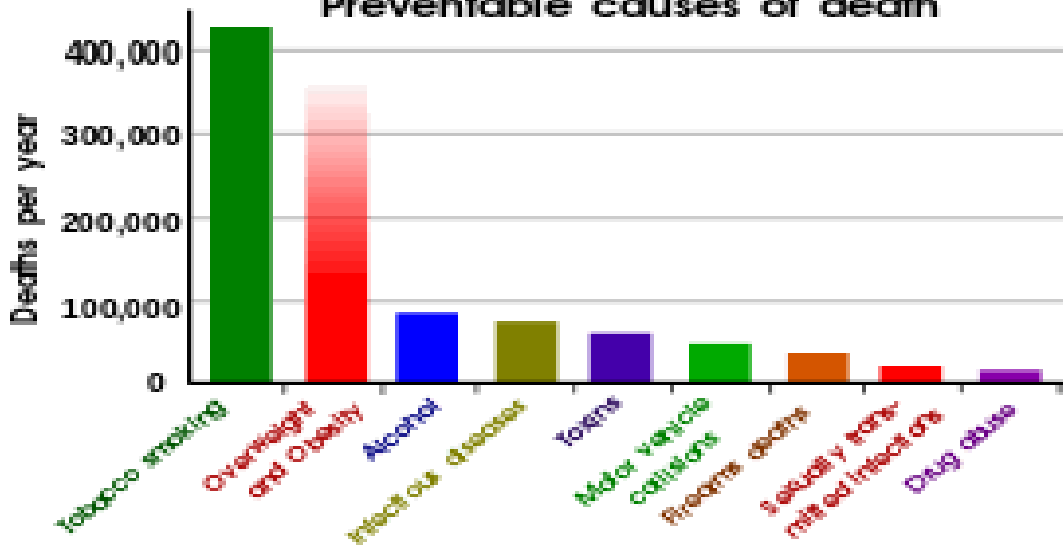
- **Honest professional disagreement among expert clinicians regarding the preferred (new) treatment, procedure or device.**
- **Equipoise exists within the expert medical community and not in the individual researcher.**
- **A randomized trial is instituted with the aim to resolve the dispute.**

Equipoise

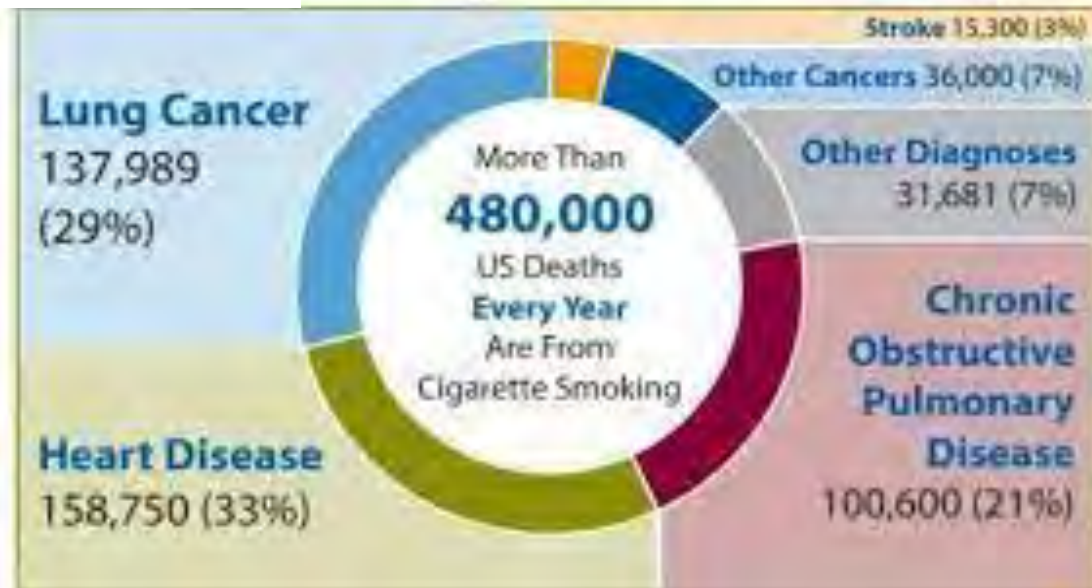


Pick Big Problems

Preventable causes of death



Deaths from Smoking, United States







AA 251 April 10, 2001

411 passengers and crew

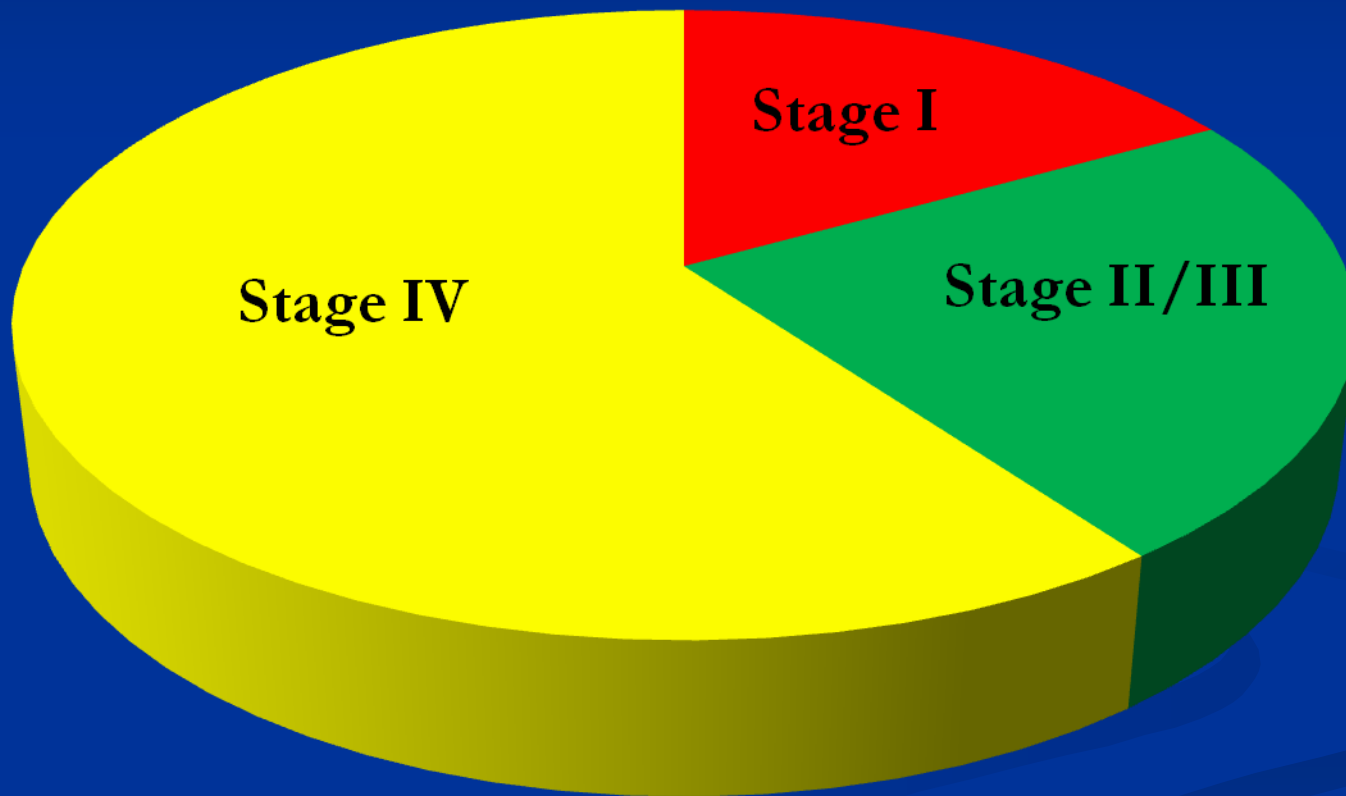
Lung Cancer Facts

400 Americans die ***DAILY***

Annual Deaths ~

Breast + Colon + Prostate + Pancreas

Stage Distribution-SEER 17



National Lung Screening Trial

- 50,000 high-risk present and former smokers randomized to CXR or CT
- Large sample size necessary to detect 20% reduction in lung cancer specific mortality in 5 years

Enrollment 2002 -2004

Screening 2002 -2007

Follow-up Complete 2009

Cost = \$200M

90% Patient Adherence*

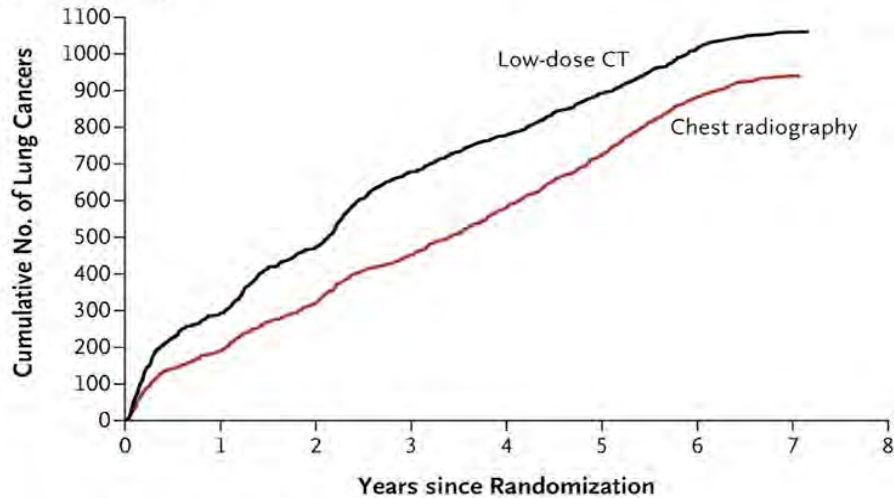


NLST & NELSON

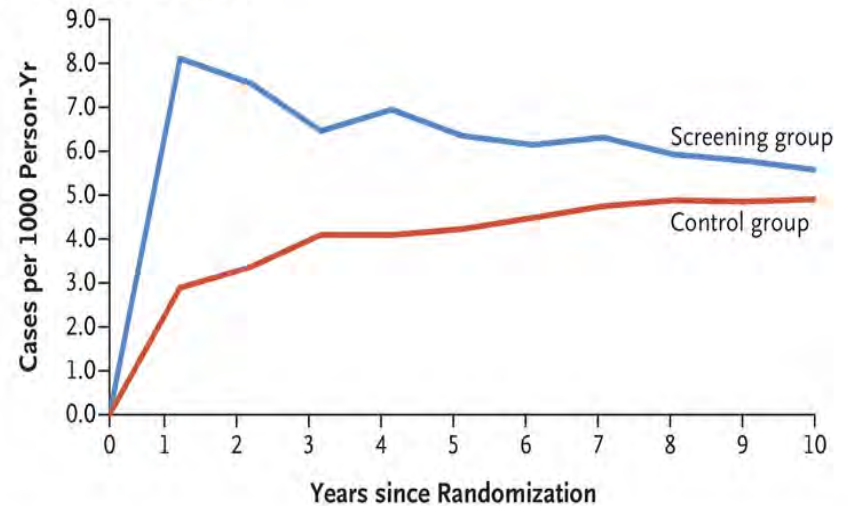
2011

2020

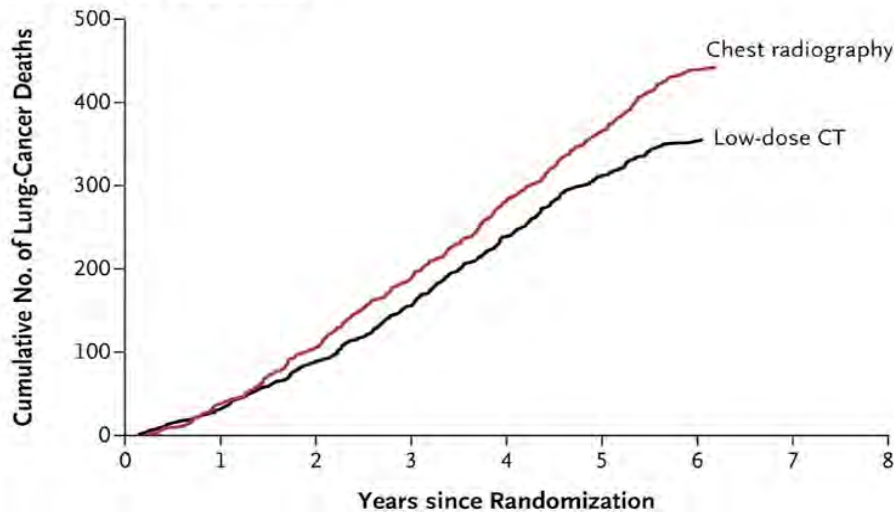
A Lung Cancer



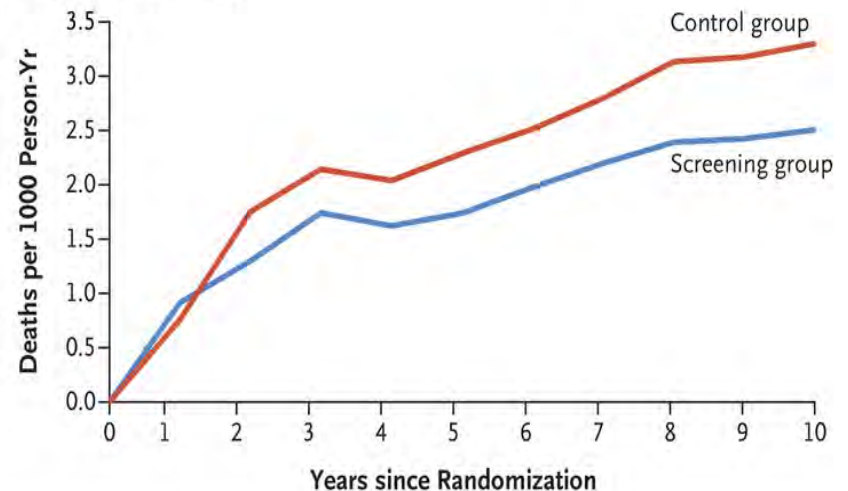
A Lung-Cancer Incidence



B Death from Lung Cancer

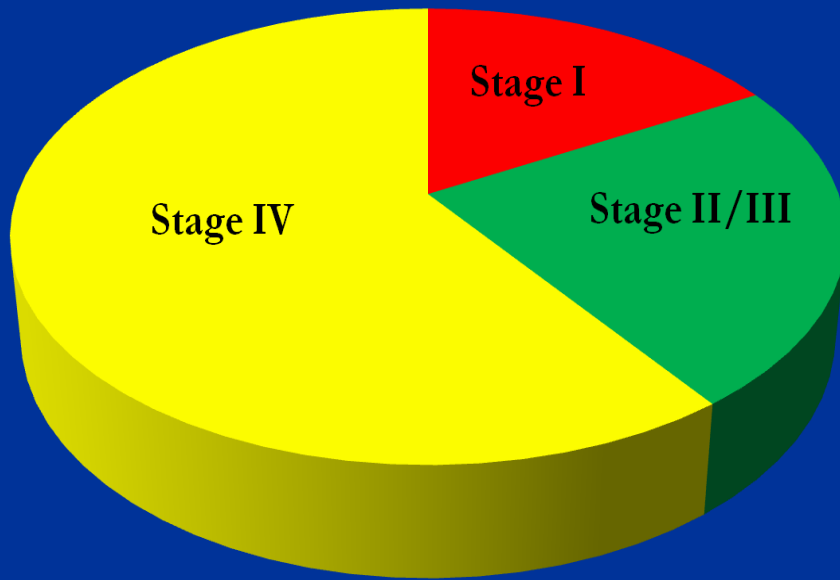


B Lung-Cancer Mortality

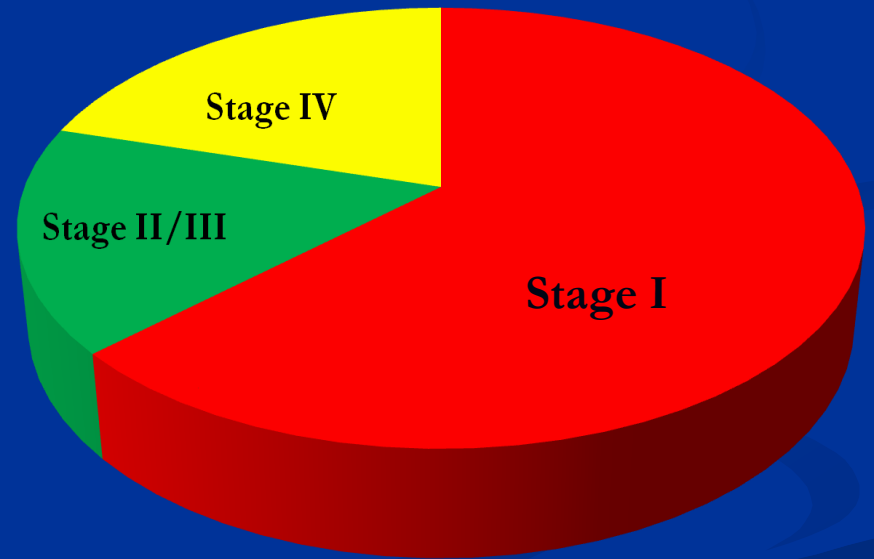


Stage Distribution

Historical



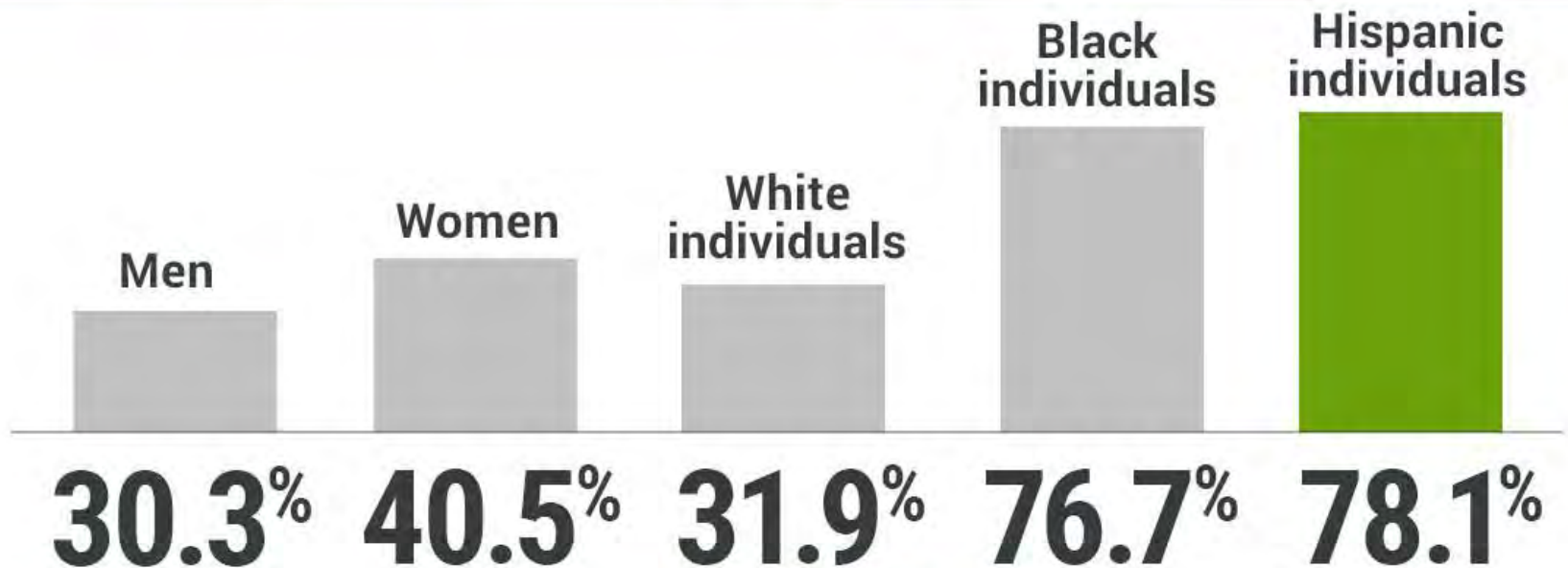
NLST



USPSTF 2020

Expanded Indications

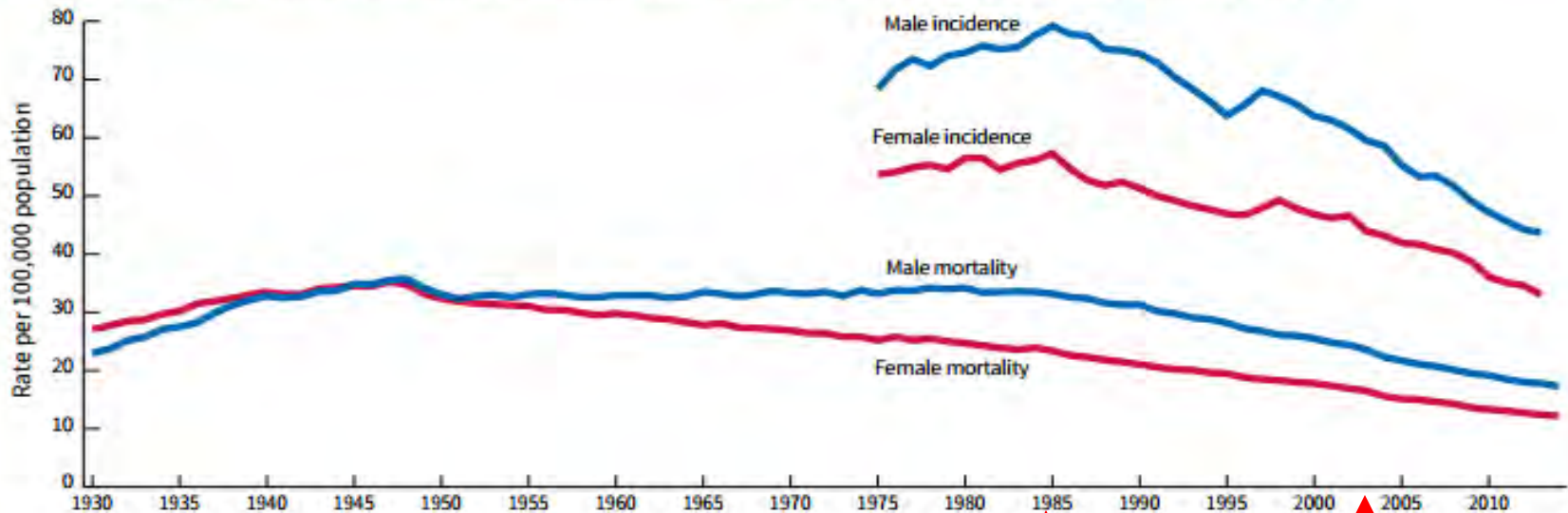
Relative increases in the proportion of individuals eligible for lung cancer screening based on revised USPSTF criteria



Does Cancer Screening Work?

Screening colonoscopy

Figure 4. Trends in Colorectal Cancer Incidence (1975-2013) and Mortality (1930-2014) Rates by Sex, US



Rates are age adjusted to the 2000 US standard population. Incidence rates are adjusted for delays in reporting due to improvements in International Classification of Diseases (ICD) coding over time, numerator data for mortality differ slightly from those presented elsewhere.

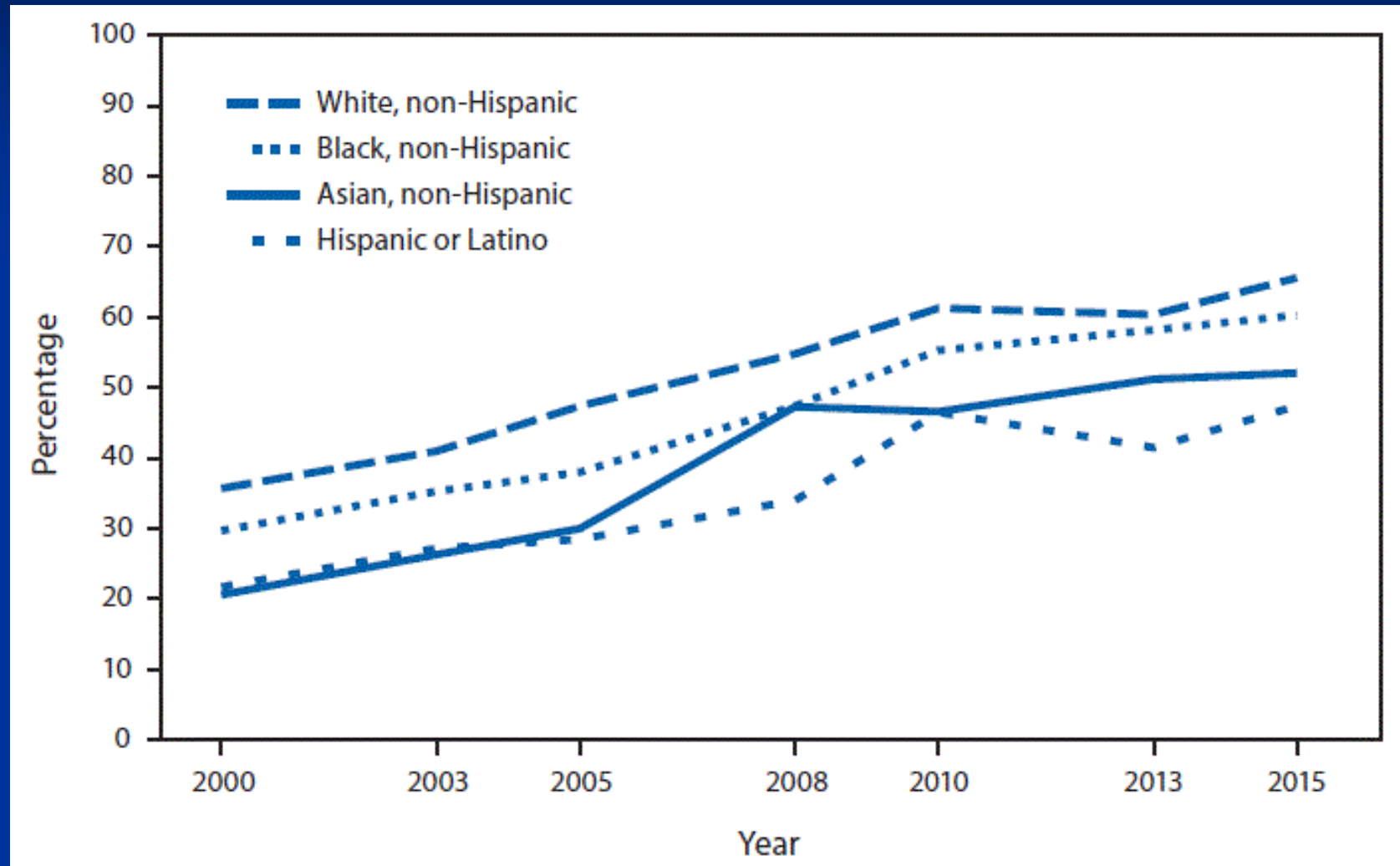
Source: Incidence - SEER Program, National Cancer Institute, 2016. Mortality - US Mortality Volumes 1930 to 1969, US Mortality Data 1960-2014, National Center for Health Statistics, Centers for Disease Control and Prevention, 2016.

© 2017 American Cancer Society, Inc., Surveillance Research

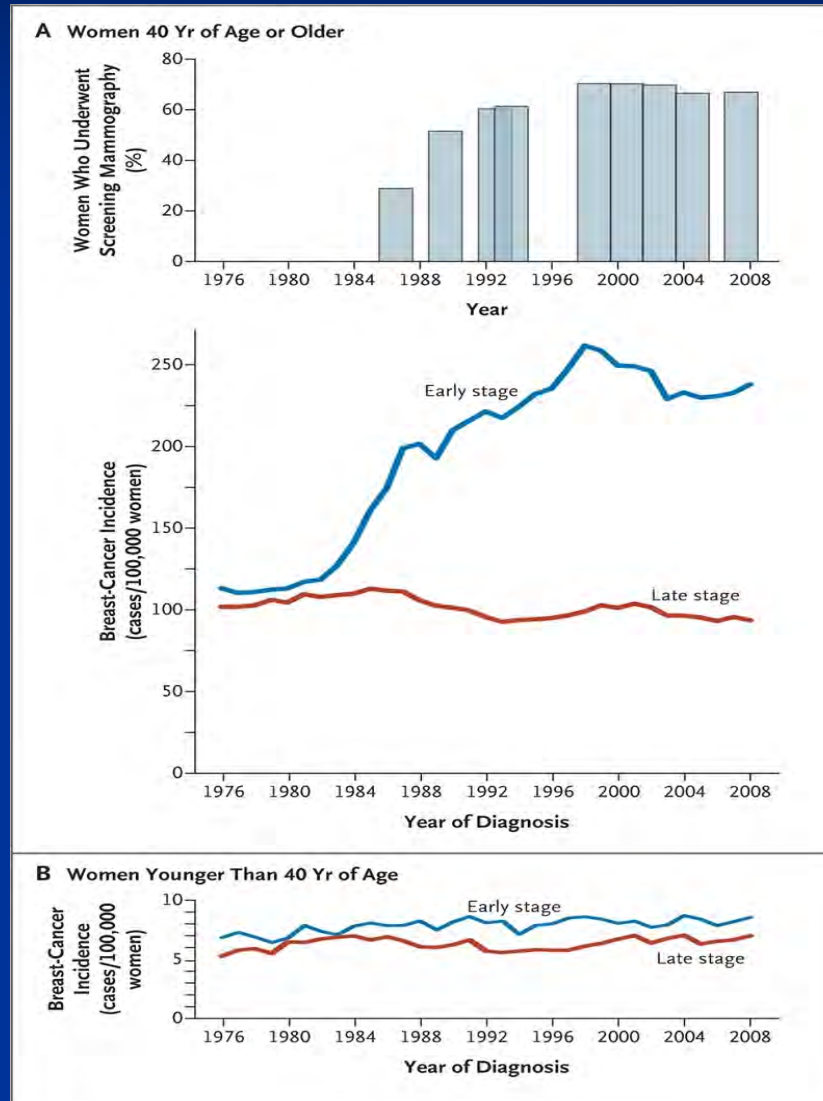
USPSTF Created

1 in 3
screened

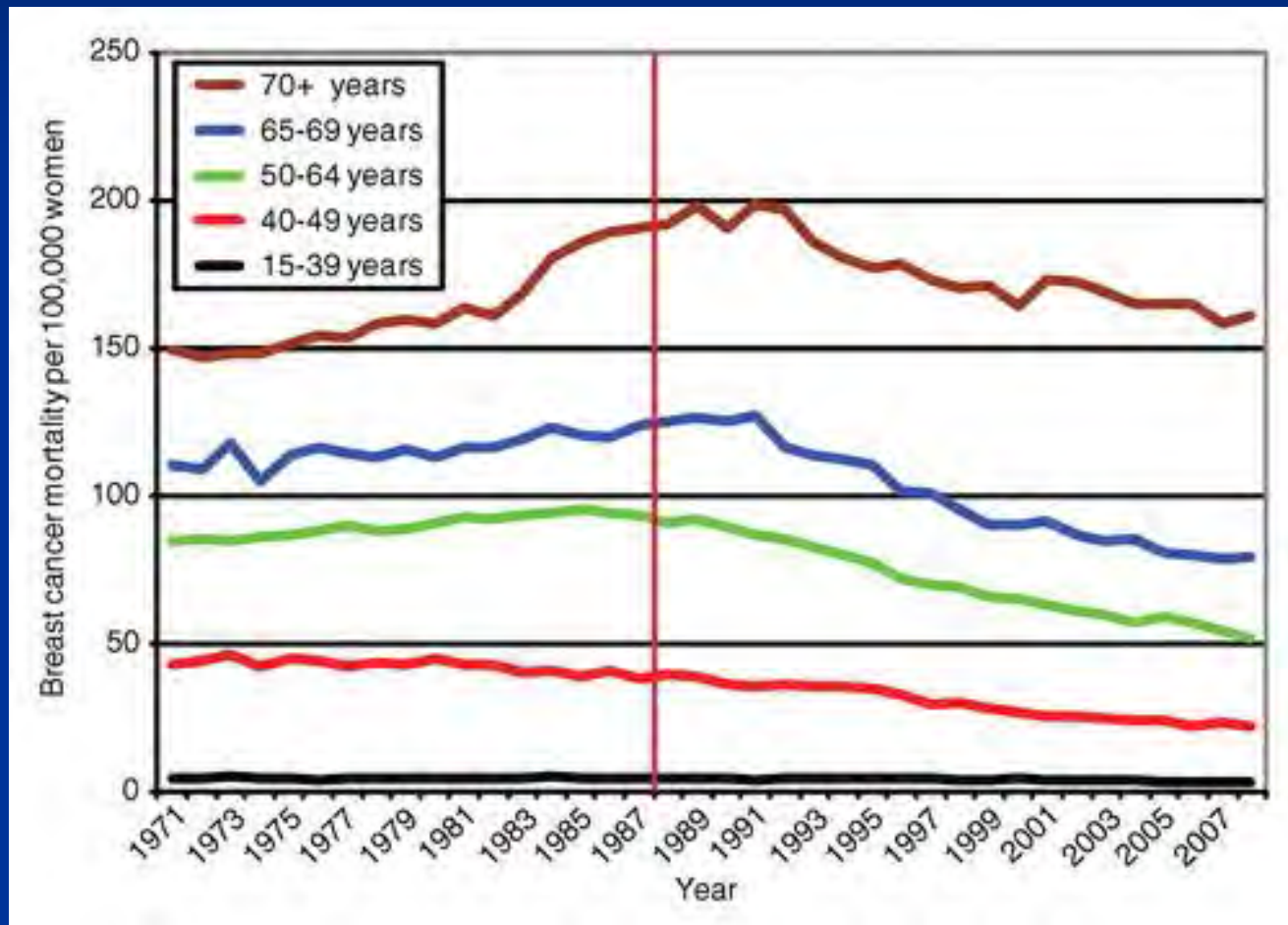
CRC Screening Prevalance



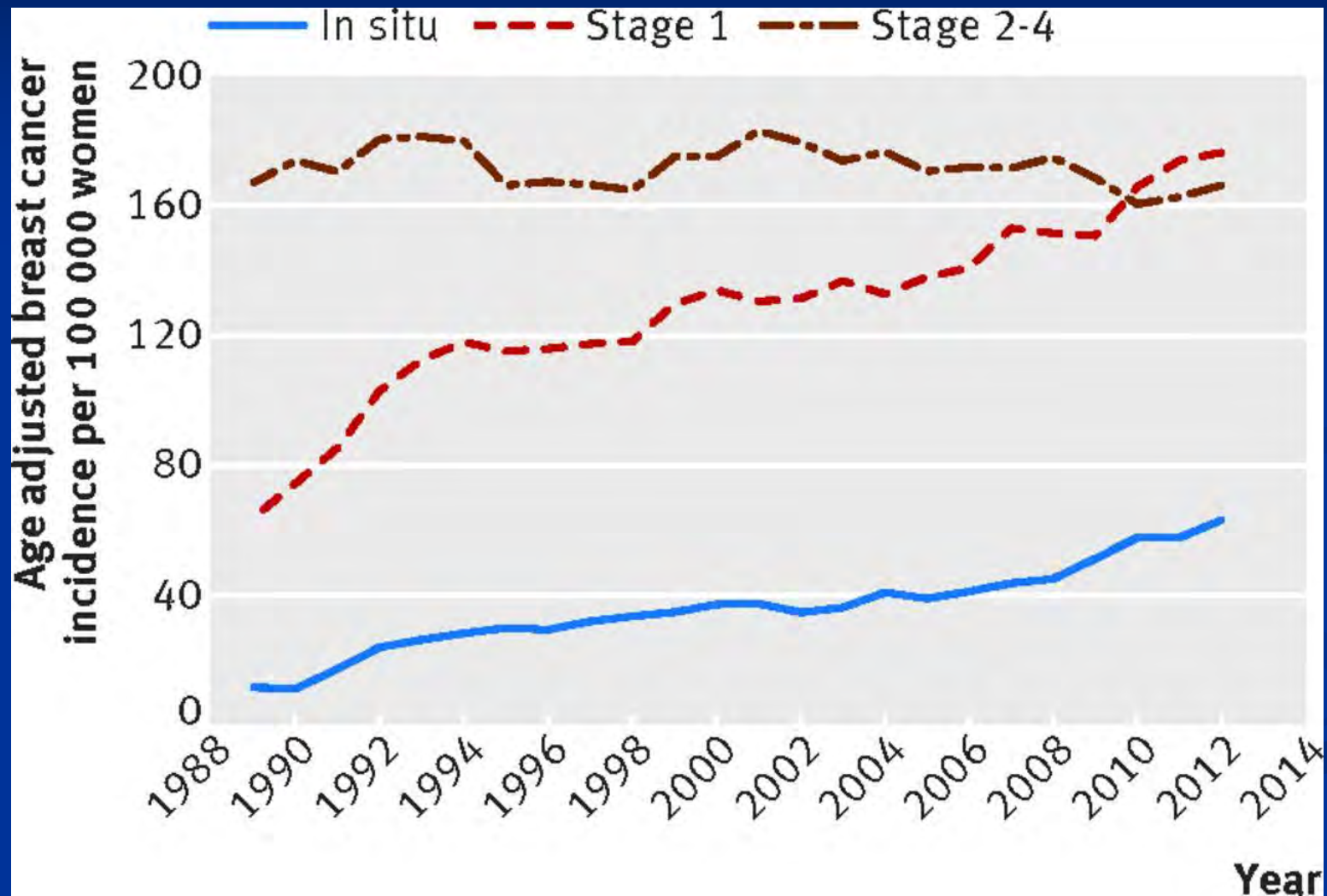
3 Decades of Mammography



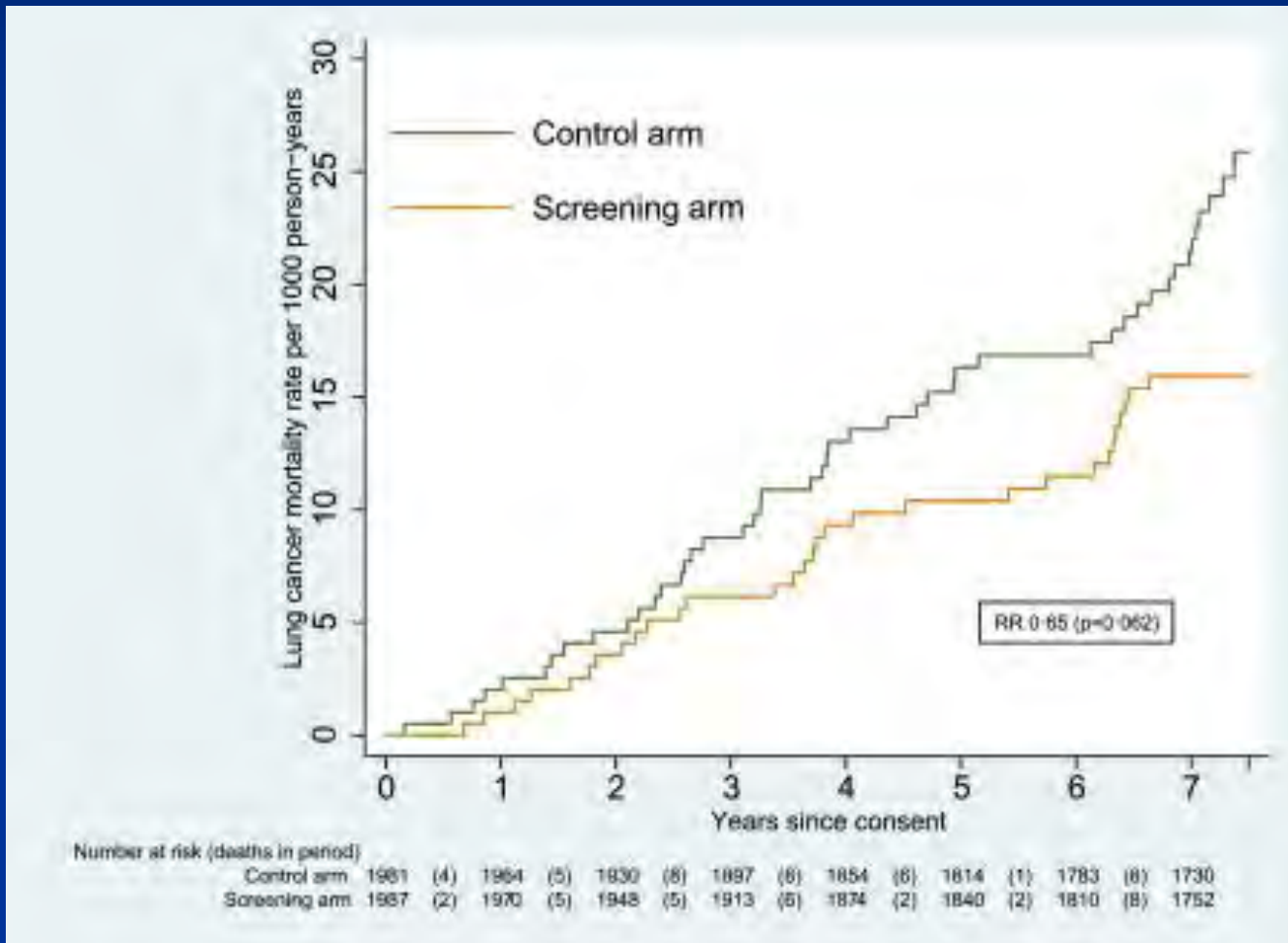
Breast Cancer Mortality



Screening Mammography Stage Distribution



LDCT Screening in Europe



LDCT Screening for Lung CA 10 years after NLST

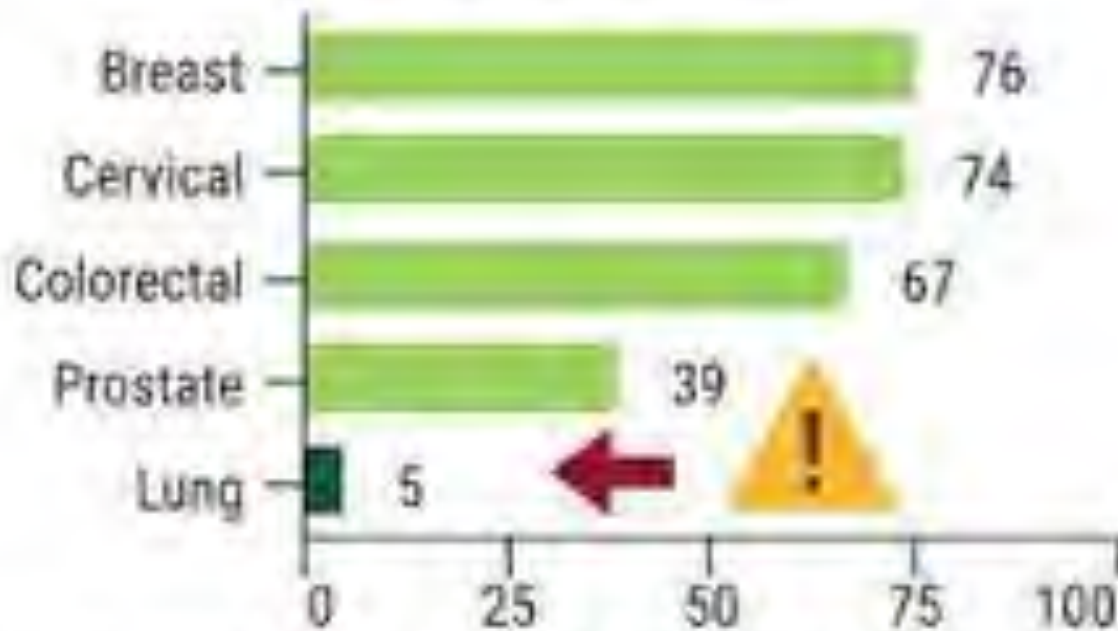
Pooled lung cancer screening adherence rate:



Among 16,863
high-risk adults
in 15 studies

Common Cancer Screening Penetrance

Patients screened who qualify for testing (by cancer type)



Source: NIH Cancer Trends Progress Report

2019

Has NLST Changed Practice?

YES.....but not much

We have a long way to go!

Does Cancer Screening Work?

YES but it takes DECADES

Barriers

- Fear of Over-diagnosis
- Specialty Care vs Primary Care
- Funding

Embedding Lung Cancer Screening into Primary Care: *Food for Thought*

- **Beta blockers after MI improve survival**
 - AHA/ACC Guidelines 1999
 - 50% adherence in 2014
- **Migraine headache prevention Rx**
 - AHS/AAN Guidelines 2000
 - 33% adherence to recommendation in 2012

Cancer and Research

2017

Federal Research Dollars/Death

Breast \$ 16,000

Prostate \$ 12,000

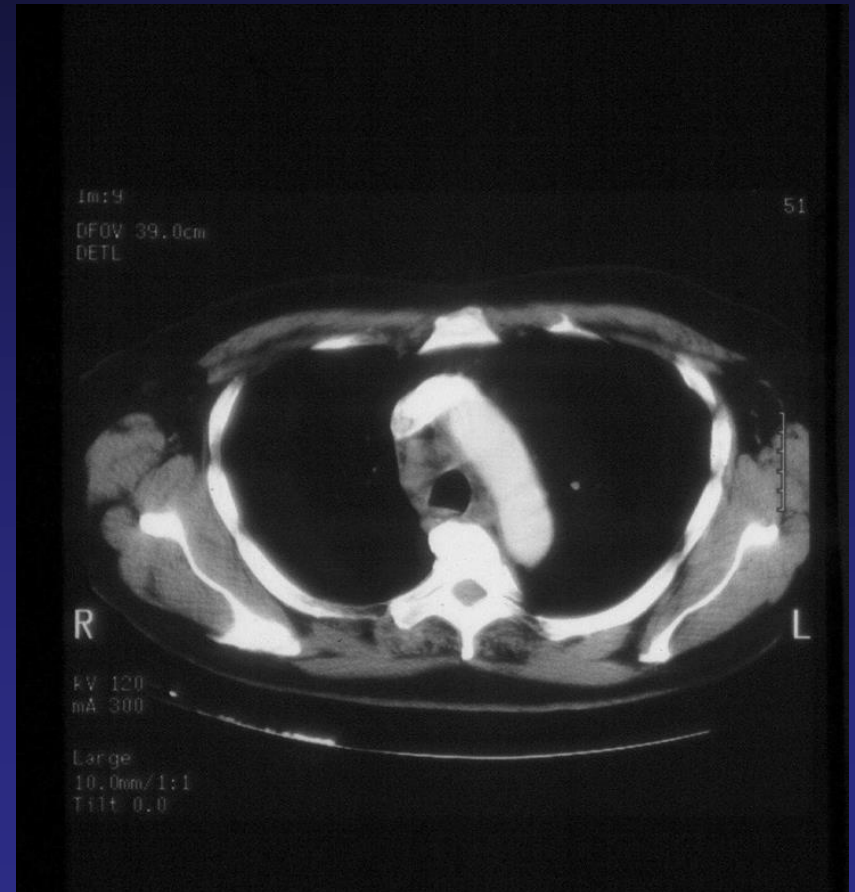
Colon \$ 4,300

Lung \$ 2,100

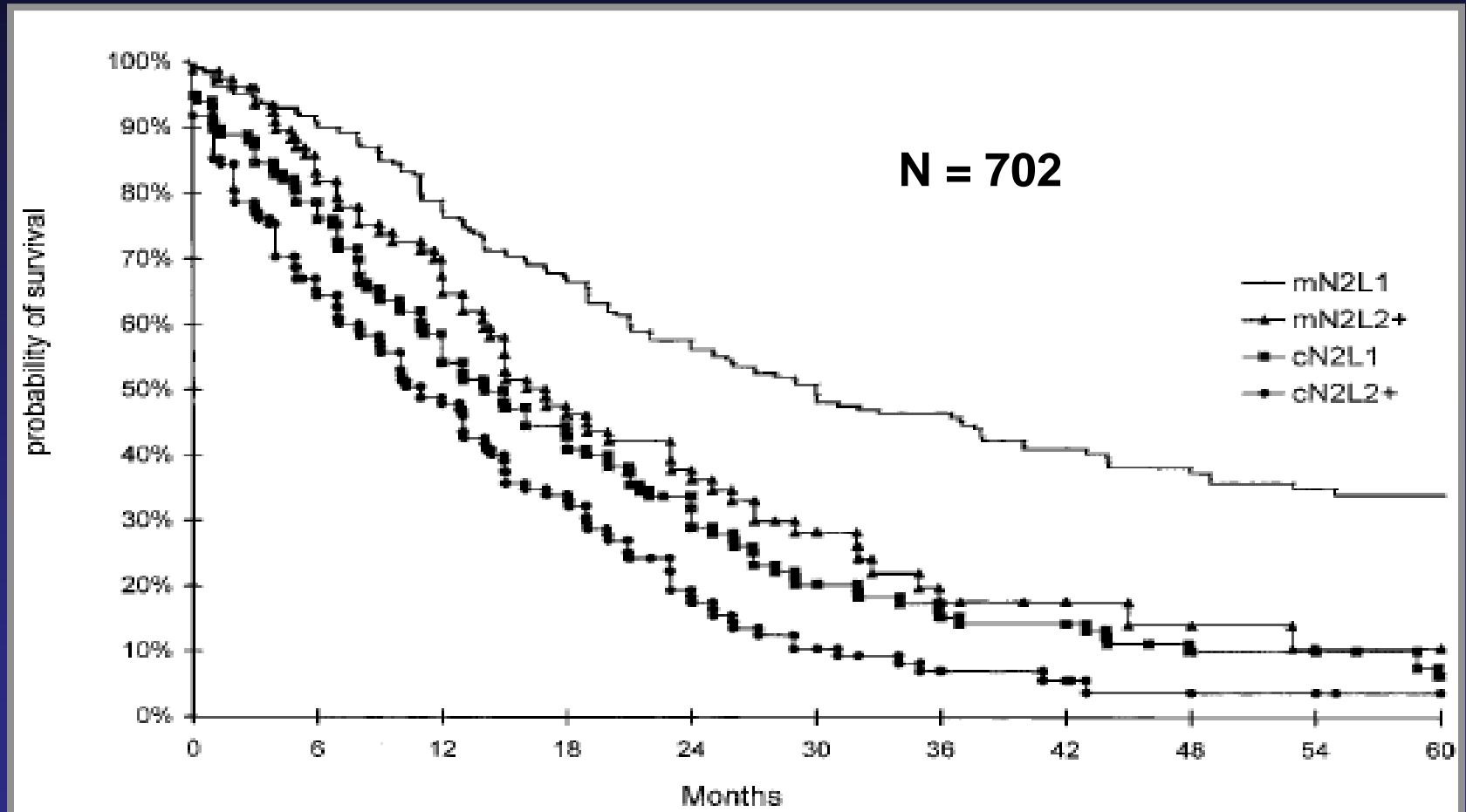
Stage IIIA NSCLC

Heterogeneity of N2 disease

Both cIIIA



Heterogeneity within the Stage IIIA N2 LN-Positive Population



André et al: J Clin Oncol 18: 2981-89, 2000

Surgery for N2 disease

Heterogeneity of population



Imaged N2 \neq EBUS N2 \neq med. N2 \neq thoracotomy N2

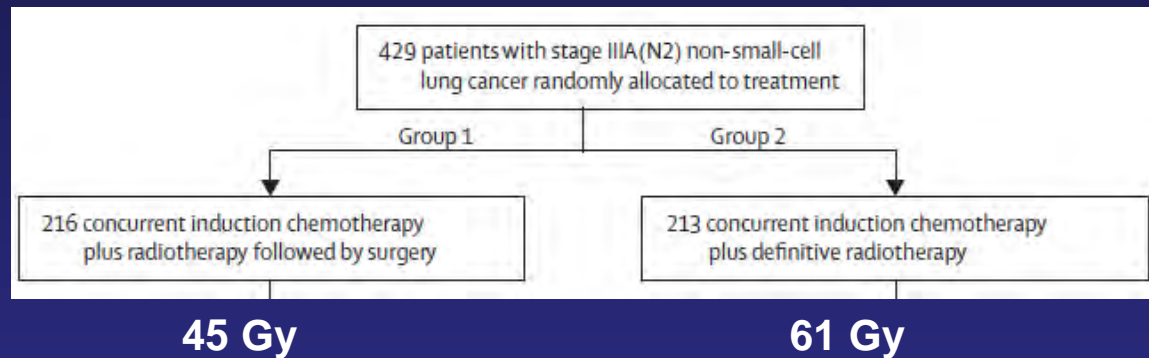


Difficult and dangerous to compare
reported series and trial results

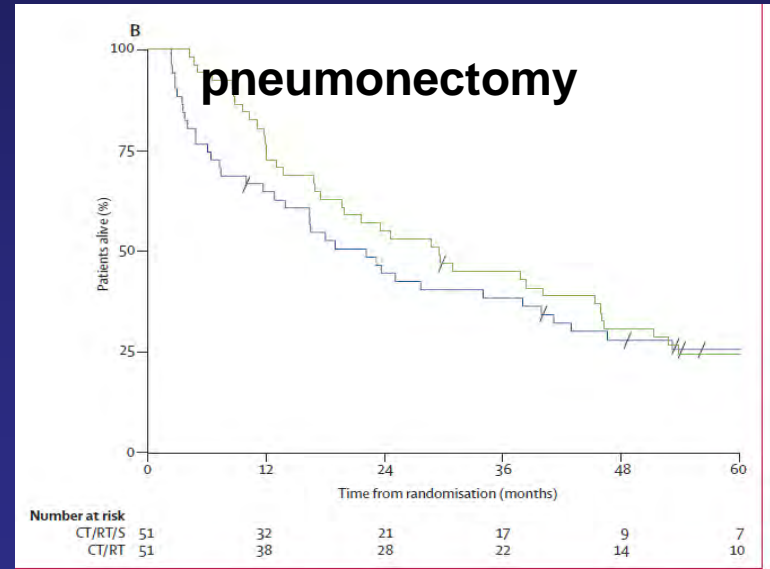
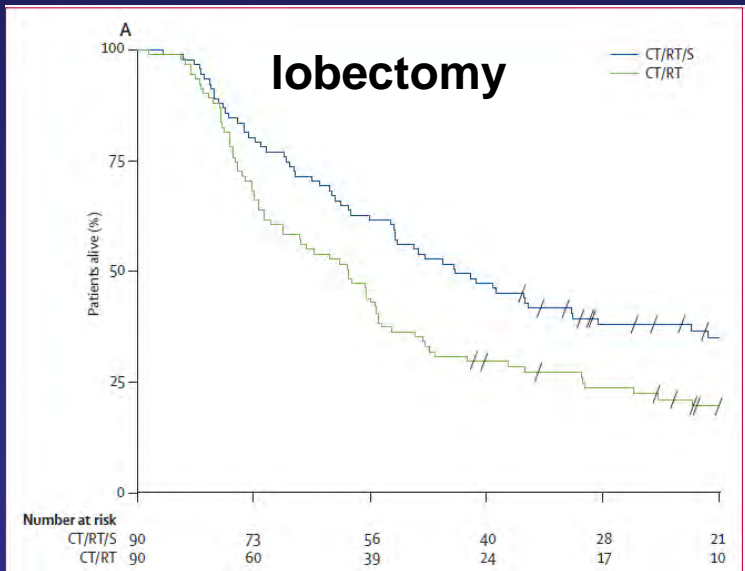
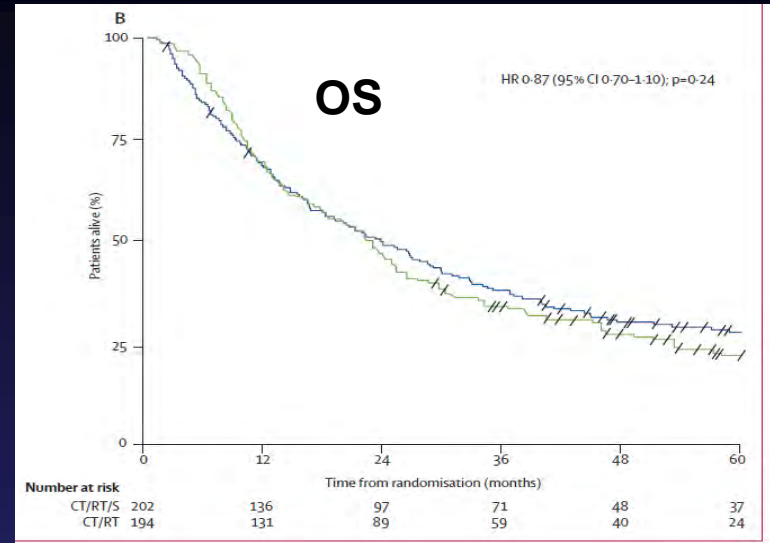
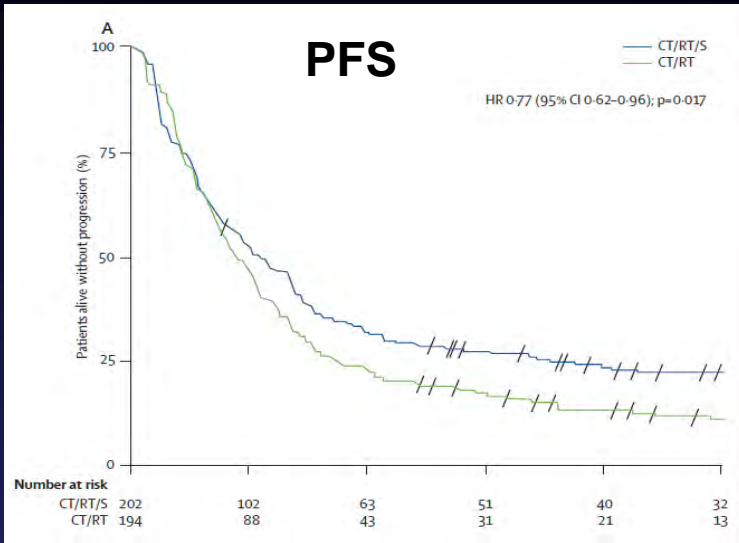
Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial



Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyan Chen, Robert B Livingston, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, William T Sause, James D Cox



Albain KS, Lancet Oncol 2009; 374: 379-86



INT 0139

- **Relapse at T site 3% vs 19%**
 - **(6.3 X) in favor of surgery arm**
- **35% pneumonectomies**
- **OS median survival: 23.6 (S) vs. 22.2 months**

Interpretation Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with stage IIIA(N2) non-small-cell lung cancer.

Albain KS, Lancet Oncol 2009; 374: 379-86

Induction Chemoradiation Is Not Superior to Induction Chemotherapy Alone in Stage IIIA Lung Cancer

Asad A. Shah, MD, Mark F. Berry, MD, Ching Tzao, MD, PhD, Mihir Gandhi, MS, Mathias Worni, MD, Ricardo Pietrobon, MD, MPH, and Thomas A. D'Amico, MD



Fig 2. Forest plot of overall survival of patients in randomized studies receiving induction chemotherapy versus induction chemoradiotherapy followed by resection. (CI = confidence interval; SE = standard error.)



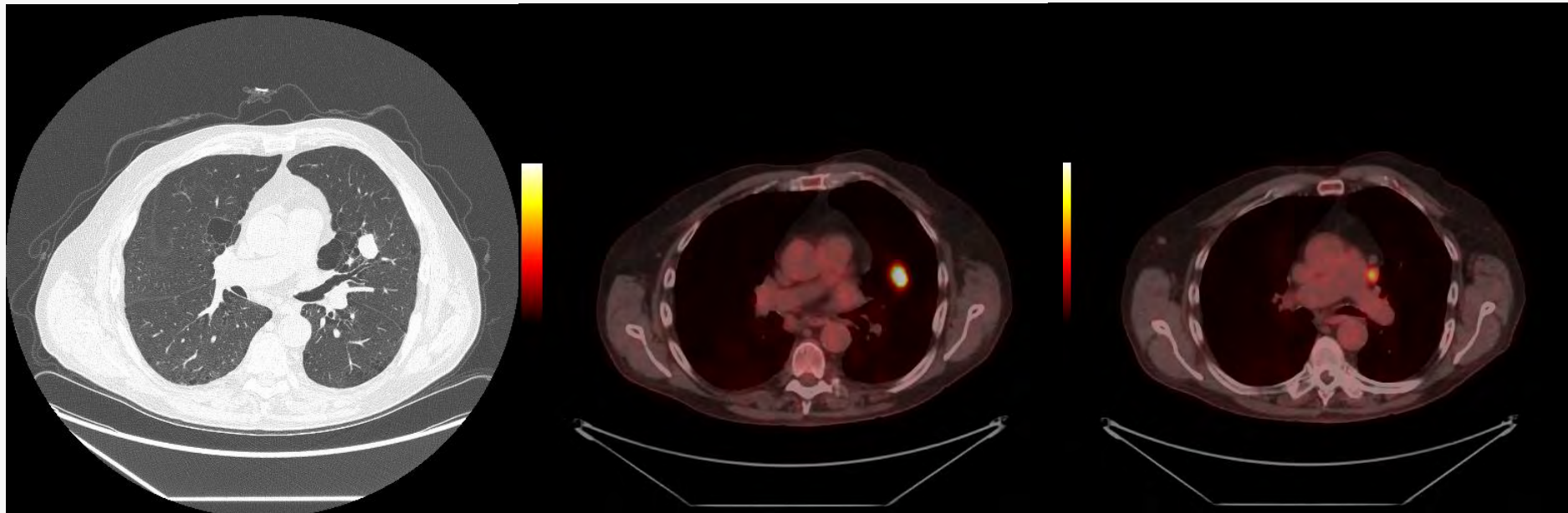
Fig 3. Forest plot of overall survival of patients in retrospective studies receiving induction chemotherapy versus induction chemoradiotherapy followed by resection. (CI = confidence interval; SE = standard error.)

New Kid on the Block

Immunotherapy



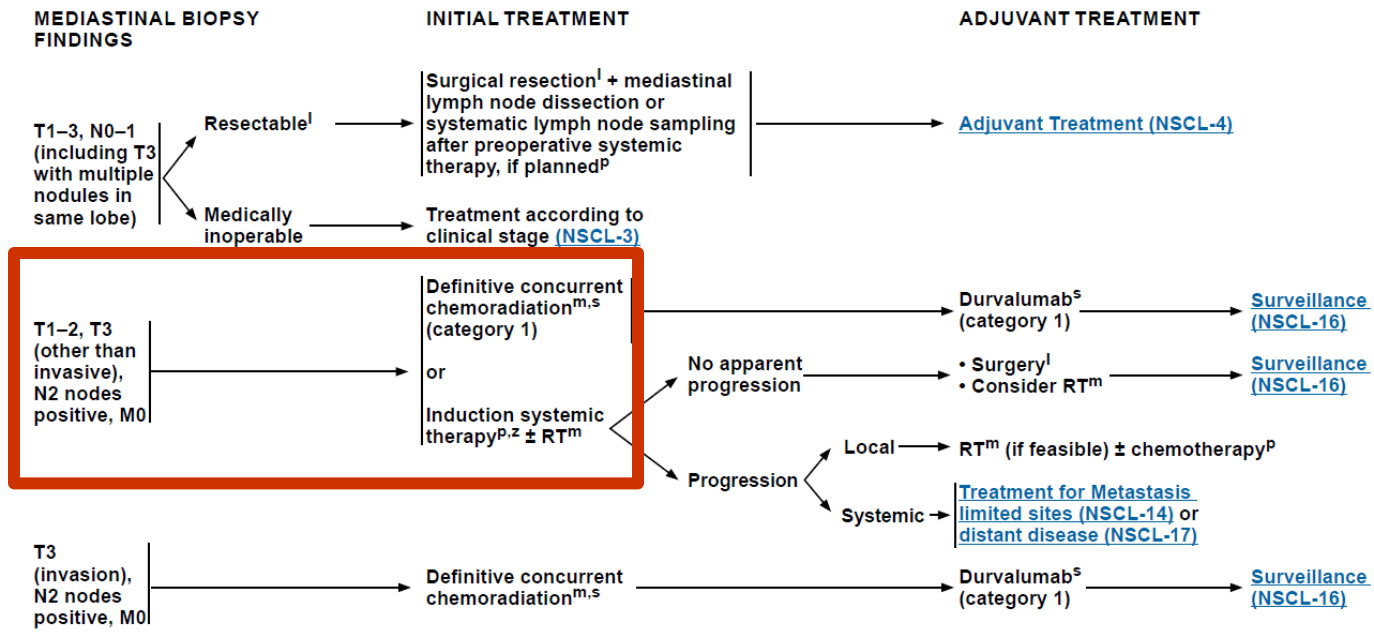
Case 3: Single station N2





Audience Polling How would you manage?

- A. Concurrent chemotherapy and radiation followed by adjuvant immunotherapy
- B. Neoadjuvant chemo-immunotherapy followed by surgery
- C. Neoadjuvant chemotherapy followed by surgery
- D. Surgery followed by adjuvant systemic therapy and then immunotherapy
- E. Surgery followed by adjuvant systemic therapy and radiation therapy



^l Principles of Surgical Therapy (NSCL-B).
^m Principles of Radiation Therapy (NSCL-C).
^p Perioperative Systemic Therapy (NSCL-E).
^s Concurrent Chemoradiation Regimens (NSCL-F).
^z Chest CT with contrast and/or PET/CT to evaluate progression.

Note: All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



Case 3: Single station N2, Co-morbidities

- 63-year-old man, 60 pack/year smoker, quit 2009, followed for multiple lung nodules
- Early 2023 LUL solid nodule increased from 8mm in Dec 21 to 18mm Jan 23 (13 months)
- FDG-PET LUL nodule SUV 15.2, Level 5 node SUV 6.7
- Robotic bronchoscopy Poorly differentiated adenocarcinoma, EBUS 4L, 4R, 7 all (-)
- cT1cN2 (single station)
- COPD FEV1 56% and DLCO 45%, predicted ppo FEV1 42%, ppo DLCO 34%
- CKD 3 (e-GFR 54)
- PDL1 50%, EGFR and ALK negative



Audience Polling How would you manage?

- A. Concurrent chemotherapy and radiation followed by adjuvant immunotherapy
- B. Neoadjuvant chemo-immunotherapy followed by surgery
- C. Neoadjuvant chemotherapy followed by surgery
- D. Surgery followed by adjuvant systemic therapy and then immunotherapy
- E. Surgery followed by adjuvant systemic therapy and radiation therapy



Resectability versus Operability

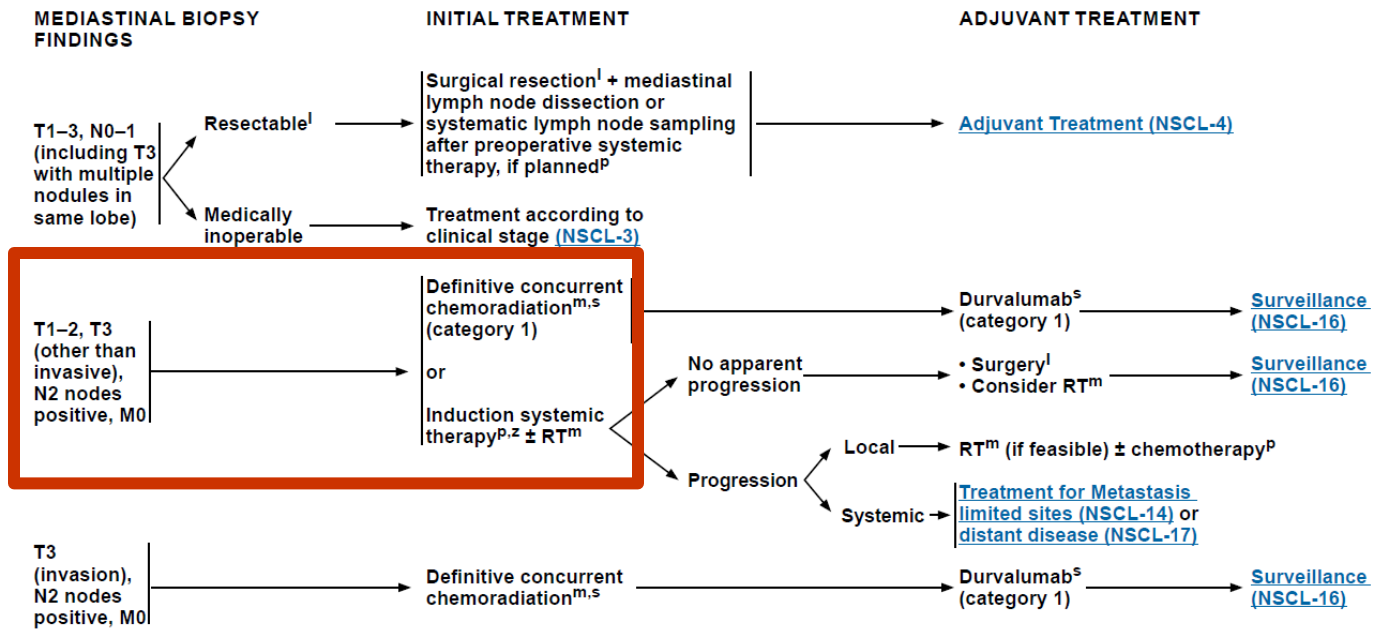
Resectability depends on:

- Anatomy
- Contiguous vital structures
- Surgical experience

Operability depends on:

- Co-morbidities
- Frailty
- Predicted postop physiology

Determination of resectability, surgical staging, and pulmonary resection should be performed by thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.



^l Principles of Surgical Therapy (NSCL-B).
^m Principles of Radiation Therapy (NSCL-C).
^p Perioperative Systemic Therapy (NSCL-E).
^s Concurrent Chemoradiation Regimens (NSCL-F).
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Journal of Clinical Oncology[®]

An American Society of Clinical Oncology Journal

original reports

Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

David R. Spigel, MD¹; Corinne Faivre-Finn, MD, PhD²; Jhanelle E. Gray, MD³; David Vicente, MD⁴; David Planchard, MD, PhD⁵; Luis Paz-Ares, MD, PhD⁶; Johan F. Vansteenkiste, MD, PhD⁷; Marina C. Garassino, MD^{8,9}; Rina Hui, PhD¹⁰; Xavier Quantin, MD, PhD¹¹; Andreas Rimner, MD¹²; Yi-Long Wu, MD¹³; Mustafa Özgüroğlu, MD¹⁴; Ki H. Lee, MD¹⁵; Terufumi Kato, MD¹⁶; Maïke de Wit, MD, PhD¹⁷; Takayasu Kurata, MD¹⁸; Martin Reck, MD, PhD¹⁹; Byoung C. Cho, MD, PhD²⁰; Suresh Senan, PhD²¹; Jarushka Naidoo, MBBCH, MHS²²; Helen Mann, MSc²³; Michael Newton, PharmD²⁴; Piruntha Thiyagarajah, MD²³; and Scott J. Antonia, MD, PhD³; on behalf of the PACIFIC Investigators



CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[€]

Preferred (nonsquamous)

- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT^{1,*,†,‡}
- Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT^{2,3,*,†,‡}
± additional 4 cycles of pemetrexed 500 mg/m²^{†,§}
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT^{4,*,†,‡} ± additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6^{†,§}

60 Gy in 2 Gy fractions concurrent with Carboplatin and Paclitaxel weekly followed by Durvalumab every 4 weeks for up to 1 year

[€] For patients with superior sulcus tumors, the recommendation is for 2 cycles concurrent with radiation therapy and 2 more cycles after surgery. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-318.

* Regimens can be used as preoperative/adjuvant chemotherapy/RT.

† Regimens can be used as definitive concurrent chemotherapy/RT.

‡ For eligible patients, durvalumab may be used after noted concurrent chemotherapy/RT regimens.

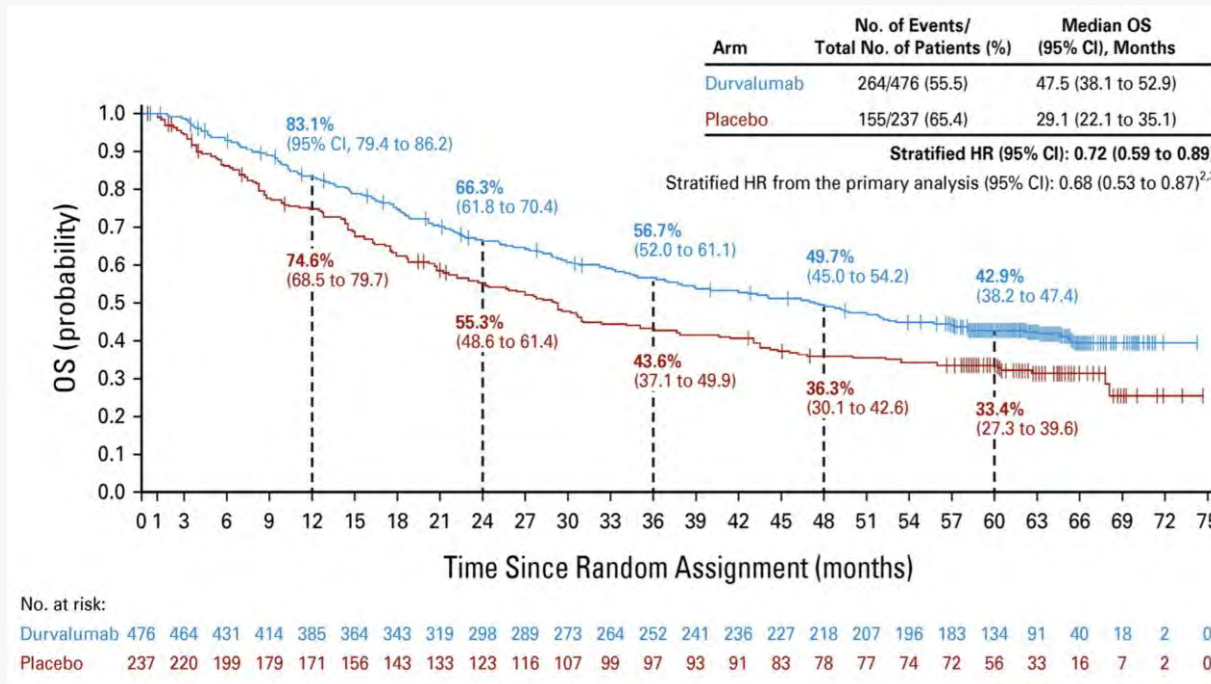
§ If using durvalumab, additional chemotherapy after radiation is not recommended.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



5-year Overall Survival



Pacific Trial:

- Unresectable Stage IIIA/B NSCLC ng Cancer
- No mention of evaluation by a thoracic surgeon
- Randomized after completing chemo-RT
- Evenly divided between IIIA and IIIB
- Did not use PDL1 status for entry
- 5- year OS 42.9% vs 33.4%
- EGFR/ALK patients did not to benefit
- PDL1<1% less benefit

RCTs and Stage III NSCLC

- Heterogeneity of IIIA disease
- These patients should all be reviewed by the MDT *including a thoracic surgeon* upfront as individualized planning is mandatory
- Bimodality treatments (CS or CRT) probably best for most patients, no need for 2 local therapies as it increases toxicity and systemic failures drive our results
- IO neoadjuvant, adjuvant or both?

Thank You



[*decamp@surgery.wisc.edu*](mailto:decamp@surgery.wisc.edu)