

Lung Cancer: 2011

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MEDICAL CENTER

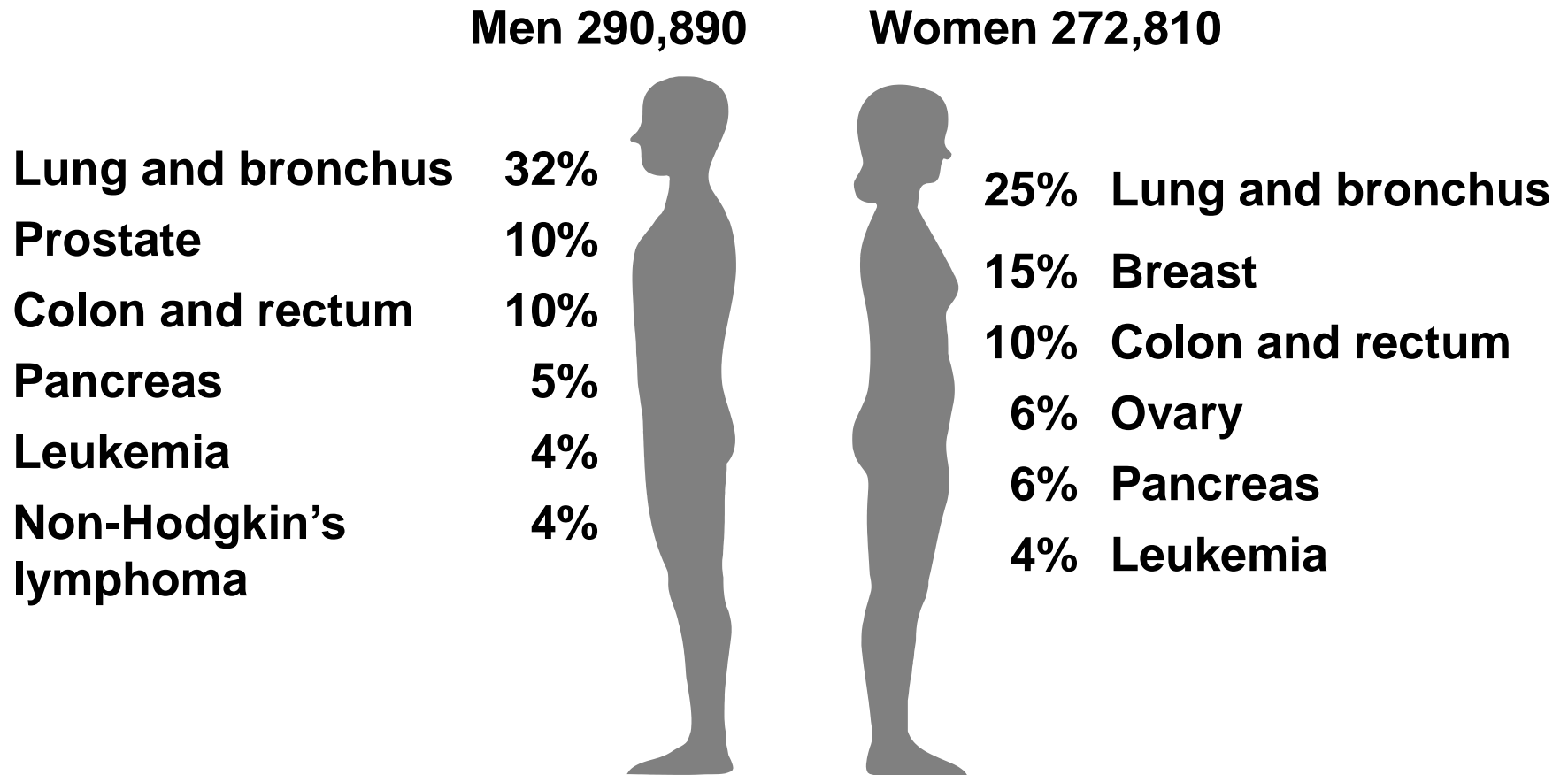
IT'S HOW MEDICINE

SHOULD BE

The End of Nihilism

- Until now, >50% present with Stage IV
- Everything is getting smaller
- Screening IS beneficial: smaller tumors
- Minimally Invasive Surgery: smaller incisions
- Stereotactic Radiotherapy: smaller radiation field
- Molecular Diagnostics

2009 Estimated US Cancer Deaths*



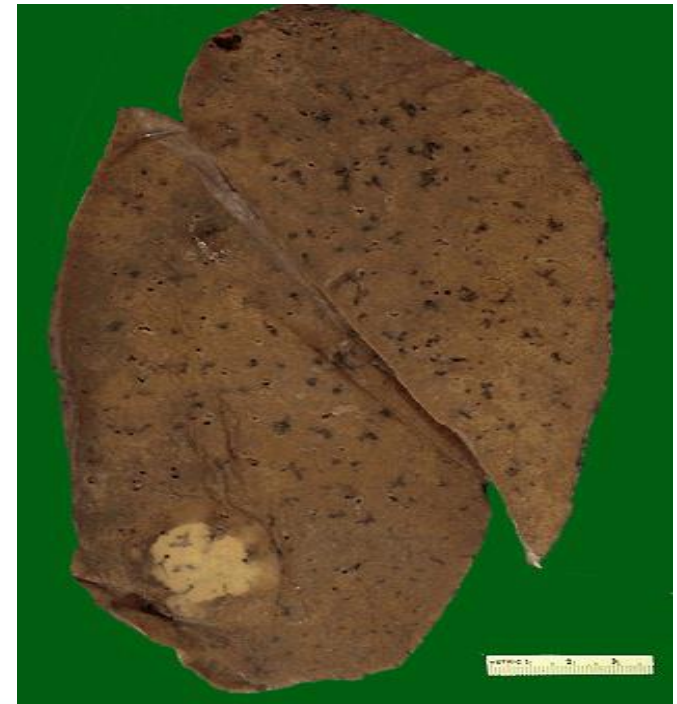
- ~160,440 patients will die of NSCLC in 2010

Lung Cancer Linked to Smoking

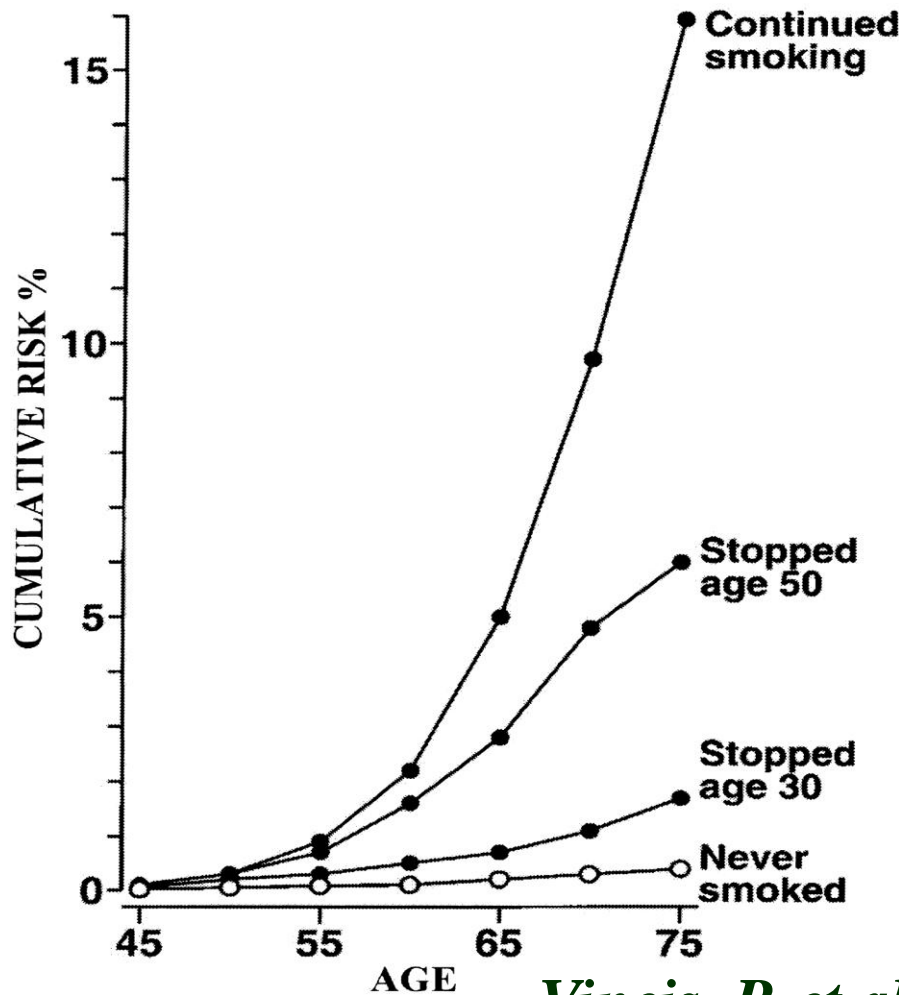
JAMA May 27, 1950

Tobacco Smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty-four proved cases

Ernest L. Wynder and Evarts A. Graham



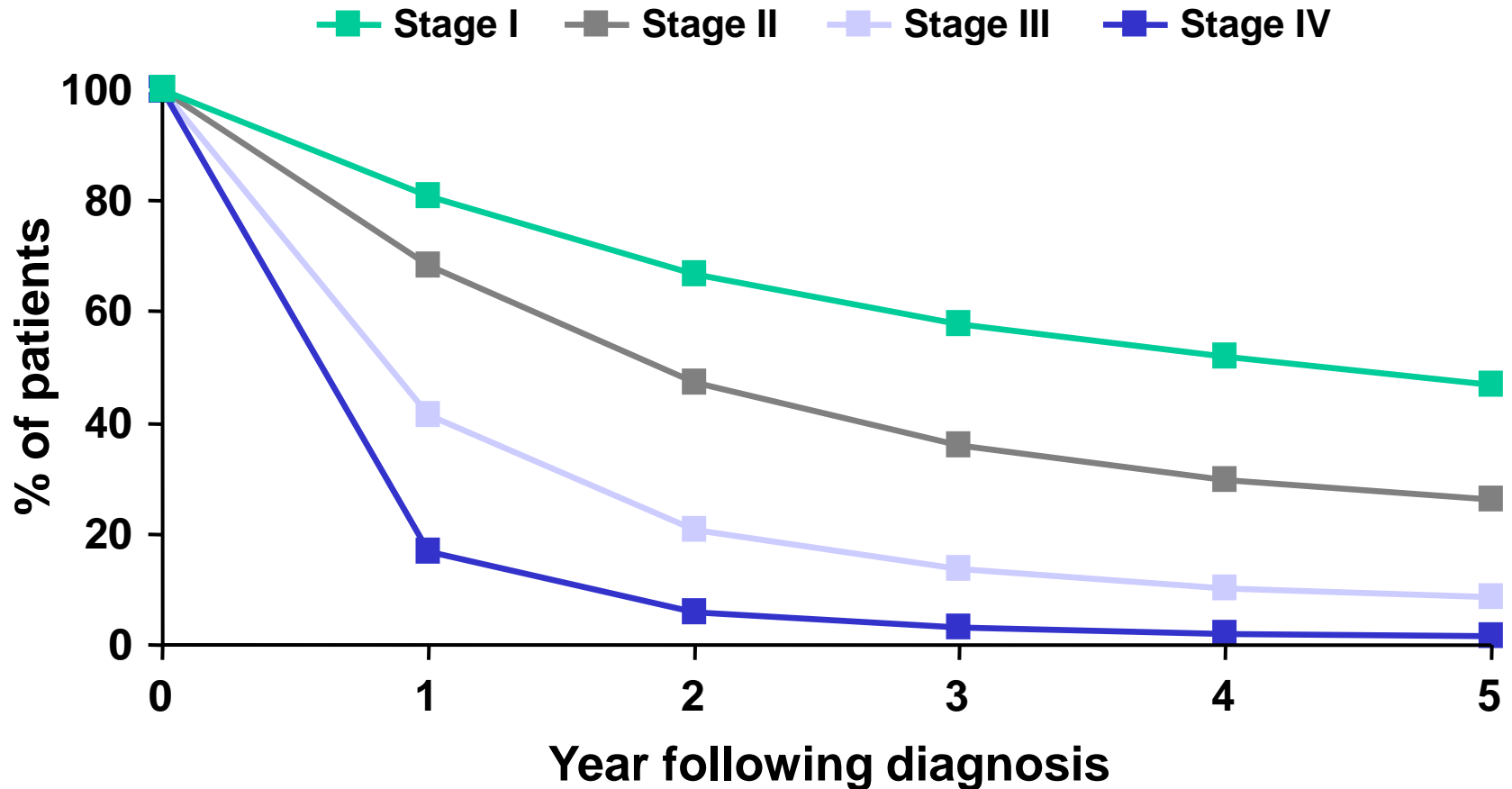
Cum. Risk of Lung CA in UK Men



Data from Sirs Doll & Peto unequivocally demonstrates that the risk of lung CA after smoking never returns to normal

Vineis, P. et al. JNCI 2004;96:99-106

NSCLC: Survival by Stage at Diagnosis

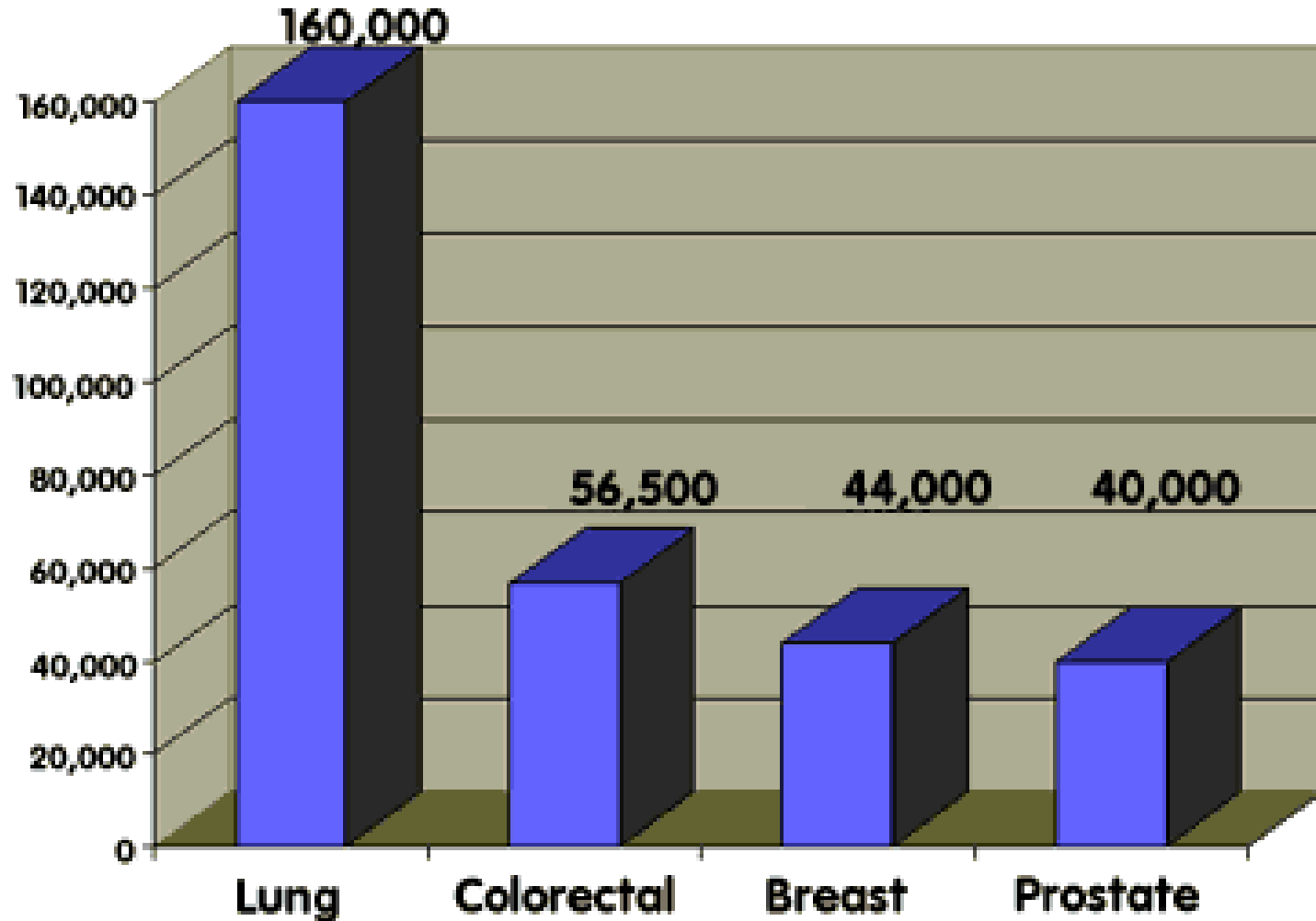


Overall 5 year Lung Cancer Survival Rate = 15%

NSCLC: Staging and Prognosis

Stage	Incidence	Description	Treatment	Prognosis (5-year survival)
I a/b	20%	1 ^o tumor only	Surgery	60-80%
II a/b	5%	Tumor spread to lymph nodes around lung	Surgery followed by Chemotherapy	40-50%
IIIa	35%	Tumor spread to lymph nodes near trachea; invasion of chest wall	Chemotherapy Surgery ???	25-30%
IIIb		Tumor has spread to other side of the chest or the neck	Chemotherapy and Radiation	5-10%
IV	40%	Tumor spread to distant structures	Chemotherapy and/or palliative care	<1%

Cancer Deaths Per Year in U.S.A.

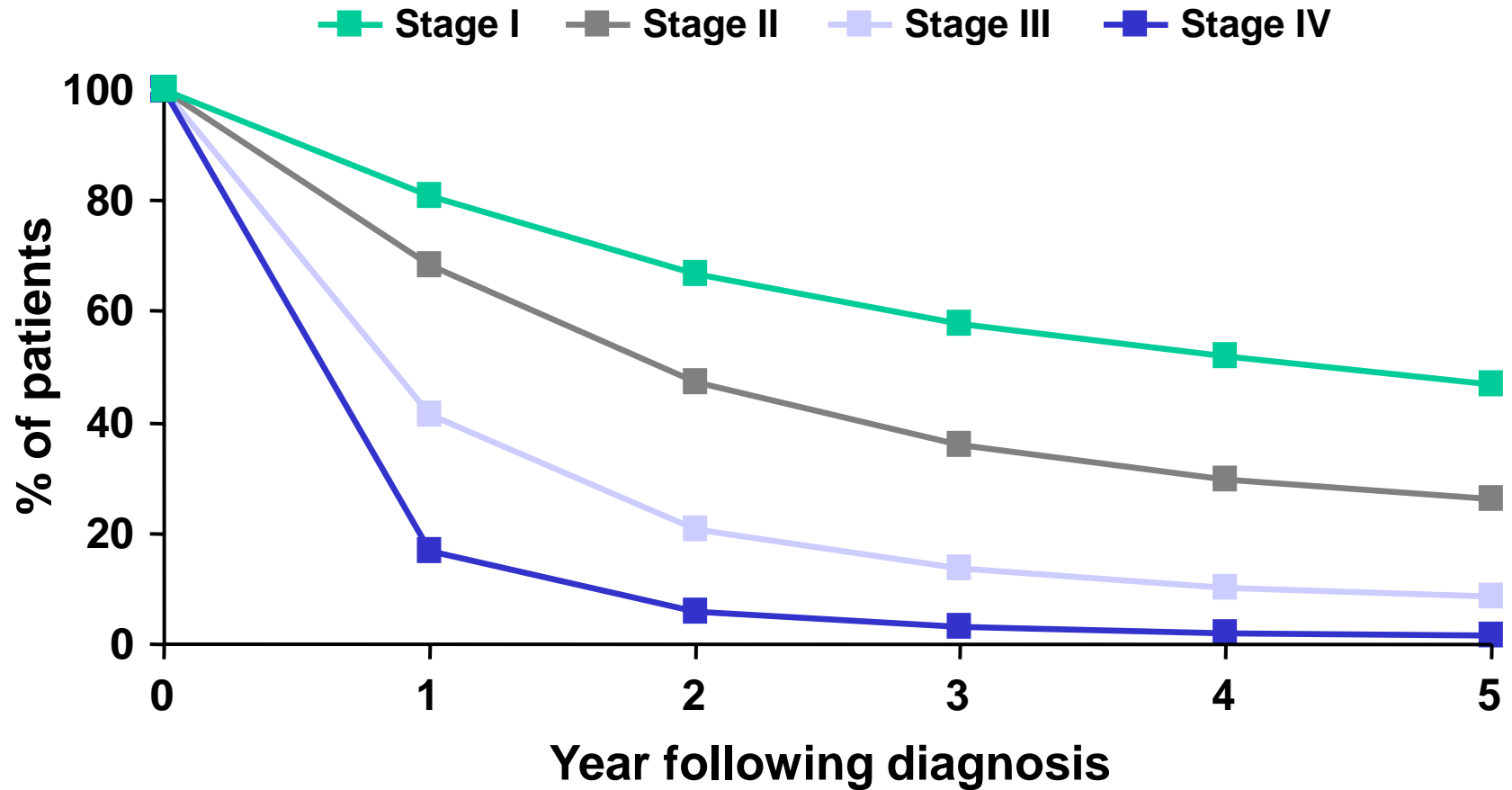


I-ELCAP Results

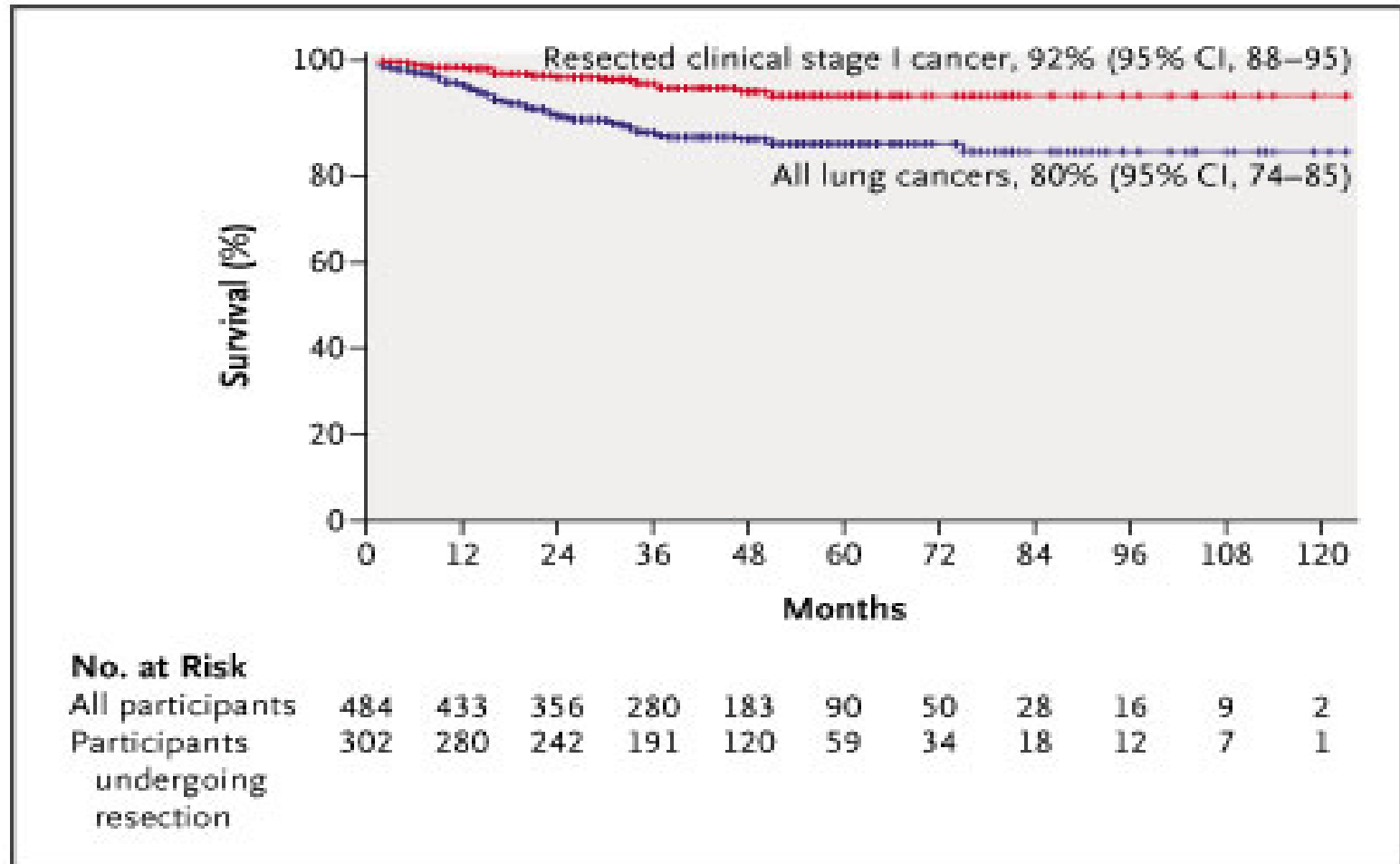
(NEJM, 355:1763-1771, 2006)

- **DXed 484 lung cancers in 31,567 participants**
- **412 (85%) stage I lung cancer**
- **10-yr survival rate- 88% (95% CI; 84-91)**
- **302 Stage I pts had surgery < 1 mos after diagnosis**
 - **Survival rate was 92% (95% CI, 88 to 95)**

NSCLC: Survival by Stage at Diagnosis



Kaplan–Meier Survival Curves



Henschke, CI et al. NEJM 355:1763, 2006

Promise of CT Scan Screening

- In non-randomized observation studies
 - 55-85% Stage I Cancers at Baseline scan
 - 60-100% Stage I Ca's at follow-up scans

Only 16% CAs diagnosed in routine care are stage I***

***** Necessary (but insufficient) indication of utility of screening**

- NCI funded Randomized Controlled Trial
- >53,000 current / former smokers (30 pack yrs)
- Randomized to low dose CT vs CXR x 3 yrs.
- 5 yr. f/u
- 354 deaths on CT arm vs. 442 with CXR (**20.3% mortality reduction**)
- Establishes validity of CT screening in high risk patients. Value of longer term screening unknown

- **More “very early” lung cancers (< 2cm)**
- **Smaller Cancers → Smaller Surgeries**
- **Maybe Localized radiation just as good**

Lung Cancer Surgery: History

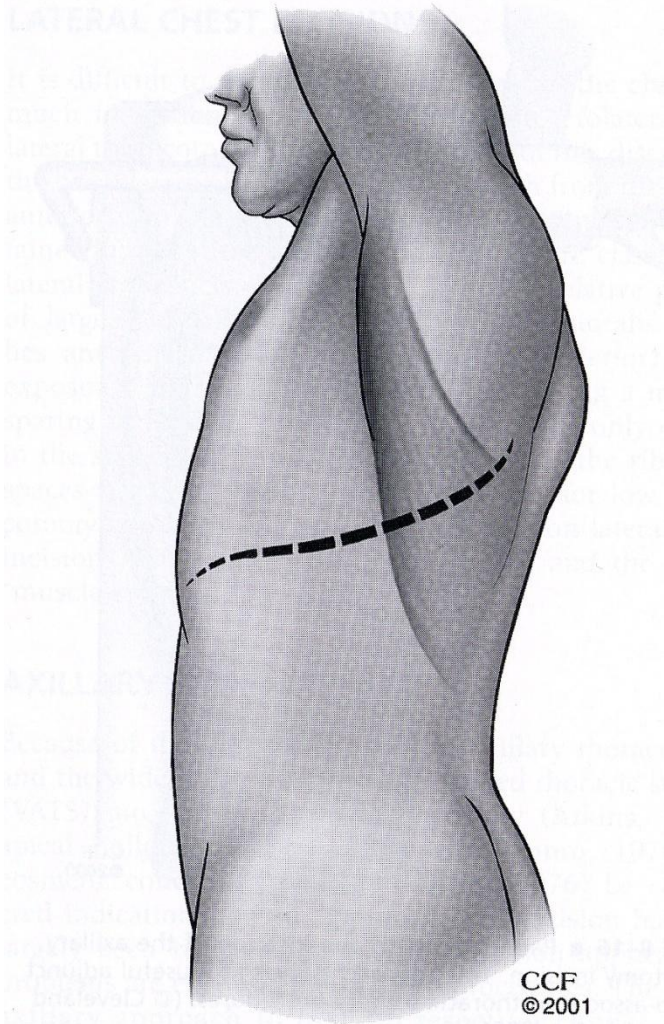


Successful removal of an entire lung for carcinoma of the bronchus

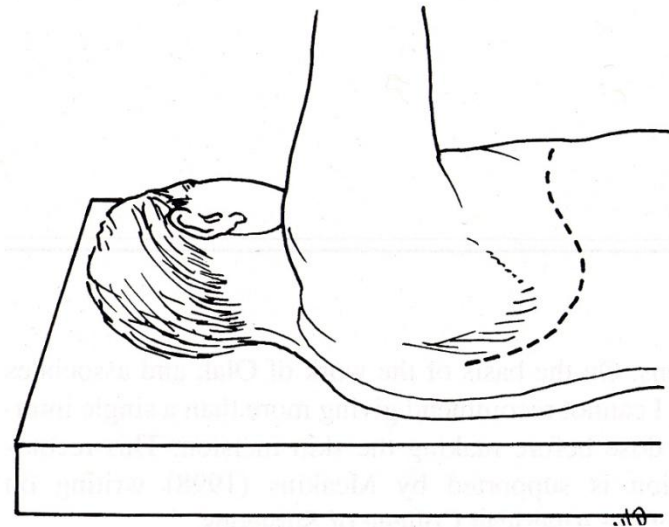
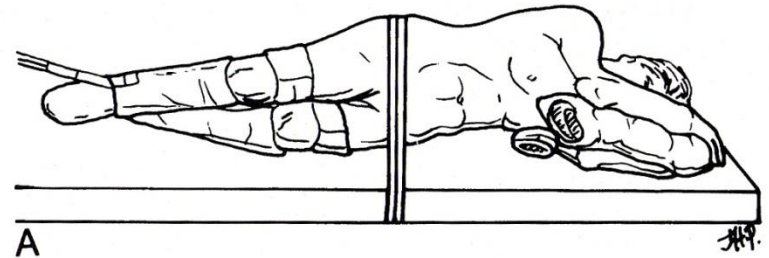
Evarts A. Graham and
James. J. Singer
JAMA Oct 28, 1933

The **left lung** and many of the tracheobronchial mediastinal glands were removed in a one stage operation because of a **carcinoma**.... apparently the **first case** in which an entire lung has been removed successfully at **one stage**.

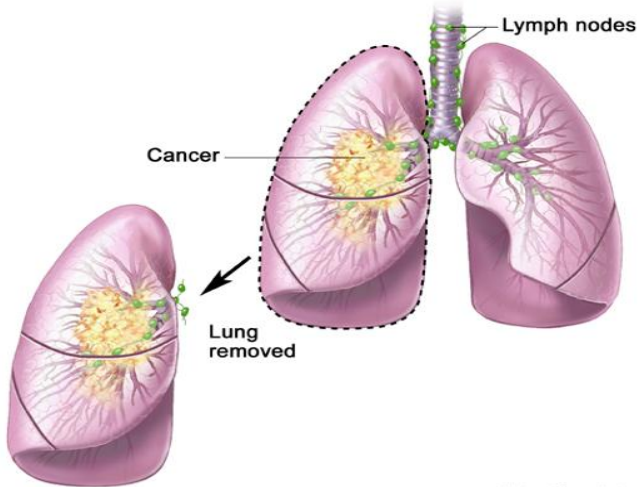
Posterolateral Thoracotomy



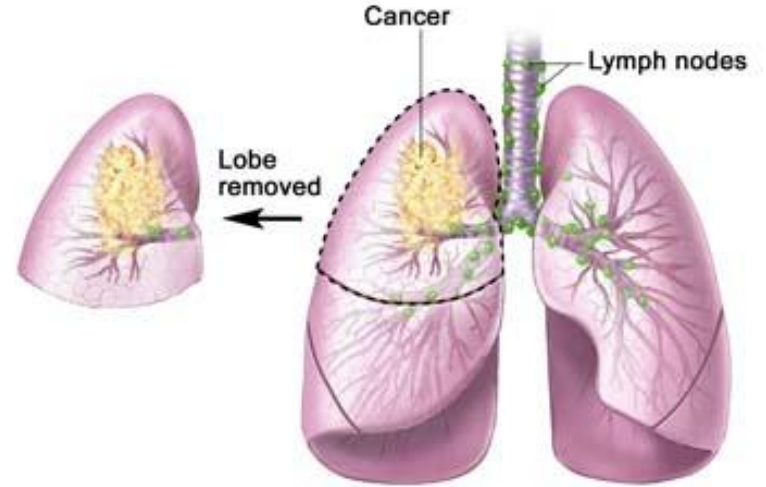
CCF
© 2001



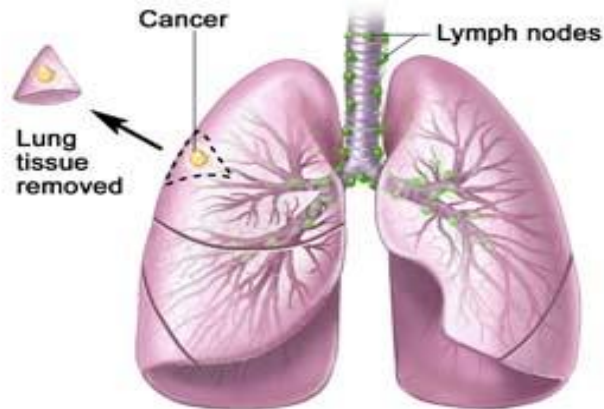
Lung Resections



National Cancer Institute

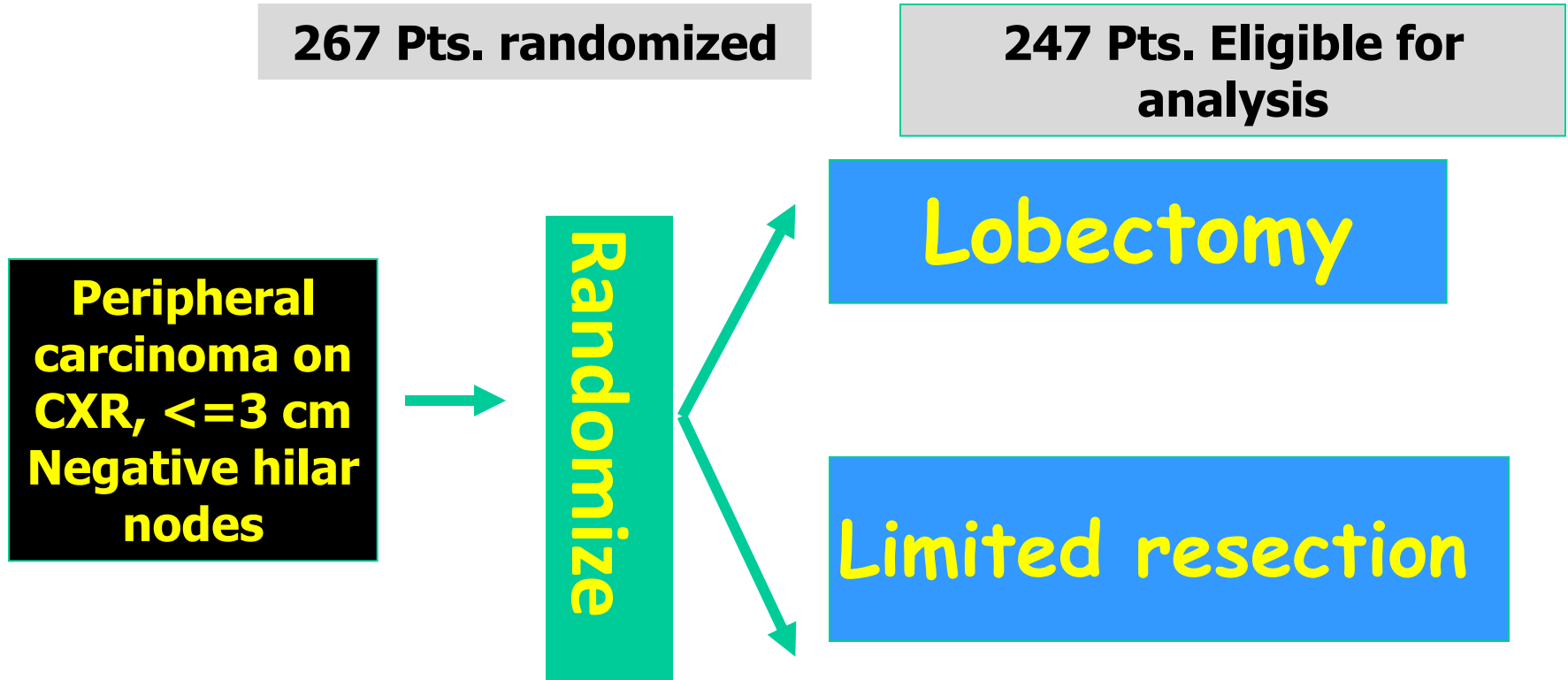


National Cancer Institute



National Cancer Institute

Lobectomy vs. Limited Resection for T1N0 NSCLC : LCSG trial 821



Endpoints:

Primary: OS

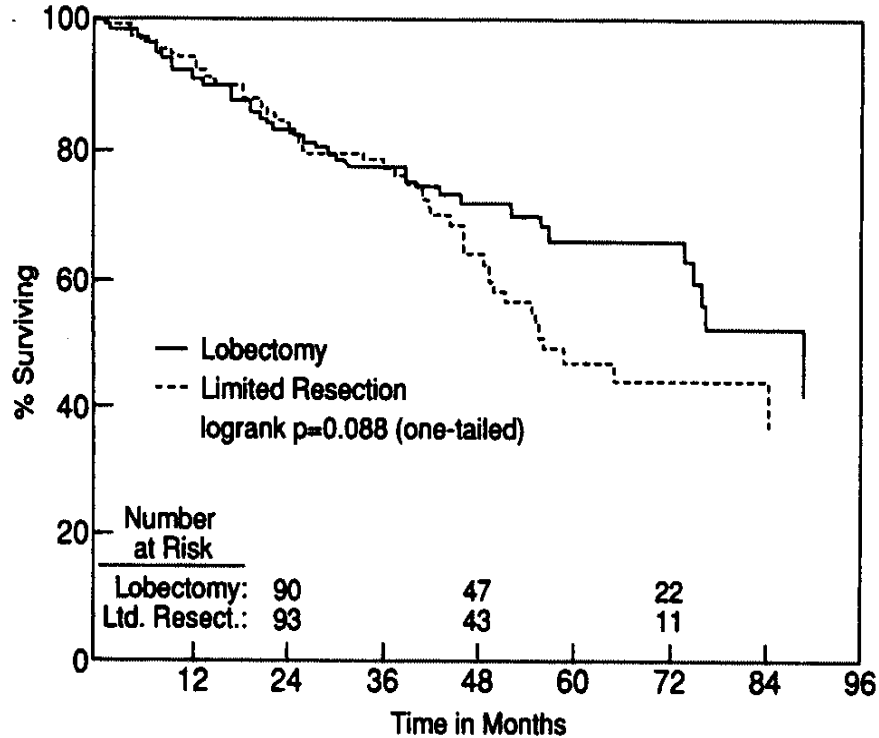
Secondary: pulmonary function

Sample size: 80 deaths and 70 recurrences to occur with a power of .90 to detect a 1.8 fold difference in median survival

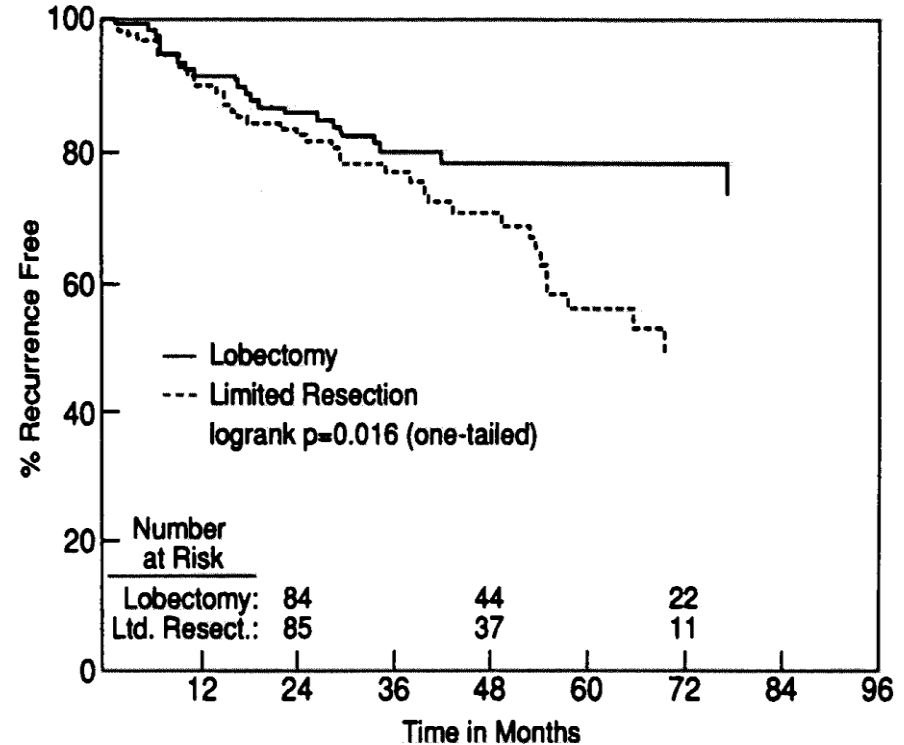
Ann Thorac Surg 1995; 60: 615-23

Lobectomy vs. Limited Resection for T1N0 NSCLC: LCSG Trial 821

Time to Death (p=0.088)

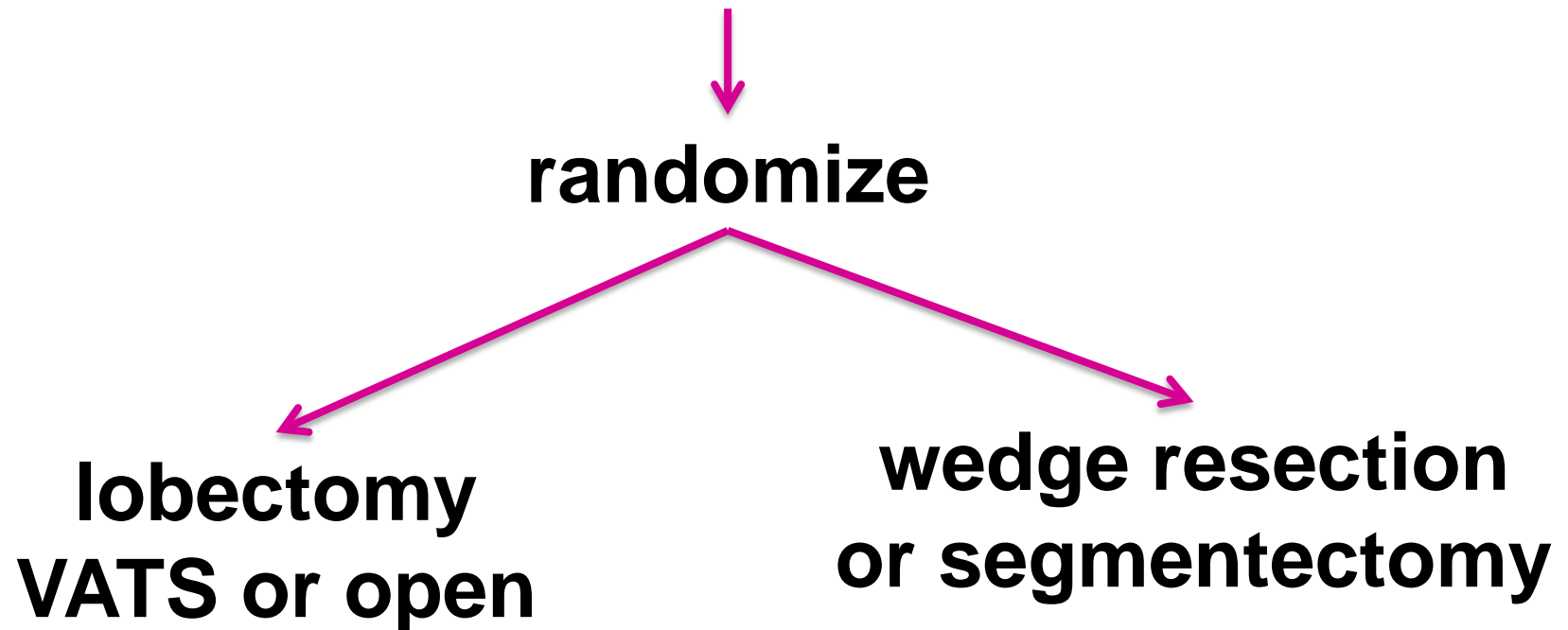


Time to Recurrence (p=0.016)



Limited Resection for NSCLC: CALGB trial 140503*

**Peripheral NSCLC \leq 2 cm
Stage Ia by CT**



*planned accrual=1297, 1° endpoint=OS

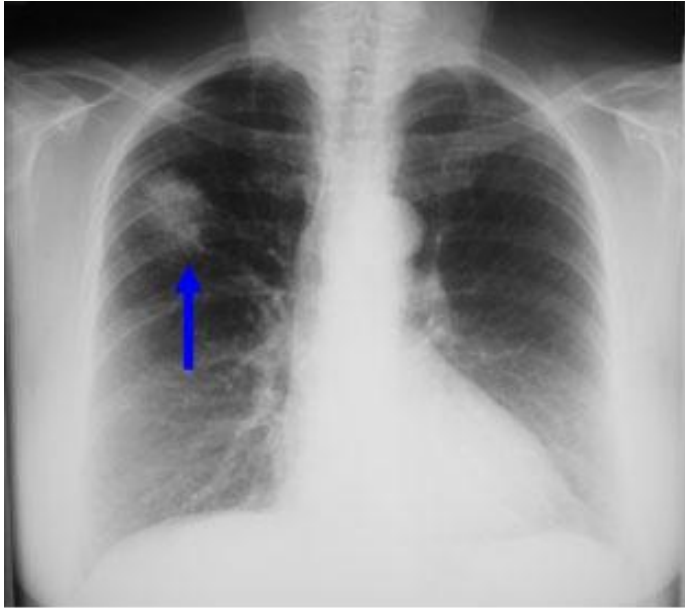
Definition

- Anatomic resection of entire lobe of lung using videoscope and access incision(s)
- No use of mechanical retractor or rib-spreading
- Same oncologic principles as thoracotomy
 - Individual dissection and ligation of vein, artery, & bronchus
 - Same lymph node management
- Specimens removed in impermeable bag

Barriers to Adoption of VATS

- Only 15% of Lobectomies performed VATS in U.S.A. (75% at RUMC)
- Learning Curve (at least 40-50 cases)
- Requires Increased Number of Skilled Assistants (Co-surgeon when starting out)
- Ill Suited to Cardiac – Vascular Surgeons performing low volume Thoracic Surgery
- RUMC surgeons perform most VATS/Lung Surgeries in Illinois.

Screening Options



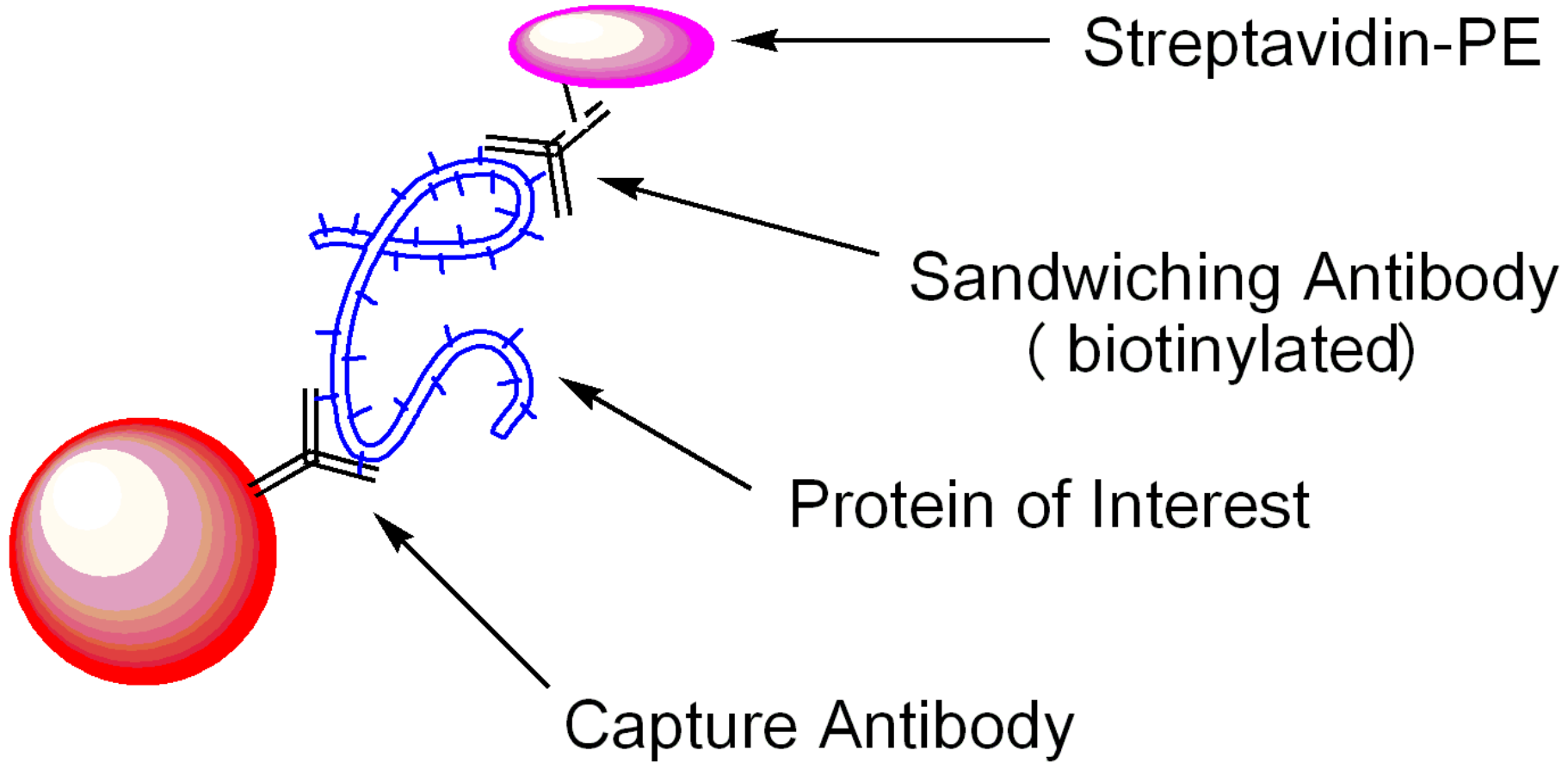
Chest X-ray

Low dose CT



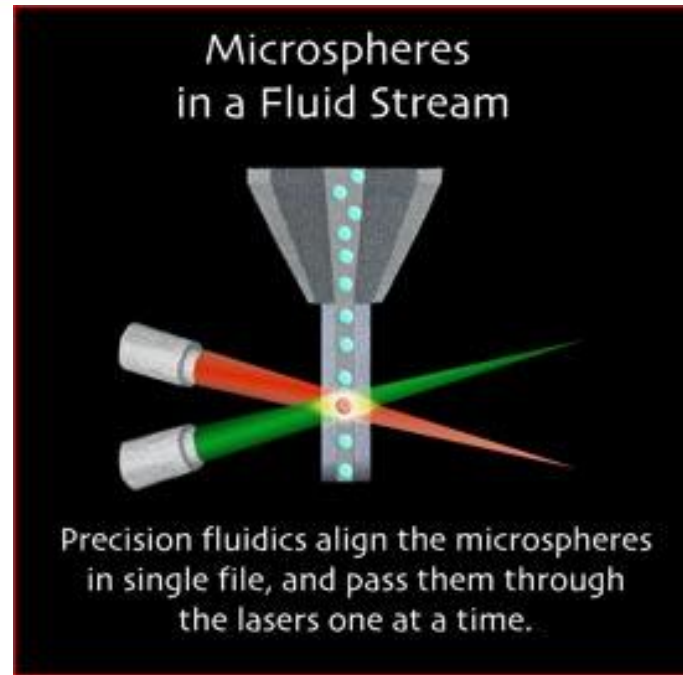
***Not ALL nodules are Cancer!
Can Molecular diagnostics play a role?***

Luminex Immunoassay Platform

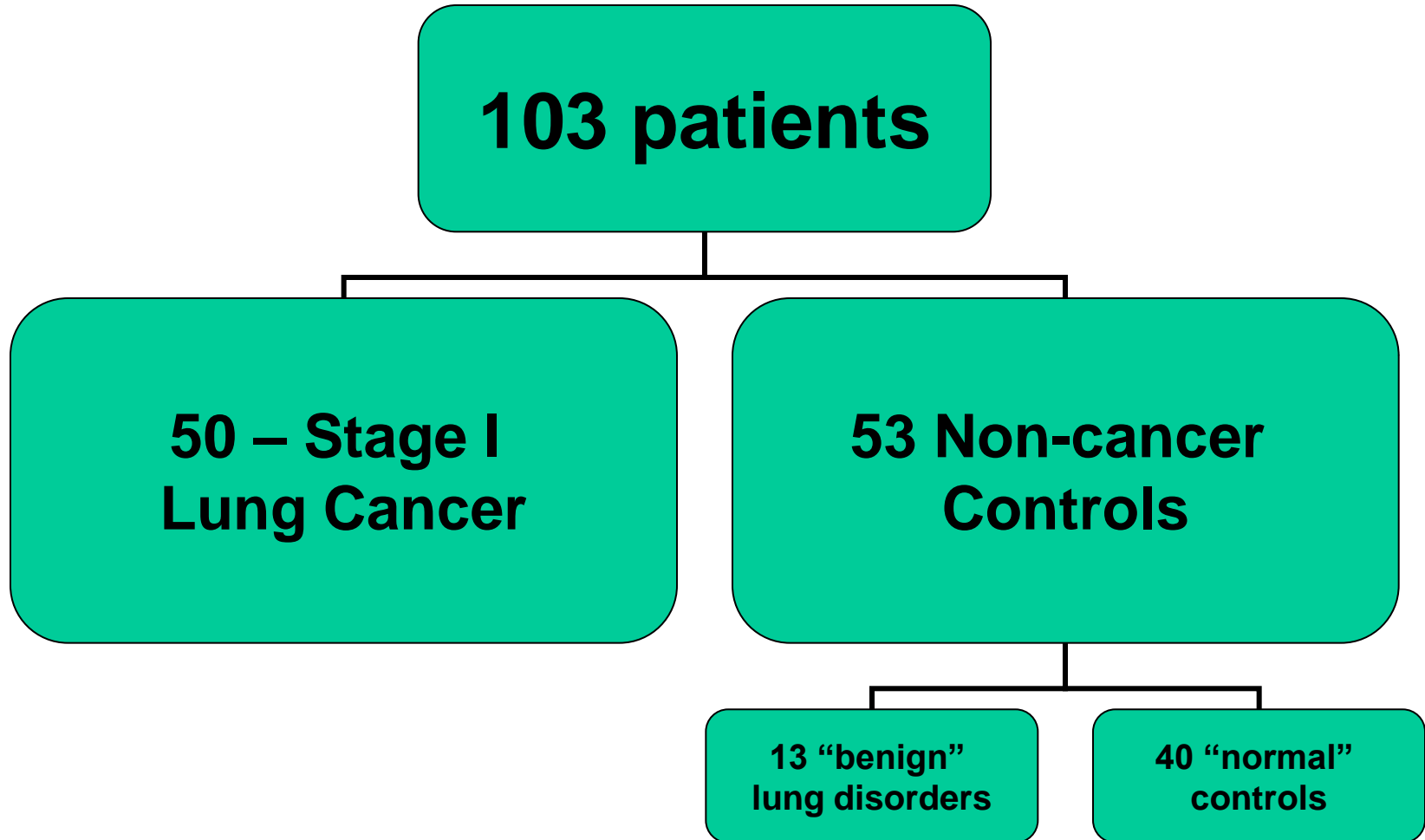


Evaluating the Beads

- Similar Specificity/
Sensitivity to ELISA
- Can multiplex up to 100
assays
- Uses low microliter
quantities of serum
- Low cost



Early Detection of Lung Cancer



Screening: 'Relevant Biomarkers'

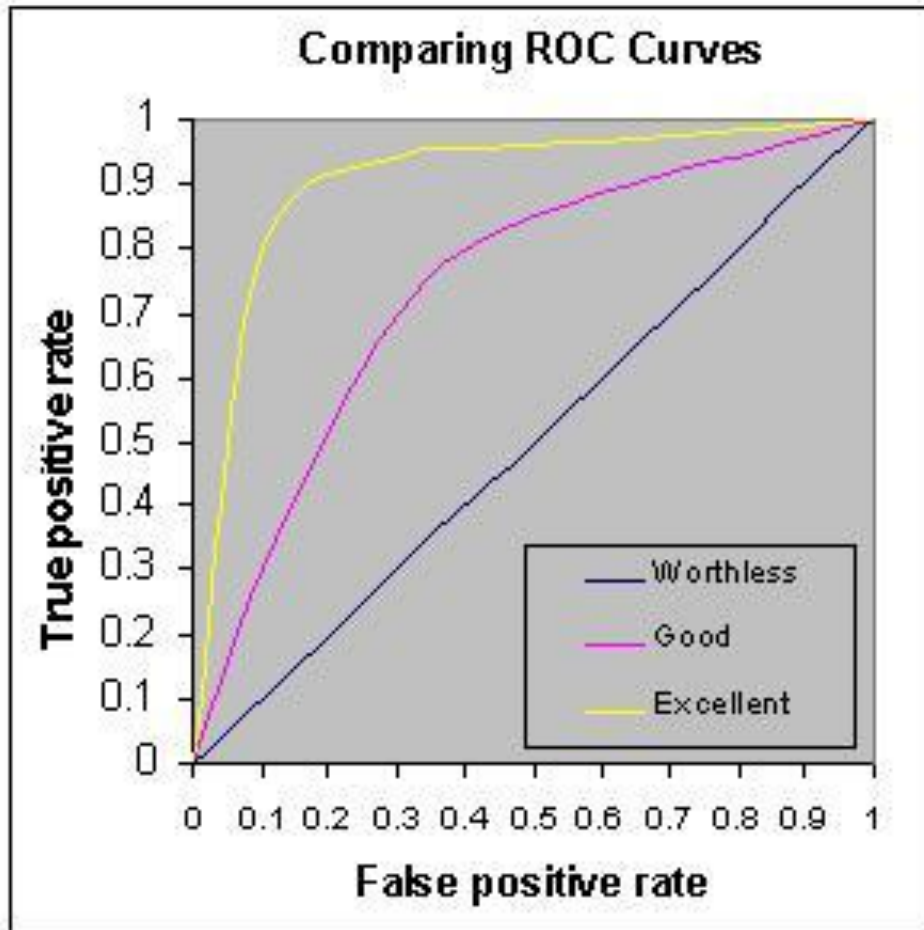
IL-1 α	IL-1 β	IL-1ra	IL-2	IL-2R	IL-6	IL-8
TNF- α	TNF-RI	TNF-RII	DR5	bFGF	IL-10	IL-15
CRP	SAA	MMP -2	MMP -3	MMP -9	MMP -13	TIMP-1
IFN- γ	RANTES	TGF- α	ICAM	E-Selectin	P-selectin	IP-10
G-CSF	M-CSF	GM-CSF	Eotaxin	MIP-1 α	MIP-1 β	MCP-1
VEGF	EGF	EGFR (erb-b1)	HER-2 (erb-b2)	SCF	SDF-1 α	
CA-125	CA-15-3	CA19-9	CEA	CYFRA 21.1	Osteopontin	

'Relevance' - a Mann-Whitney p value < 0.05 or an area under the ROC curve > 0.600

Screening: Final Panel

IL-1 α	IL-1 β	IL-1ra	IL-2	IL-2R	IL-6	IL-8
TNF- α	TNF-RI	TNF-RII	DR5	bFGF	IL-10	IL-15
CRP	SAA	MMP -2	MMP -3	MMP -9	MMP -13	TIMP-1
IFN- γ	RANTES	TGF- α	ICAM	E-Selectin	P-selectin	IP-10
G-CSF	M-CSF	GM-CSF	Eotaxin	MIP-1 α	MIP-1 β	MCP-1
VEGF	EGF	EGFR (erb-b1)	HER-2 (erb-b2)	SCF	SDF-1 α	
CA-125	CA-15-3	CA19-9	CEA	CYFRA 21.1	Osteopontin	

‘Relevance’ - a Mann-Whitney p value < 0.05 or an area under the ROC curve > 0.600



Area Under the Curve (AUC)

.90-1 = excellent (A)

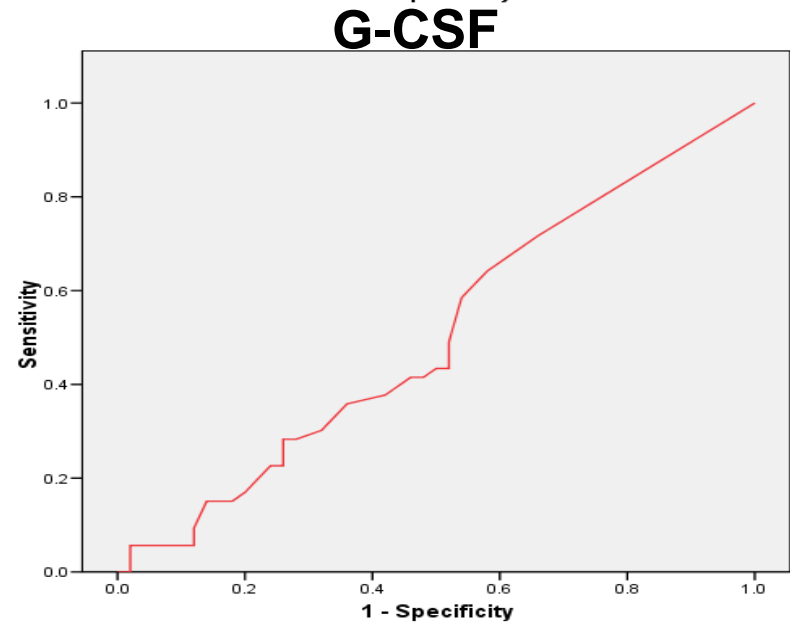
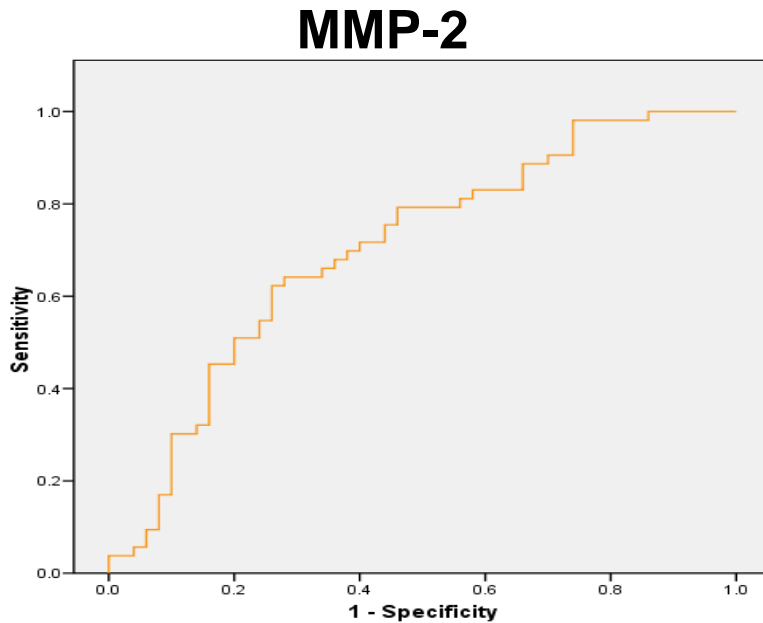
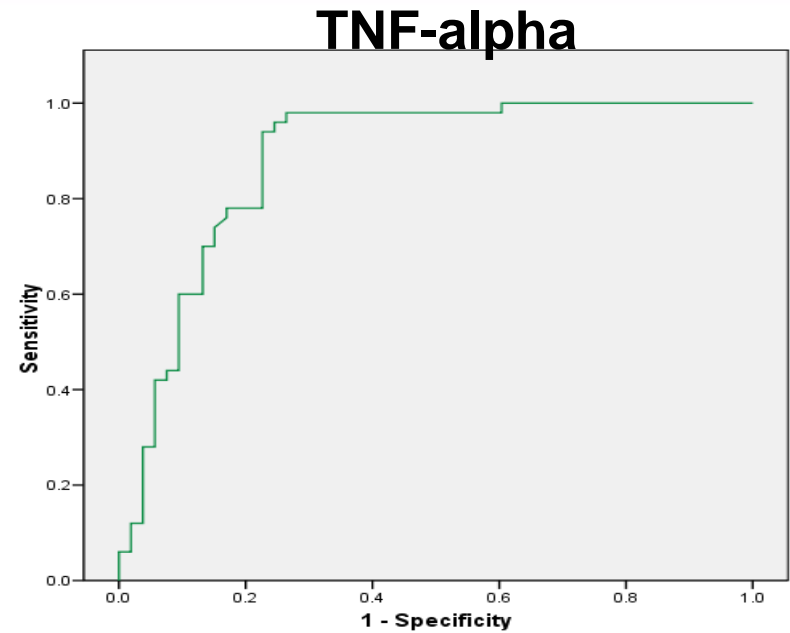
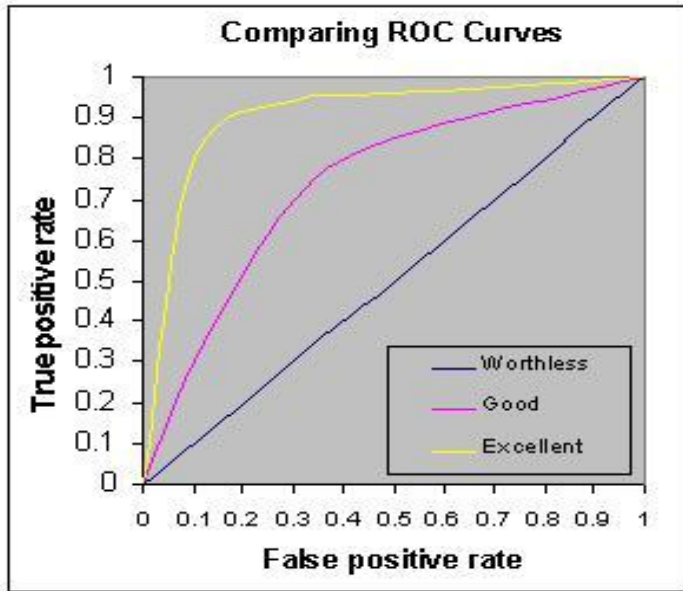
.80-.90 = good (B)

.70-.80 = fair (C)

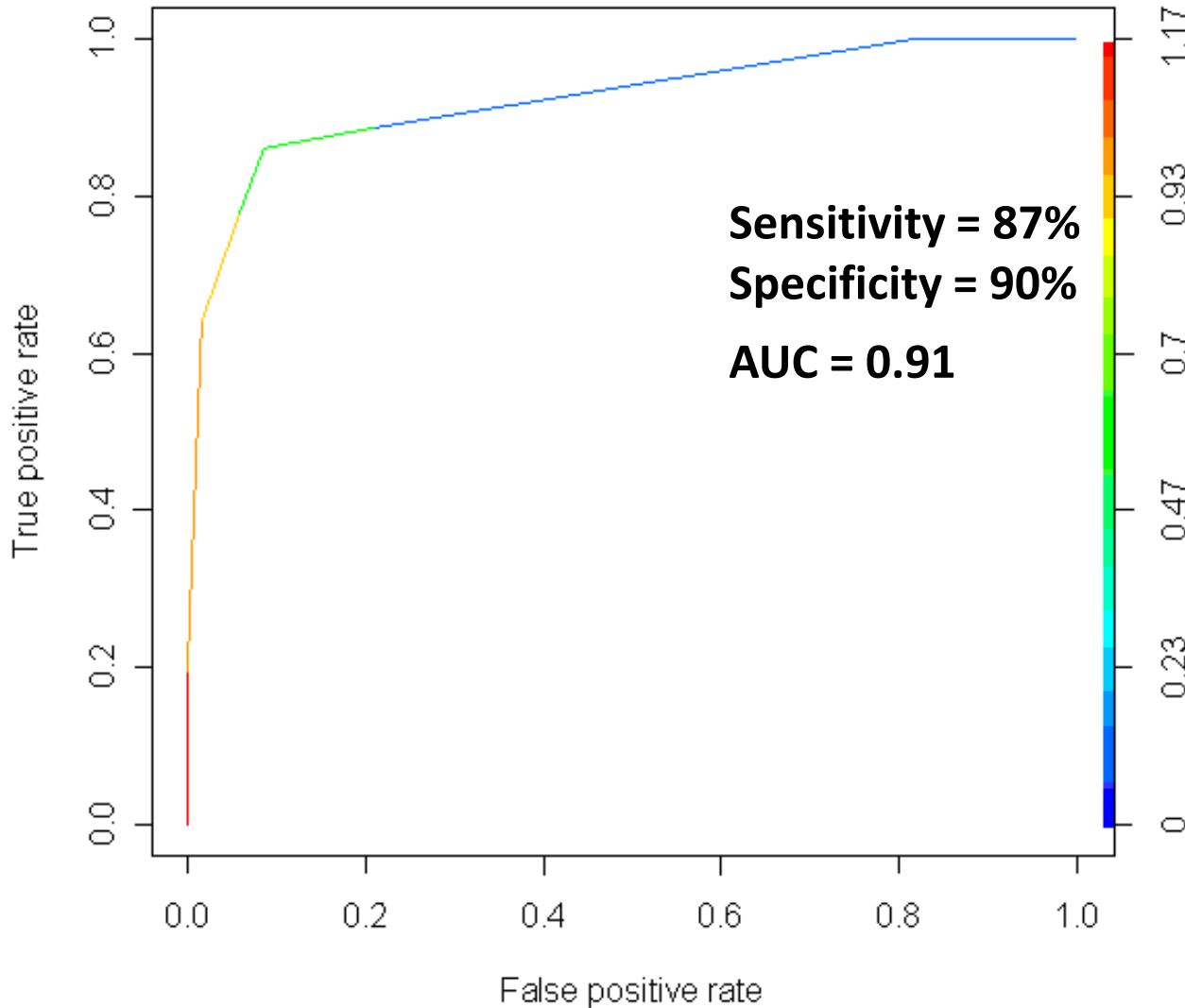
.60-.70 = poor (D)

.50-.60 = fail (F)

Receiver Operator Characteristic curves



Receiver Operator Curve



- CRP**
- MCP-1**
- CYFRA 21.1**
- TNF- α**
- SDF-1 α**
- IL-1ra**
- IL-6**
- IL-2r**
- sE-Selectin**
- sP-Selectin**
- MMP-2**
- MMP-3**
- Rantes**

Lung Cancer : 2011

- Nihilism transforms to Hopeful Optimism
- Smoking Cessation
- Regular CT screening for “at risk” population
- Less invasive local therapies (VATS, SBRT, RFA)
- Molecular Diagnostics aid in Early Detection and Targeted Treatments