Non-Invasive Strategies: Optimizing the Staging of NSCLC

6th Annual Atlanta Lung Cancer Symposium

February 7, 2009

Thomas A. D'Amico MD
Professor of Surgery, Duke University Medical Center
Program Director, Thoracic Surgery
Co-Director, Thoracic Oncology Research Laboratory
Director, Clinical Oncology, Duke Comprehensive Cancer Center

Disclosure

No conflicts related to this presentation

Poor Outcomes with Lung Cancer

- Late diagnosis
- Inaccurate staging
- Ineffective systemic therapy

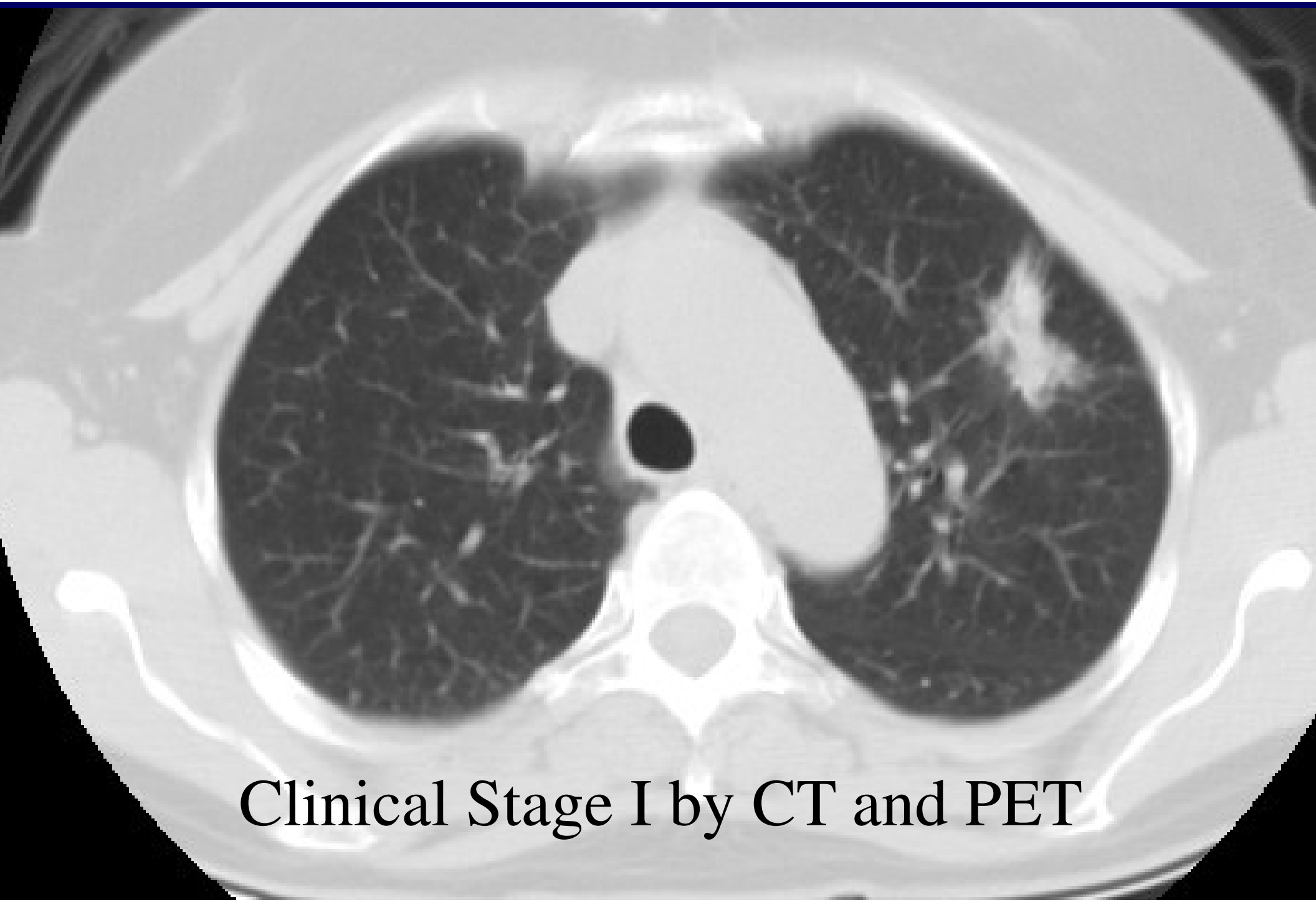
Objectives

- Review staging algorithms for lung cancer
- Discuss how developments in molecular staging will translate into improved outcomes for patients with early stage lung cancer

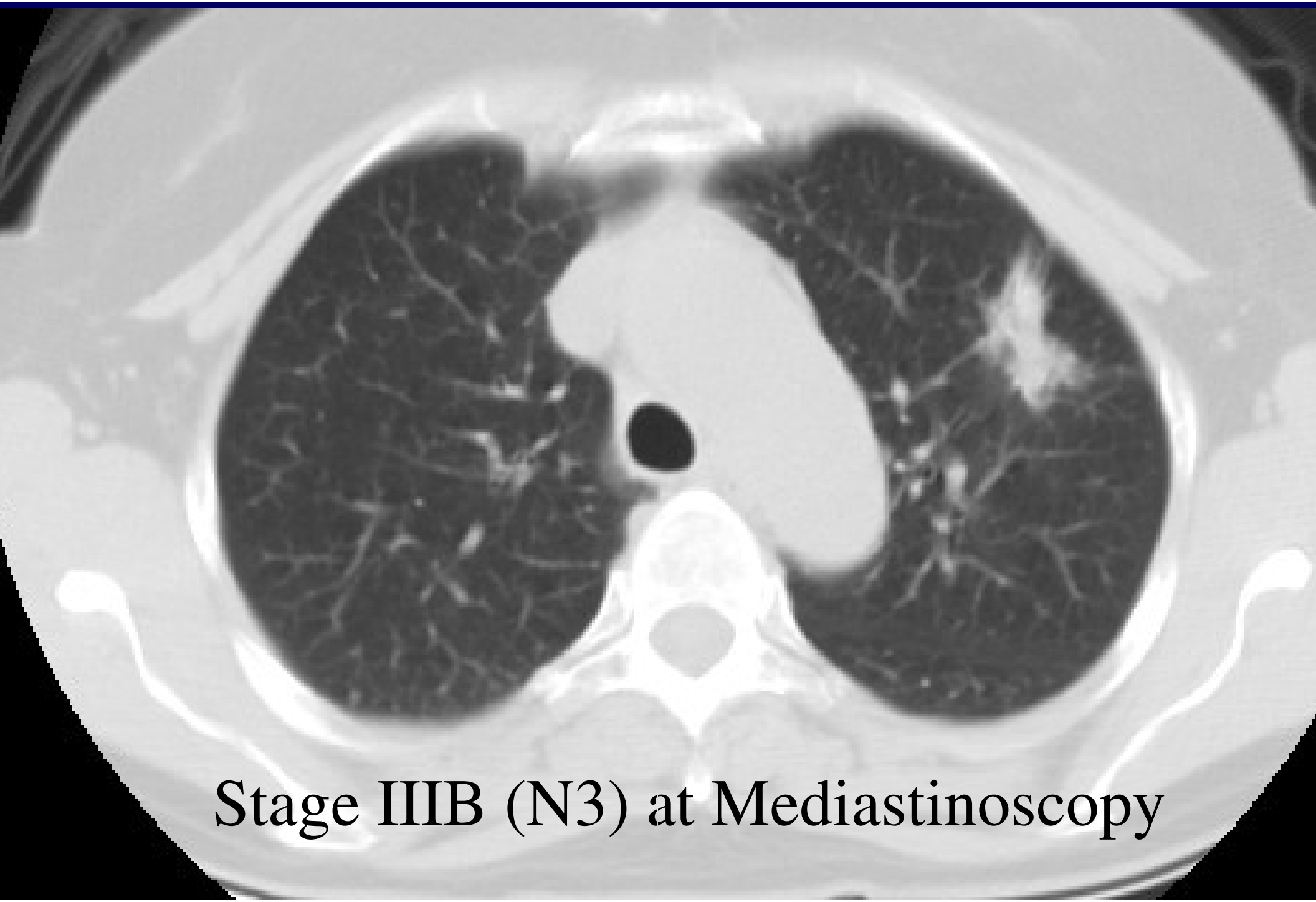
Staging Lung Cancer

- Clinical staging of lung cancer is inaccurate
- Even pathologic staging (TNM) is suboptimal

	5-year survival
Clinical Stage I	57%
Pathologic Stage I	67%

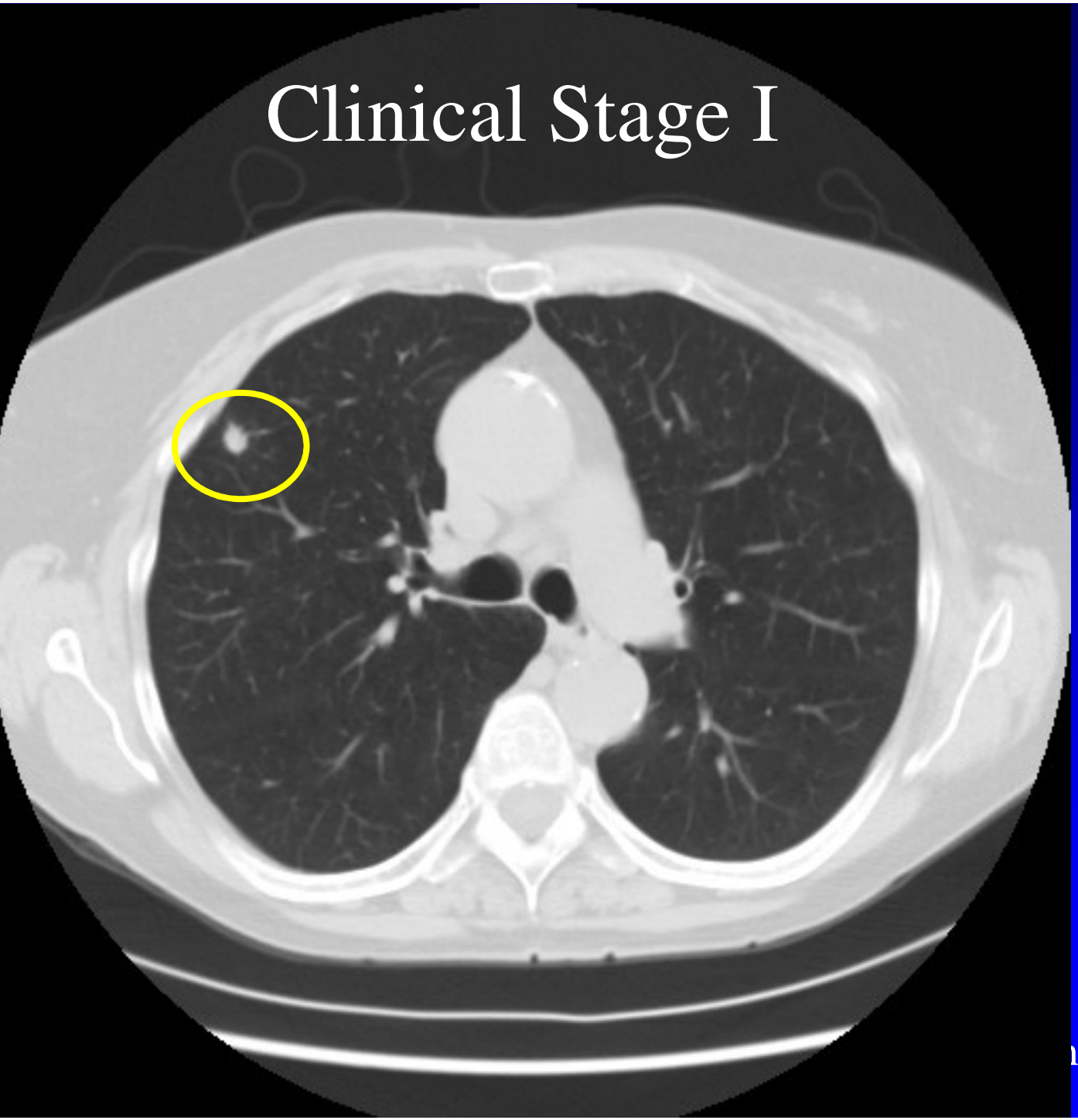


Clinical Stage I by CT and PET



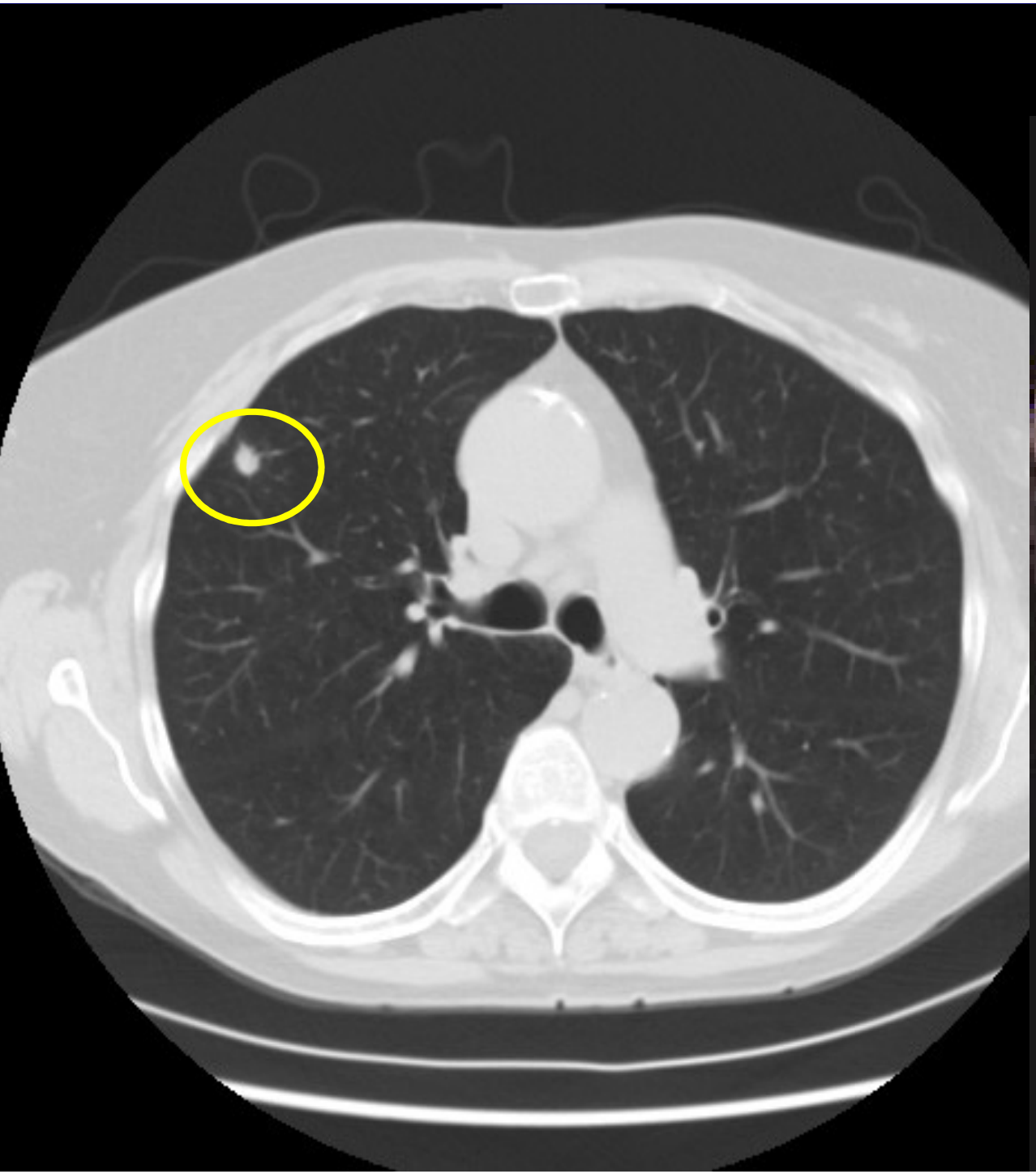
Stage IIIB (N3) at Mediastinoscopy

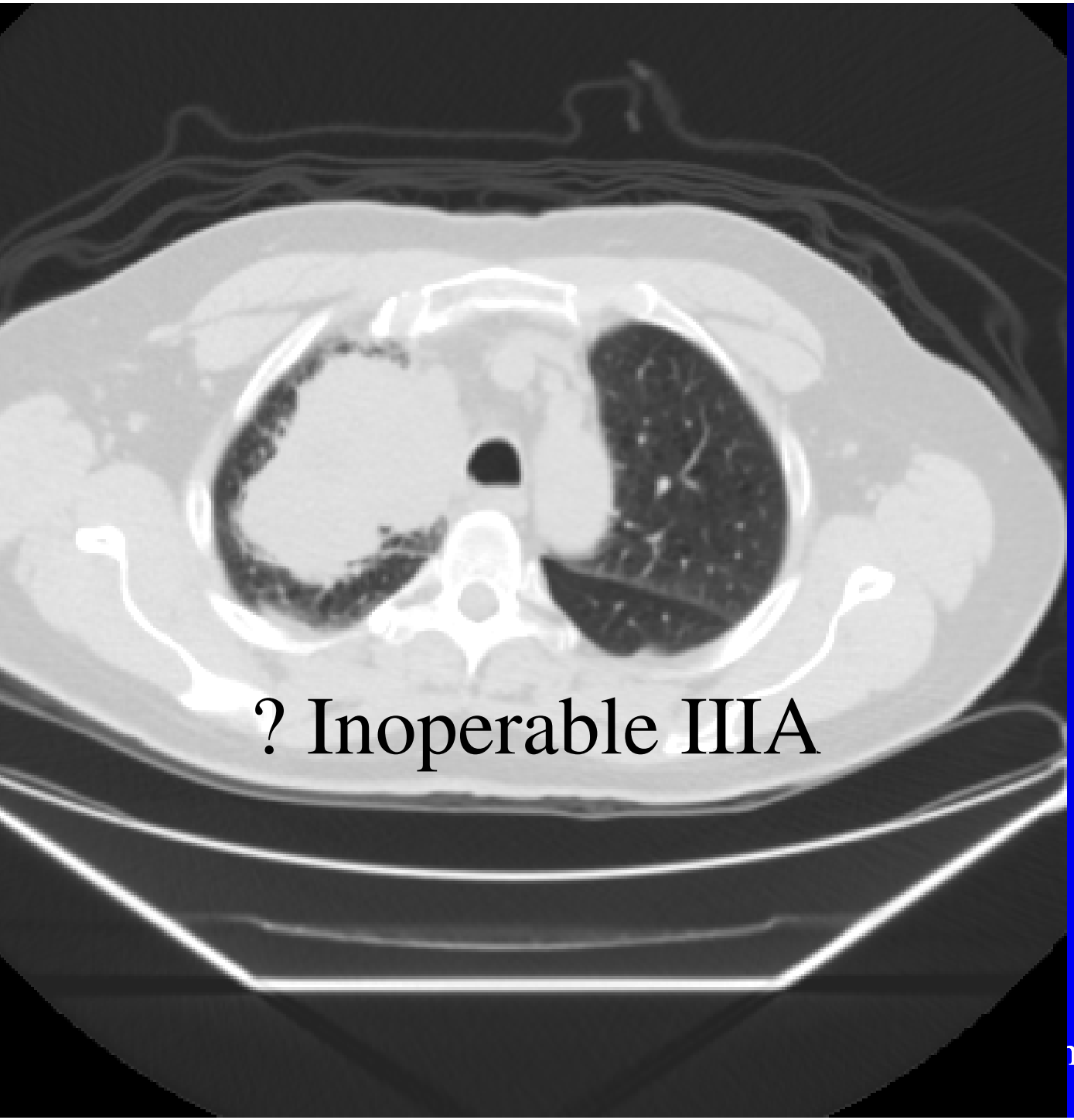
Clinical Stage I



horacic Oncology Program

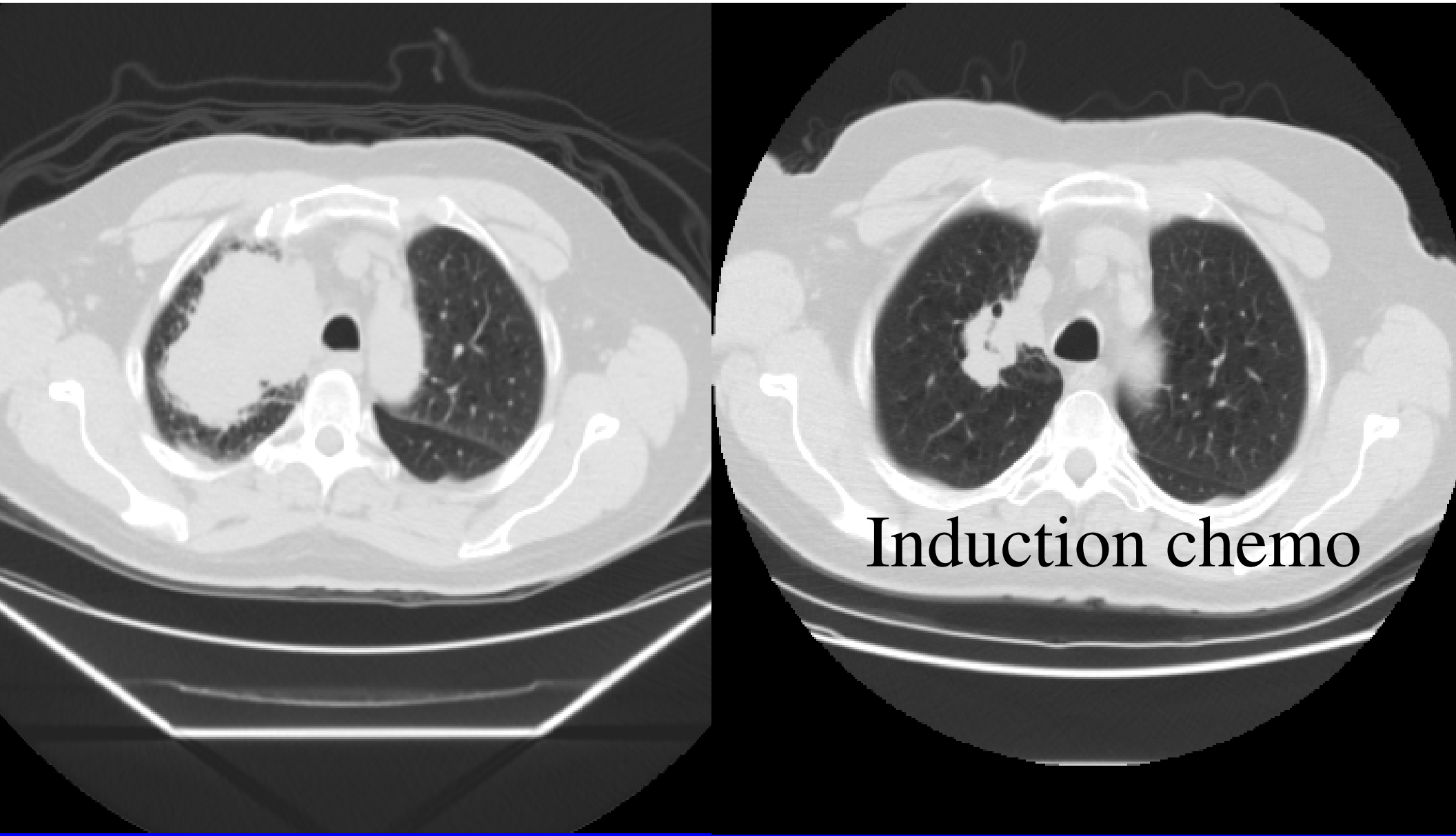
Stage IV





? Inoperable IIIA

horacic Oncology Program


Induction chemo

Lung Cancer Staging

Inaccurate staging negatively effects outcomes

- Under-staged patients do not receive the benefit of systemic therapy, or may have futile resections

- Over-staged patients may be denied curative therapy: locally advanced disease may be resectable

Proposals for the Revision of the TNM Classification for Lung Cancer

Rami-Porta R, et al. J Thorac Oncol 2007; 2:593-602

- Sub-classify T1 (0-3 cm)
  - T1a < 2 cm
  - T1b 2-3 cm
- Sub-classify T2 (3-7 cm)
  - T2a 3-5 cm
  - T2b 5-7 cm
- Re-classify T2 >7cm as T3

Proposals for the Revision of the TNM Classification for Lung Cancer

Postmus P, et al. J Thorac Oncol 2007; 2:686-693

Re-classify

- Satellite nodules in the same lobe (T4) as T3
- Nodules in a different ipsilateral lobe (M1) as T4
- Nodules in contralateral lung as M1a
- Pleural dissemination (T4) as M1a
- Distant metastases as M1b

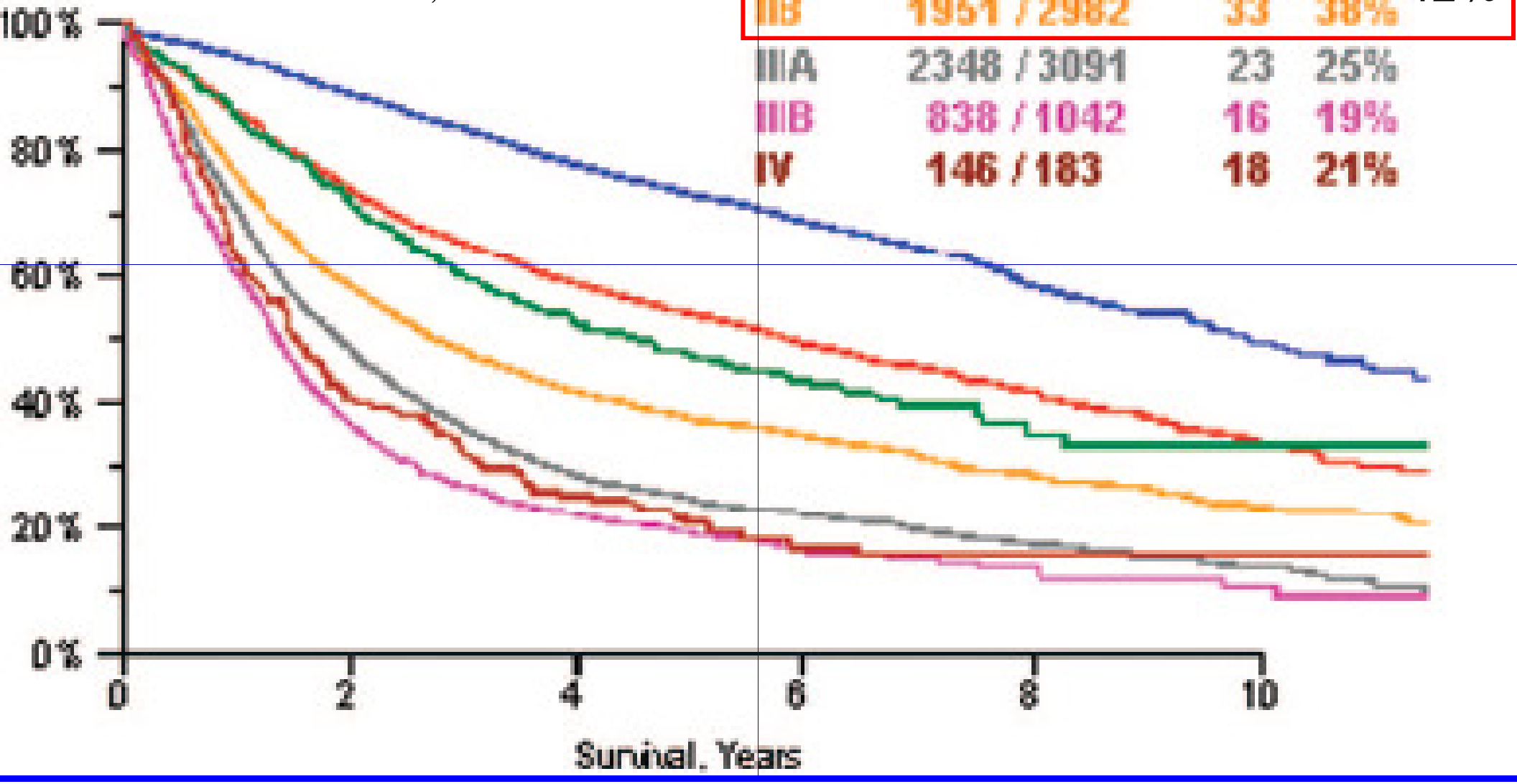
IASLC Staging Project: Proposed Changes

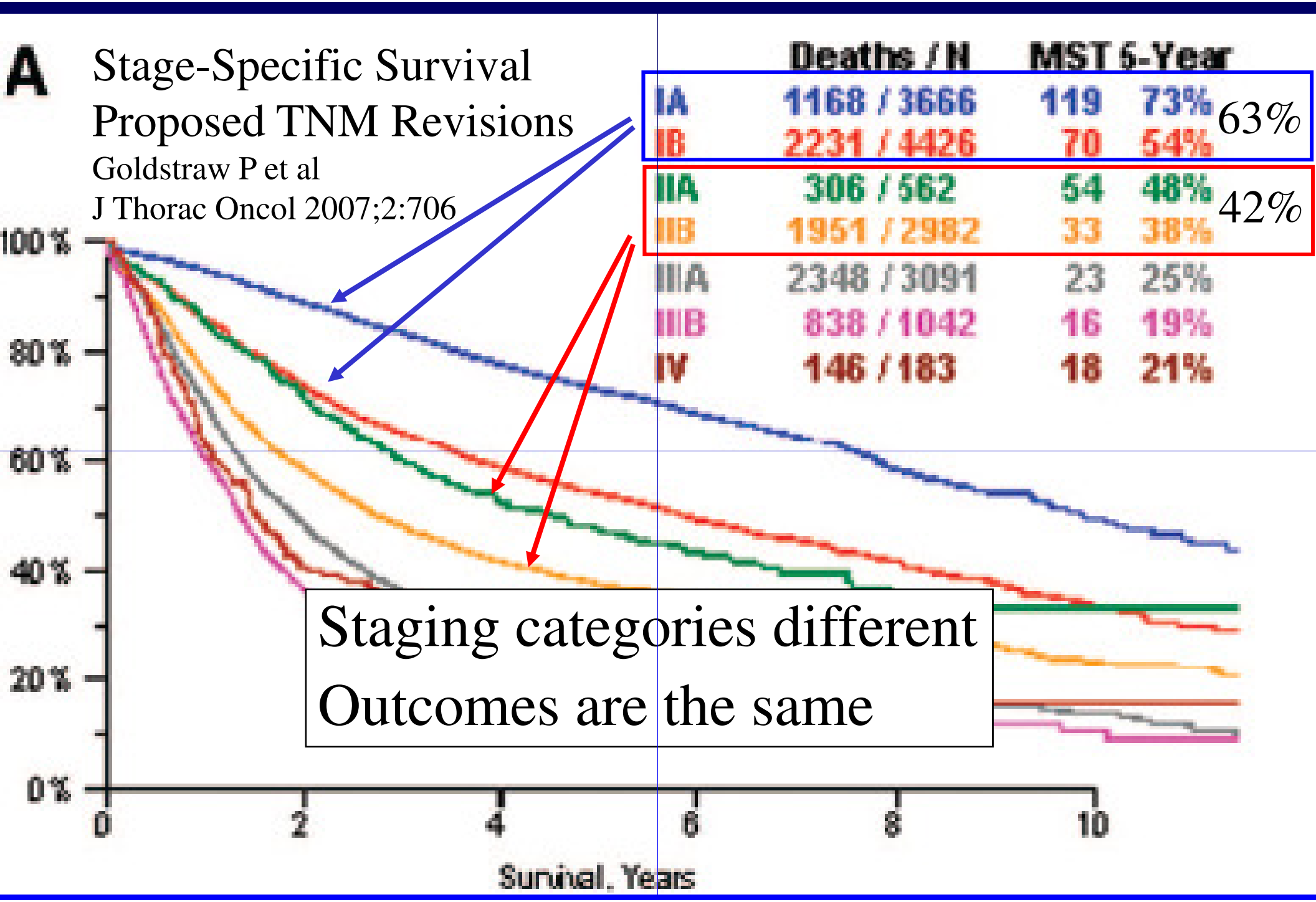
6th Edition Descriptor	Proposed	N0	N1	N2	N3
T1 (≤ 2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (2 – 3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (3 ≤ 5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (5 – 7 cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (> 7 cm)	T3	IIB	IIIA	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)	T4	IIIA	IIIA	IIIB	IIIB
T4 (pleural dissemination)	M1a	IV	IV	IV	IV
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Changes are highlighted

A Stage-Specific Survival Proposed TNM Revisions

Goldstraw P et al
J Thorac Oncol 2007;2:706



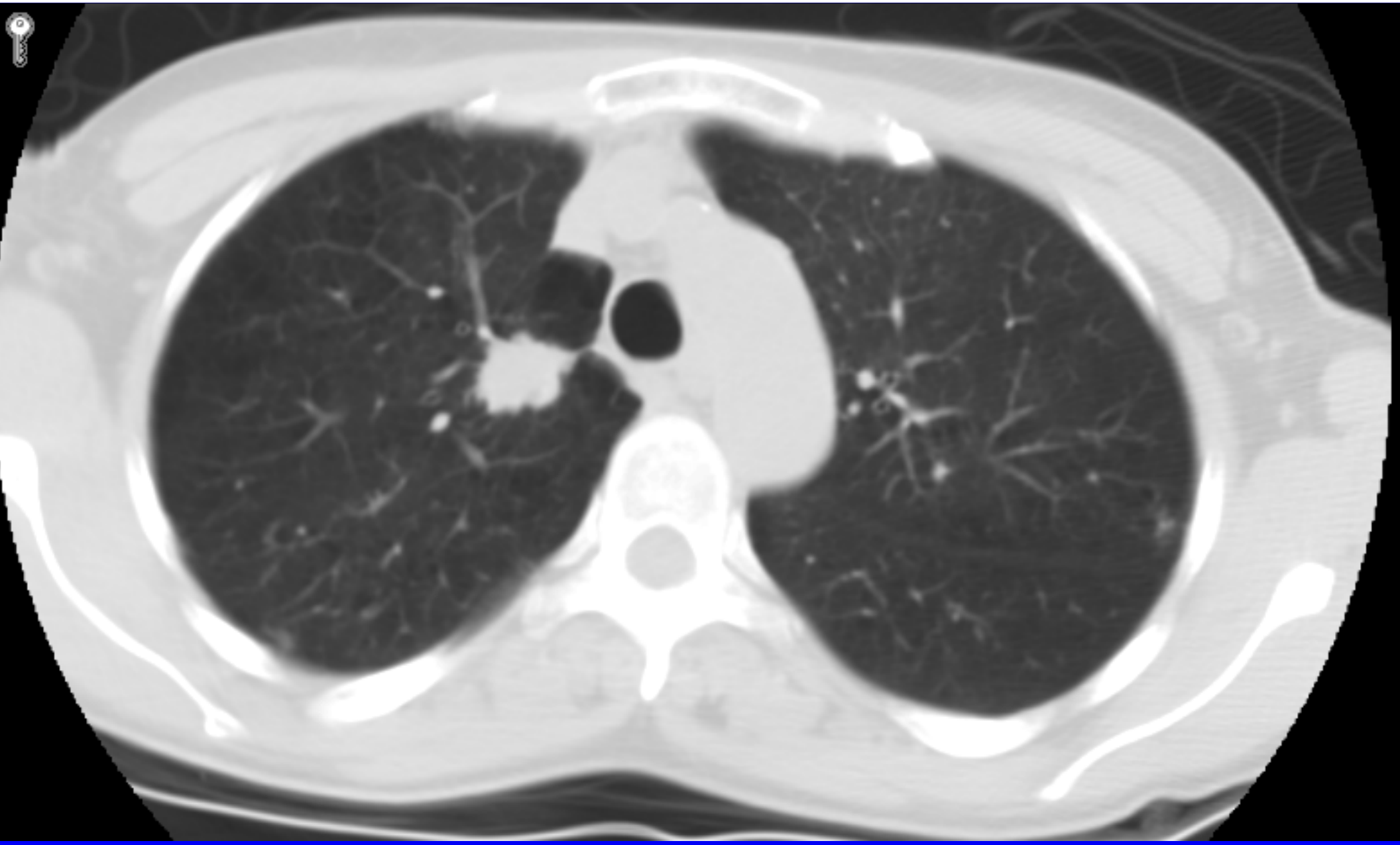

A
Stage-Specific Survival
Proposed TNM Revisions
Goldstraw P et al
J Thorac Oncol 2007;2:706
Deaths / N
MST
5-Year
IA 1168 / 3666 119 73%
IB 2231 / 4426 70 54%
63%
IIA 306 / 562 54 48%
IIB 1951 / 2982 33 38%
42%
IIIA 2348 / 3091 23 25%
IIIB 838 / 1042 16 19%
IV 146 / 183 18 21%
100%
80%
60%
40%
20%
0%
0
2
4
6
8
10
Survival, Years
Staging categories different
Outcomes are the same

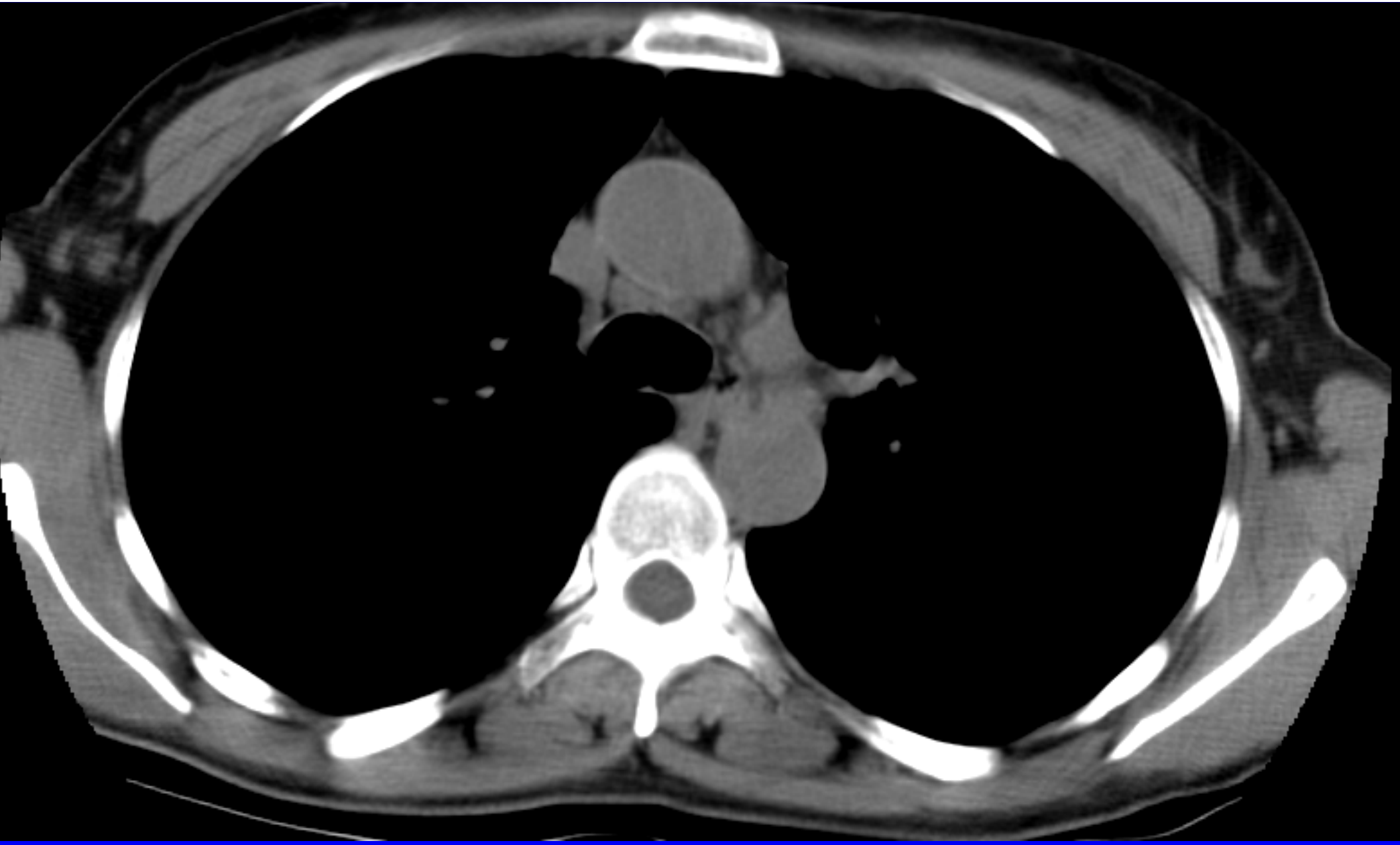
Staging

- Radiologic staging
- Minimally invasive surgical staging
- Biologic staging

Clinical Scenario

- 56 yo woman, former smoker, new pulmonary nodule
- No weight loss, no symptoms
- CT: 1.5 cm nodule, no mediastinal adenopathy
- PET: positive in the nodule, negative elsewhere





Clinical Scenario

What is the next step:

a. Follow-up CT scan in 3 months
b. Transthoracic needle aspiration
c. Mediastinoscopy
d. Wedge resection for diagnosis, followed by lobectomy if malignant

Clinical Scenario

What is the next step:

a. Follow-up CT scan in 3 months
b. Transthoracic needle aspiration
c. Mediastinoscopy
d. Wedge resection for diagnosis, followed by lobectomy if malignant

Results

- Pathology

  Multi-station N2 and N3
- Treatment

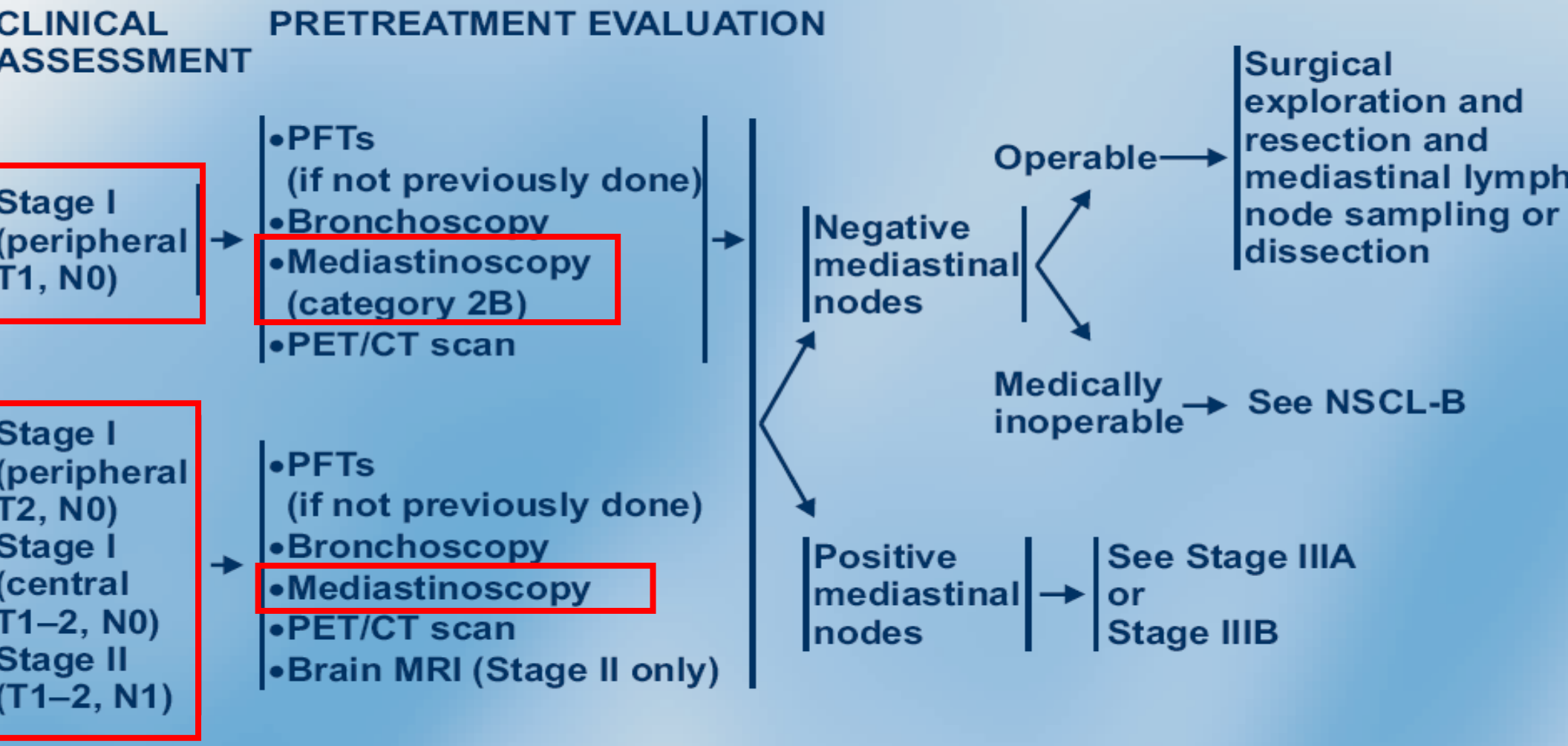
  Definitive chemotherapy and radiation therapy

Early stage lung cancer must be proved to be early stage

NCCN National Comprehensive Cancer Network®

Non-Small Cell Lung Cancer

Clinical Practice Guidelines in Oncology – v.1.2009



NCCN National Comprehensive Cancer Network®

Non-Small Cell Lung Cancer

Clinical Practice Guidelines in Oncology – v.1.2009

Clinical Stage II-III

CLINICAL ASSESSMENT	PRETREATMENT EVALUATION	CLINICAL EVALUATION
Stage IIB (T3, N0) Stage IIIA, IIIB (T3-4, N1)	•PFTs (if not previously done) •Bronchoscopy •Mediastinoscopy •Brain MRI •MRI of spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels •PET/CT scan	Superior sulcus tumor Chest wall Proximal airway or mediastinum Metastatic disease

Mediastinal Staging with PET

Study	N	Sensitivity	Specificity
Iowa (*Ann Thorac Surg* 2002;73:394)	237	82%	82%
Duke University Medical Center (*J Thorac Cardiovasc Surg* 2003; 126: 1900-5)	203	64%	77%
ACOSOG Z0050 (*J Thorac Cardiovasc Surg* 2003;126:1943-1951)	287	61%	84%
	727	68%	81%

Mediastinal Lymph Node Staging

Modality	Stations
Cervical mediastinoscopy	2, 3, 4, 7
EBUS	2, 3, 4, 7
Extended mediastinoscopy	5, 6
Thoracoscopy	Unilateral staging
EUS	7, 8, 9

Nine-year Single Center Experience With Cervical Mediastinoscopy

Lemaire A, et al. Ann Thorac Surg 2006;82:1185-1190

- 2145 consecutive mediastinoscopies (1996-2005)
- 23/2145 patients (1.1%) with complications
  - Hemorrhage 0.3%
  - Vocal cord dysfunction 0.6%
  - Tracheal injury 0.1%
  - Pneumothorax 0.1%
  - Death 0.05%

Nine-year Single Center Experience With Cervical Mediastinoscopy

Lemaire A, et al. Ann Thorac Surg 2006;82:1185-1190

- 26% with lung cancer had + mediastinoscopy
- False negative rate 17/1068 (1.6%)
- 4 false negatives were at level 8 or 9
- Actual false negate rate 1.1%
- Accuracy 99%

Endobronchial Ultrasound FNA of Lymph Nodes In The Radiologically Normal Mediastinum

Krasnik M et al. Eur Respir J 2006; 28:910-914

- NSCLC patients with CT scans showing no enlarged MLN (>1 cm) underwent EBUS-FNA
- 2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, 11L
- All pts underwent subsequent surgical staging
- Diagnoses based on aspiration results were compared with those based on surgical results

Endobronchial Ultrasound FNA of Lymph Nodes In The Radiologically Normal Mediastinum

Krasnik M et al. Eur Respir J 2006; 28:910-914

- In 100 patients, 119 lymph nodes ranging 5–10 mm in size were detected and sampled
- Malignancy was detected in 19 patients but missed in 2; false negative rate 10%
- Sensitivity 92.3%
- Negative predictive 96.3%

EUS-FNA in the Diagnosis and Staging of Lung Cancer and Its Impact on Surgical Staging

Rabe et al. J Clin Oncol 2005; 33:8357-8361

- 242 patients: suspected (n=142) or proven (n=100) lung cancer and enlarged (> 1 cm) MLN scheduled for med (94%) or resection (6%)
- Before surgery, all patients underwent EUS-FNA
- If EUS-FNA established LN metastases, surgical interventions were cancelled (primary end point)

EUS-FNA in the Diagnosis and Staging of Lung Cancer and Its Impact on Surgical Staging

Rabe et al. J Clin Oncol 2005; 33:8357-8361

- EUS-FNA prevented 70% of scheduled surgical procedures because of LN metastases (52%), T4 (4%), T4 and LN metastases (5%), SCLC (8%)
- Sensitivity 91%
- Specificity 100%
- Accuracy 93%
- recommended to completely resected patients (good performance status) with NSCLC Stage II-III (possibly IB if T>4cm or other adverse factors)

Biologic Staging

- Improve measurement of Extent of Disease
- Improve Assessment of Prognosis
- More effective Assignment of Therapy

ORIGINAL ARTICLE

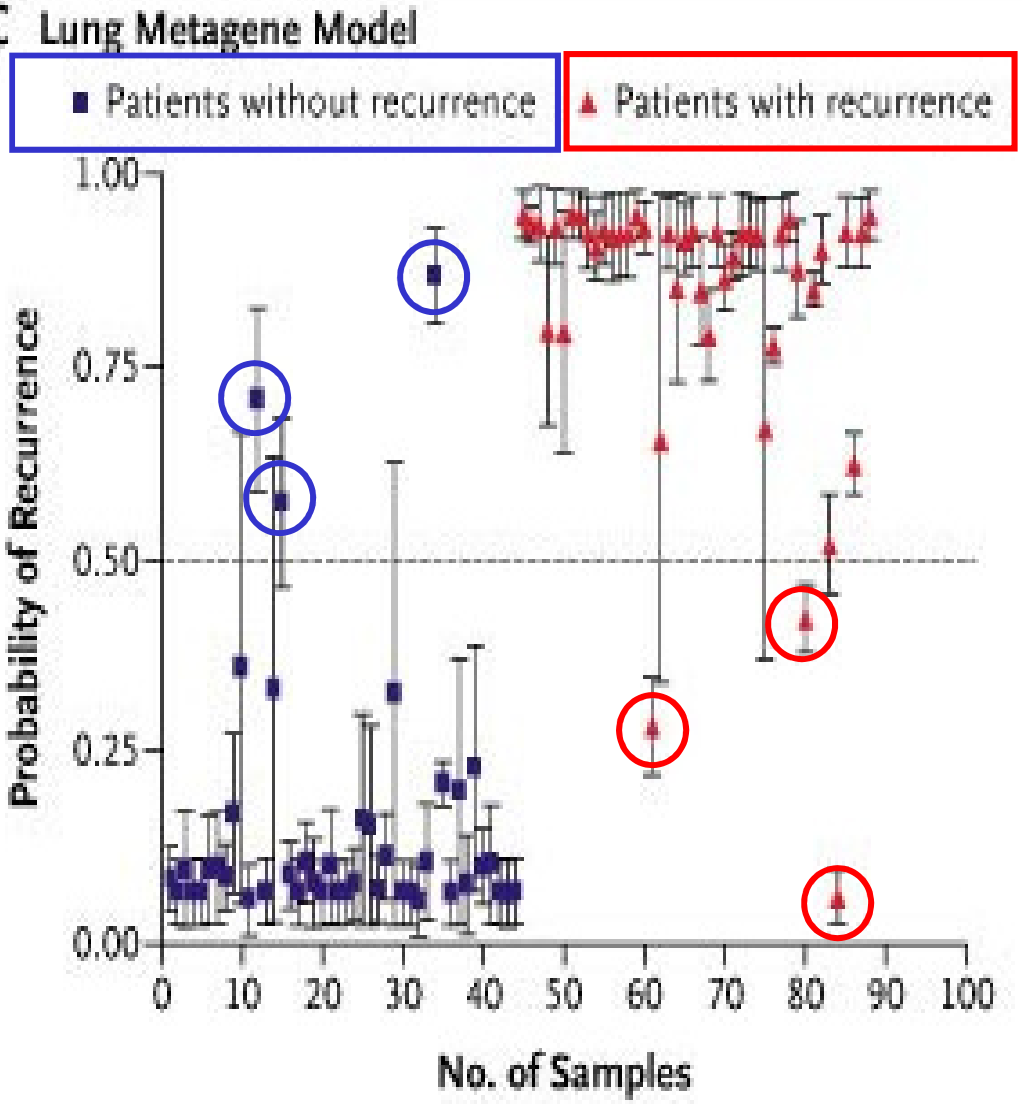
A Genomic Strategy to Refine Prognosis in Early-Stage Non–Small-Cell Lung Cancer

Anil Potti, M.D., Sayan Mukherjee, Ph.D., Rebecca Petersen, M.D., Holly K. Dressman, Ph.D., Andrea Bild, Ph.D., Jason Koontz, M.D., Robert Kratzke, M.D., Mark A. Watson, M.D., Ph.D., Michael Kelley, M.D., Geoffrey S. Ginsburg, M.D., Ph.D., Mike West, Ph.D., David H. Harpole, Jr., M.D., and Joseph R. Nevins, Ph.D.

Potti A, et al. Duke University Medical Center
New Engl J Med 2006;355: 570-80

A Genomic Strategy to Refine Prognosis in Early Stage NSCLC Potti A, et al. New Engl J Med 2006;355: 570-80

- Gene expression profiles assessed to develop a *Meta-gene risk model* in 89 Stage I patients: training set
- Tested in 2 independent cohorts ACOSOG Z0030 (n=25) and CALGB 9761 (n=84): validation sets
- Metagene model predicted recurrence better than pathologic factors

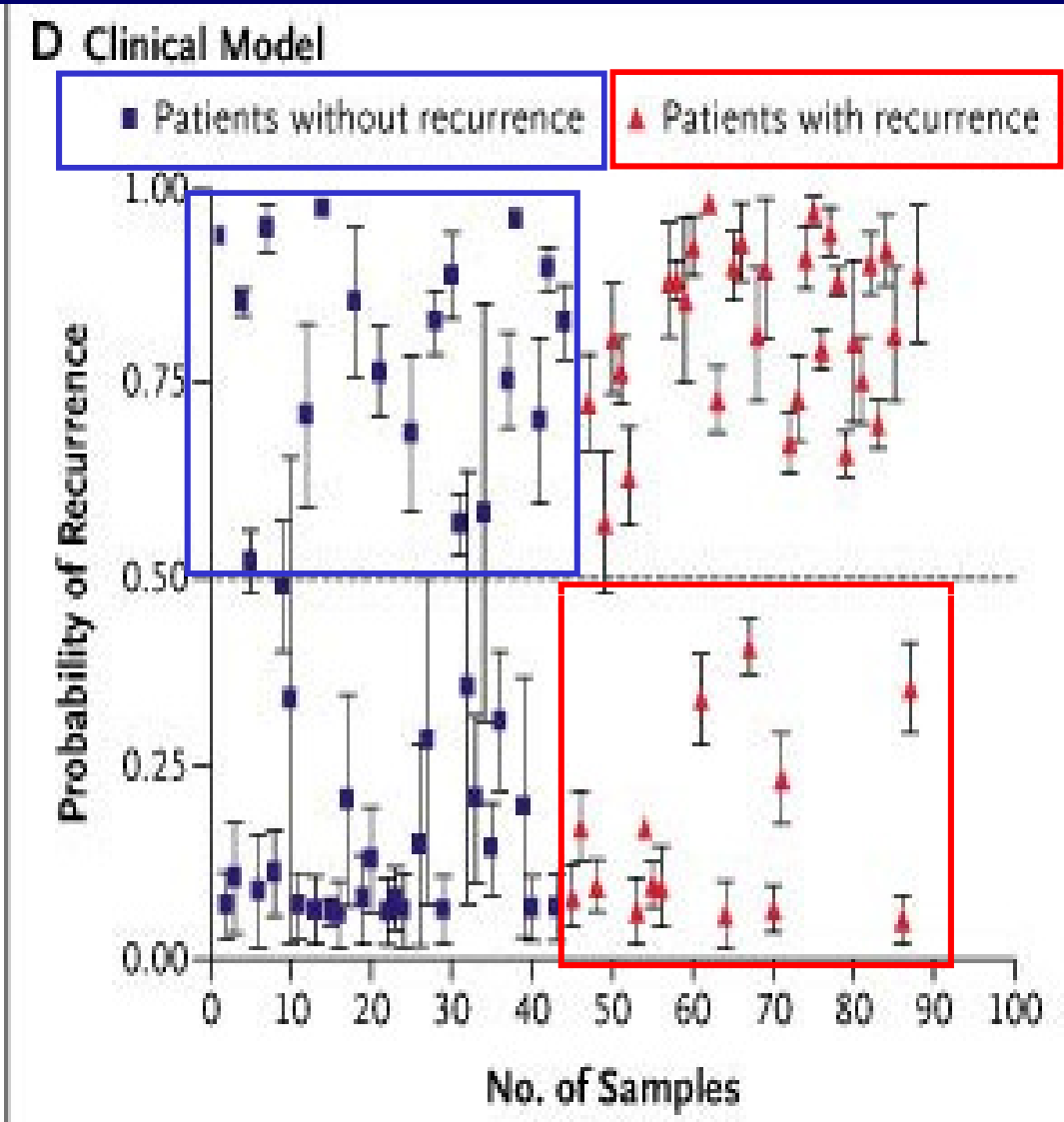


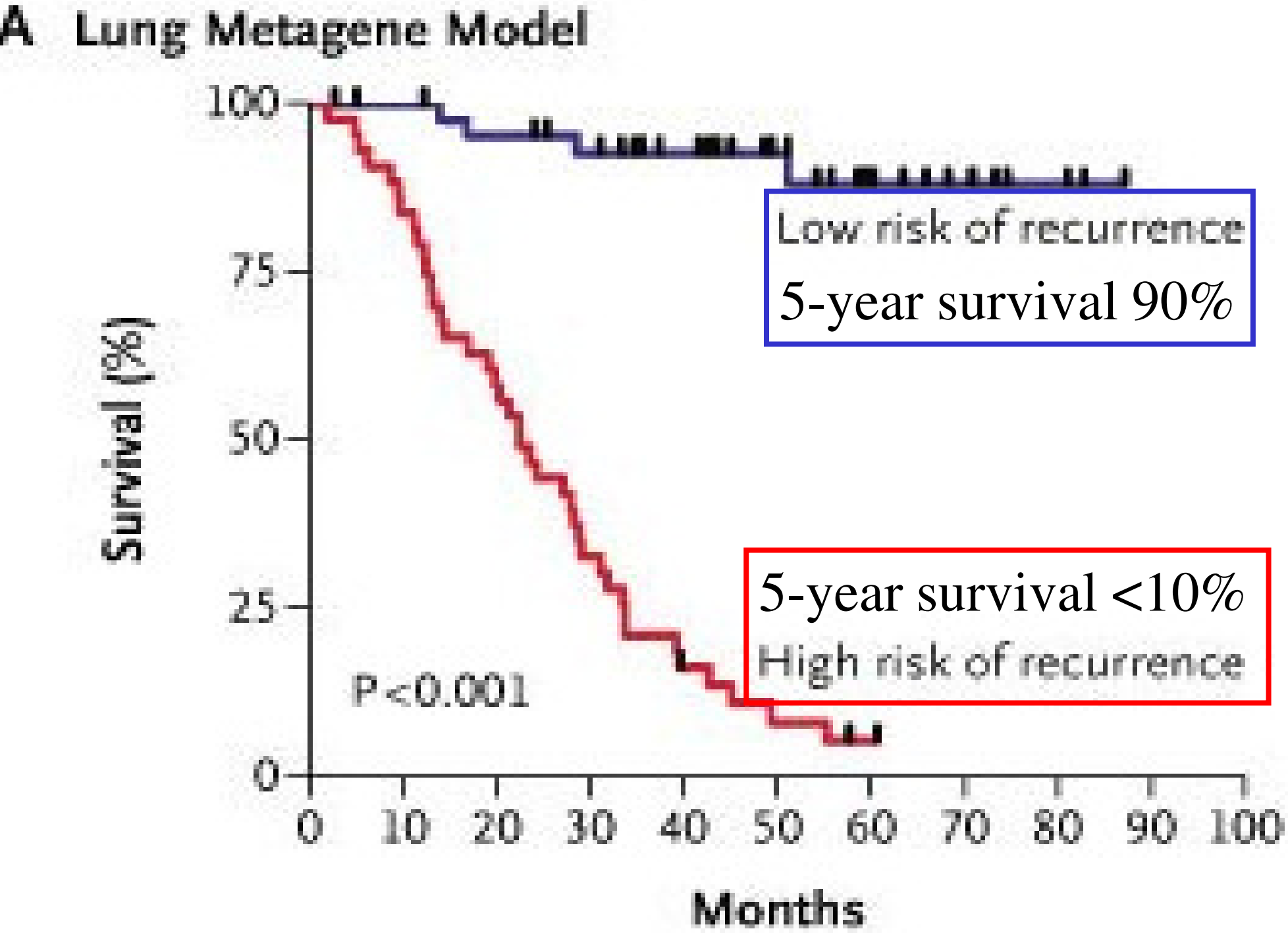
Patients without recurrence: Metagene model correctly predicts "No Recurrence" in all but 3 patients

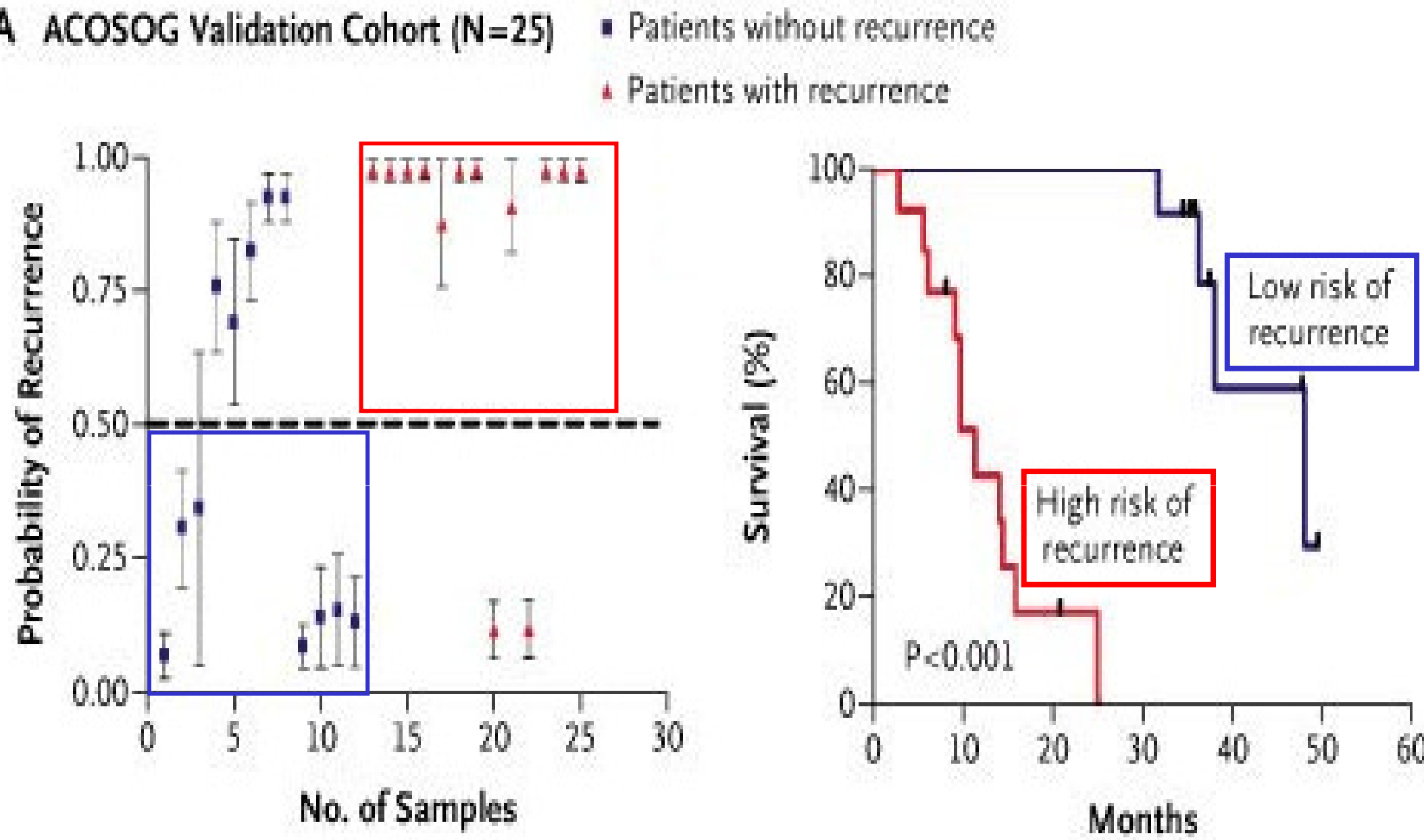
Patients with recurrence: Metagene model correctly predicts "Recurrence" in all but 3 patients

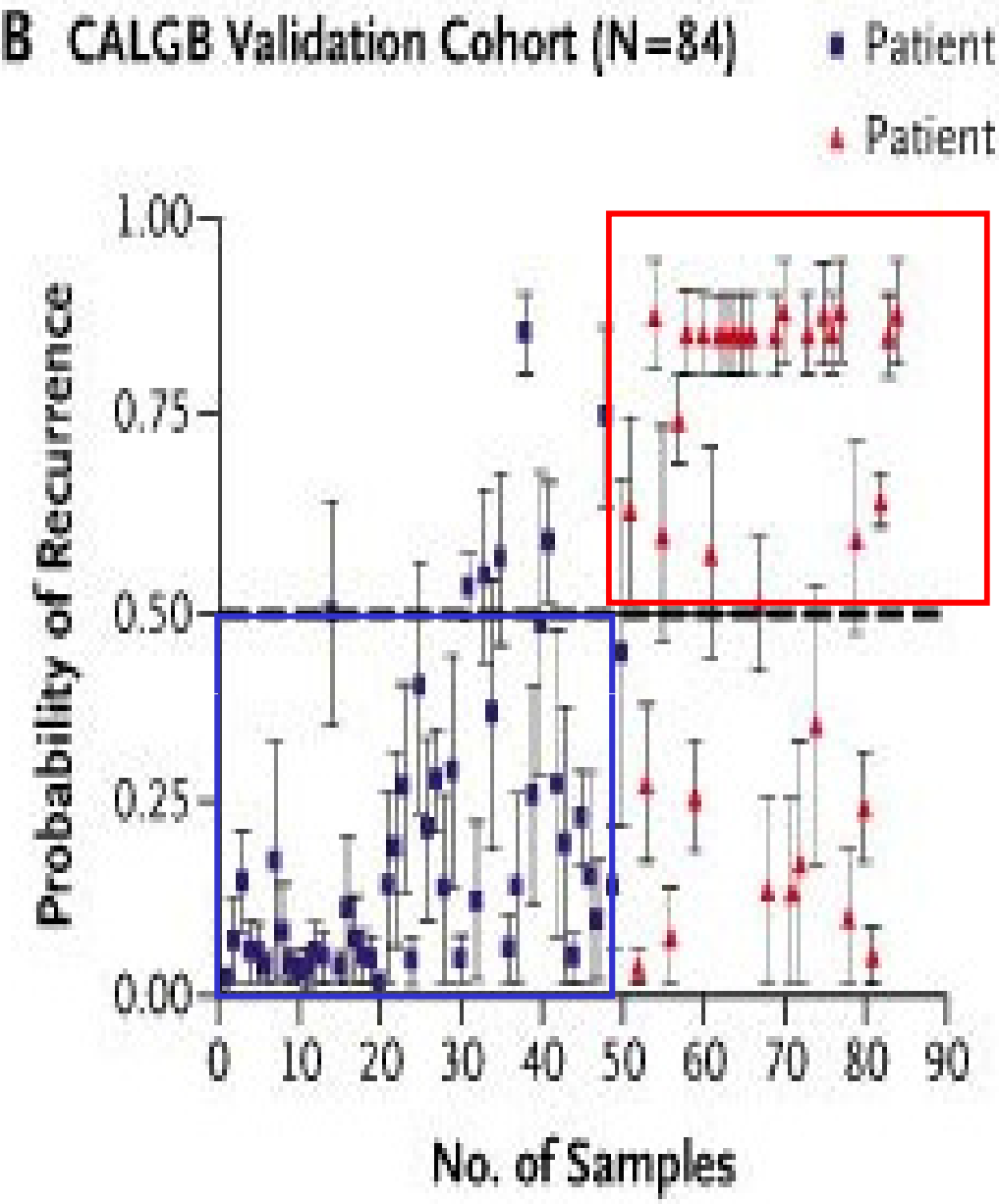
Patients without recurrence: Clinical model correctly predicts “No Recurrence” in <50% patients

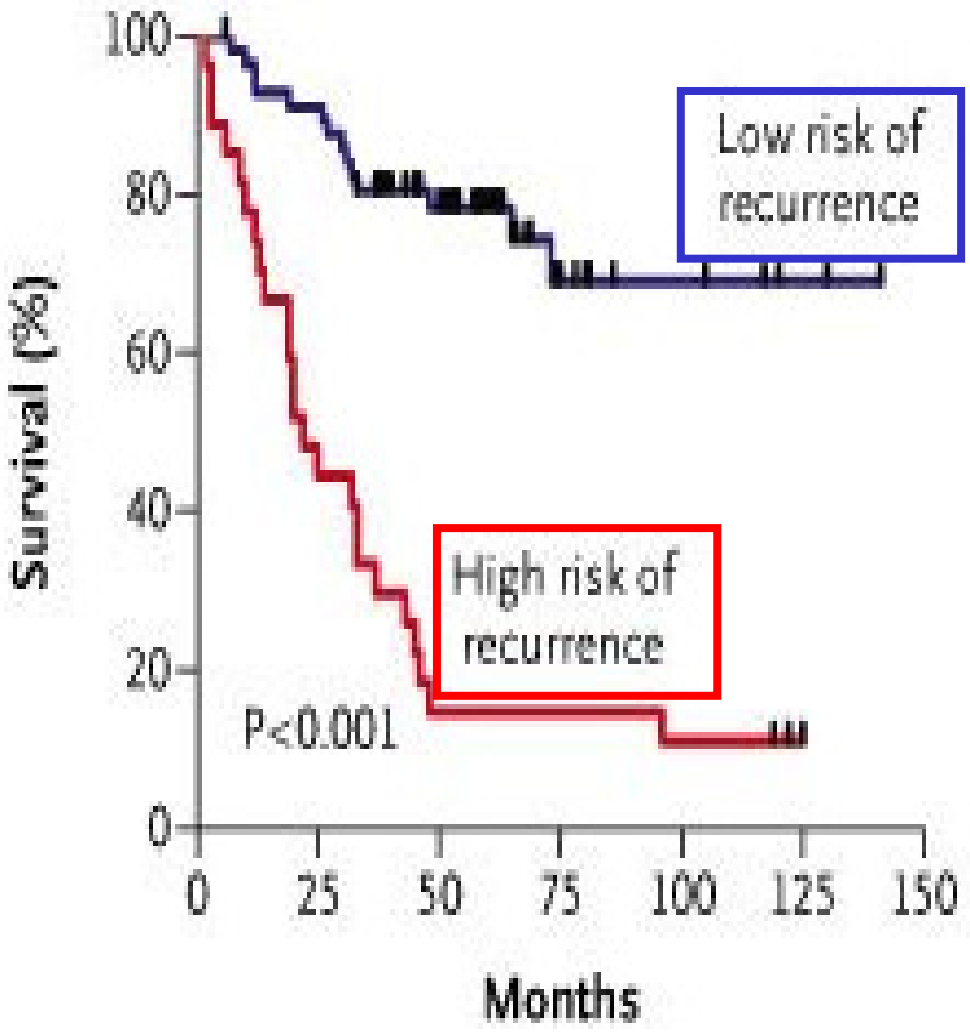
Patients with recurrence: Clinical model correctly predicts “Recurrence” in <50% patients

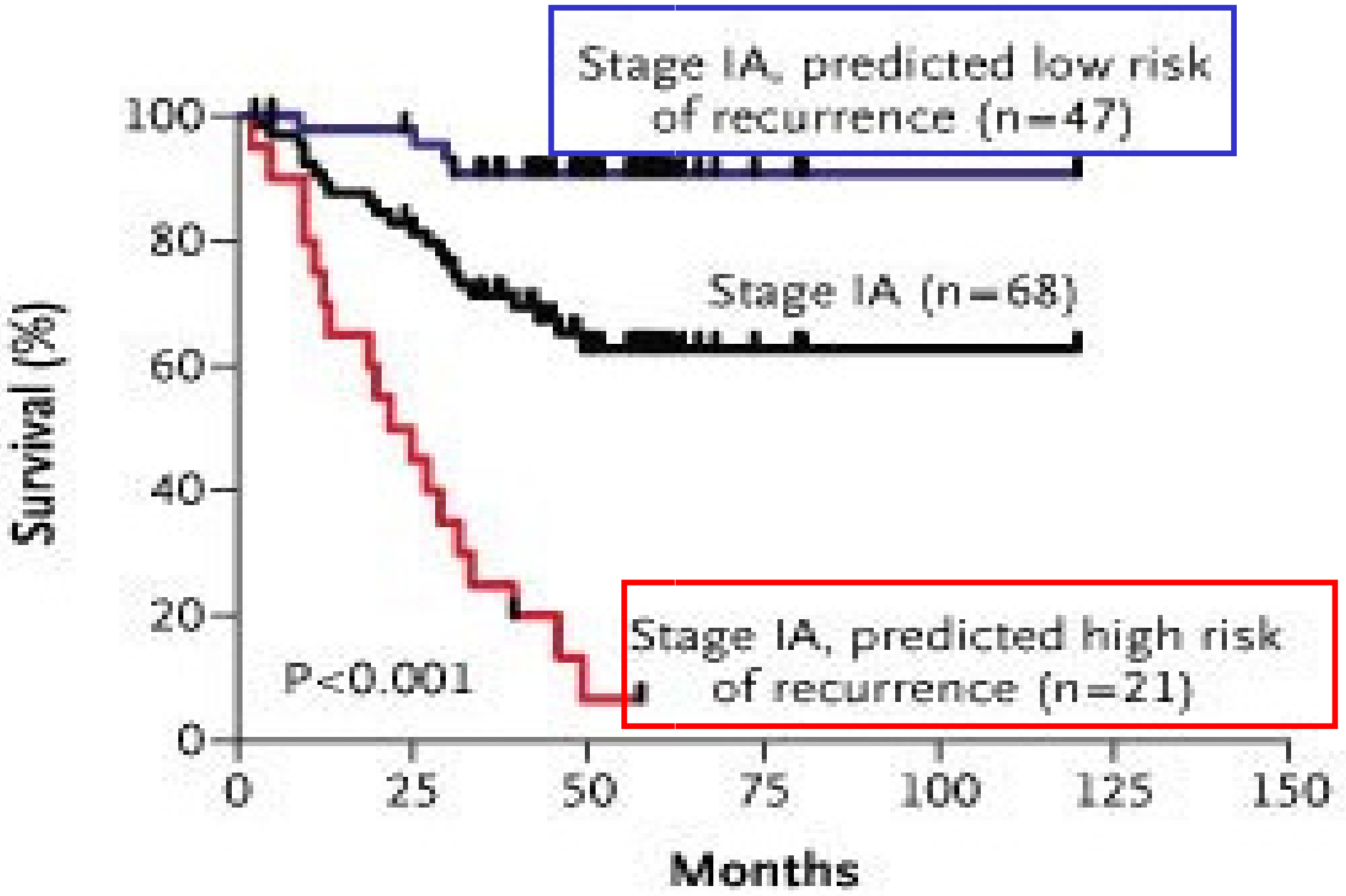



A Lung Metagene Model
100
75
50
25
0
Survival (%)
0
10
20
30
40
50
60
70
80
90
100
Months
P<0.001
Low risk of recurrence
5-year survival 90%
5-year survival <10%
High risk of recurrence


A ACOSOG Validation Cohort (N=25)
Patients without recurrence
Patients with recurrence
Probability of Recurrence
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
30
No. of Samples
Survival (%)
100
80
60
40
20
0
Low risk of recurrence
High risk of recurrence
P<0.001
0
10
20
30
40
50
60
Months

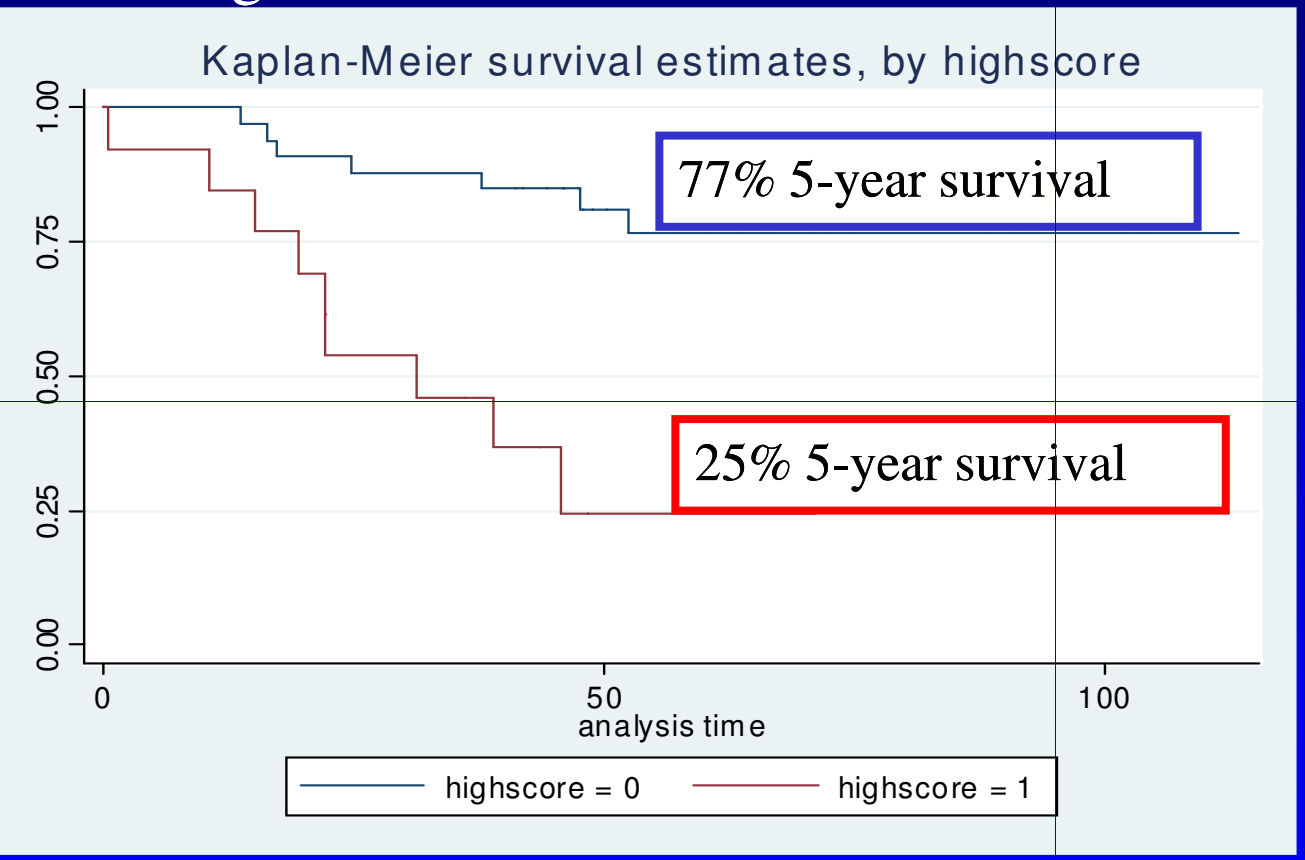

B CALGB Validation Cohort (N=84)
Patients without recurrence
Patients with recurrence
Probability of Recurrence
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60 70 80 90
No. of Samples


Survival (%)
100
80
60
40
20
0
Low risk of recurrence
High risk of recurrence
P<0.001
0 25 50 75 100 125 150
Months


Stage IA, predicted low risk of recurrence (n=47)
Stage IA (n=68)
Stage IA, predicted high risk of recurrence (n=21)
P<0.001
Survival (%)
100
80
60
40
20
0
0
25
50
75
100
125
150
Months

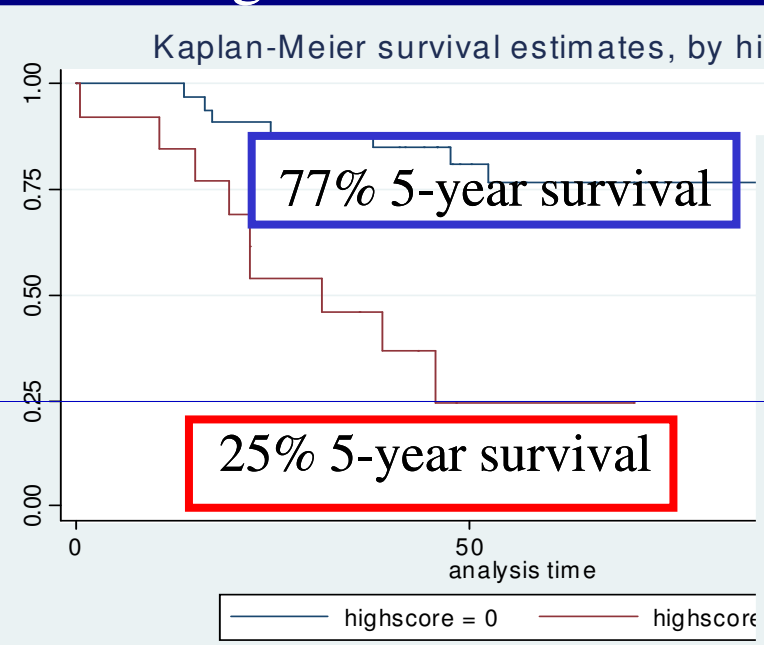
Stage I Adenocarcinoma
RT-PCR 8-gene analysis (UCSF)

Training set

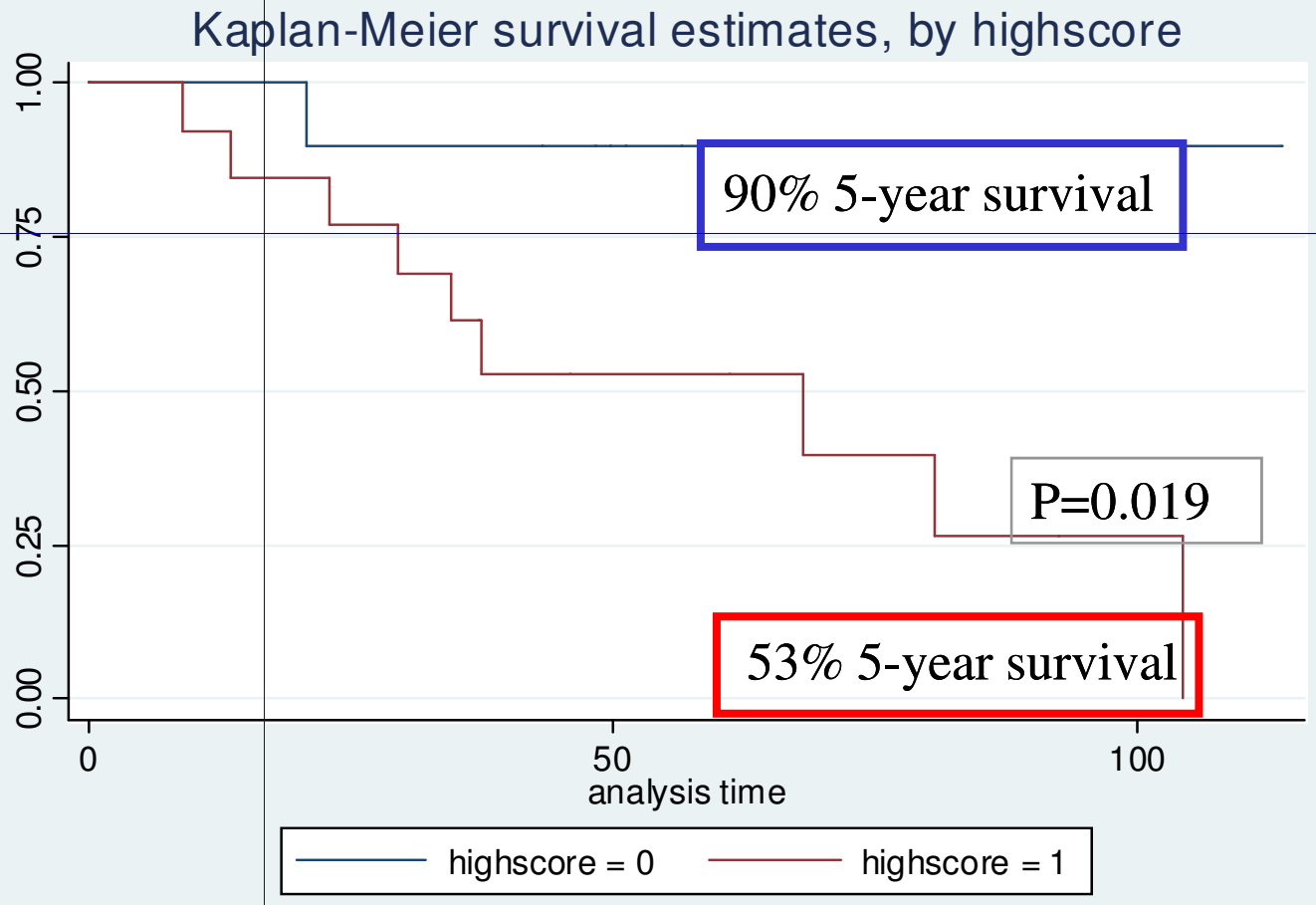


Stage I Adenocarcinoma
RT-PCR 8-gene analysis (UCSF)

Training set



Validation set

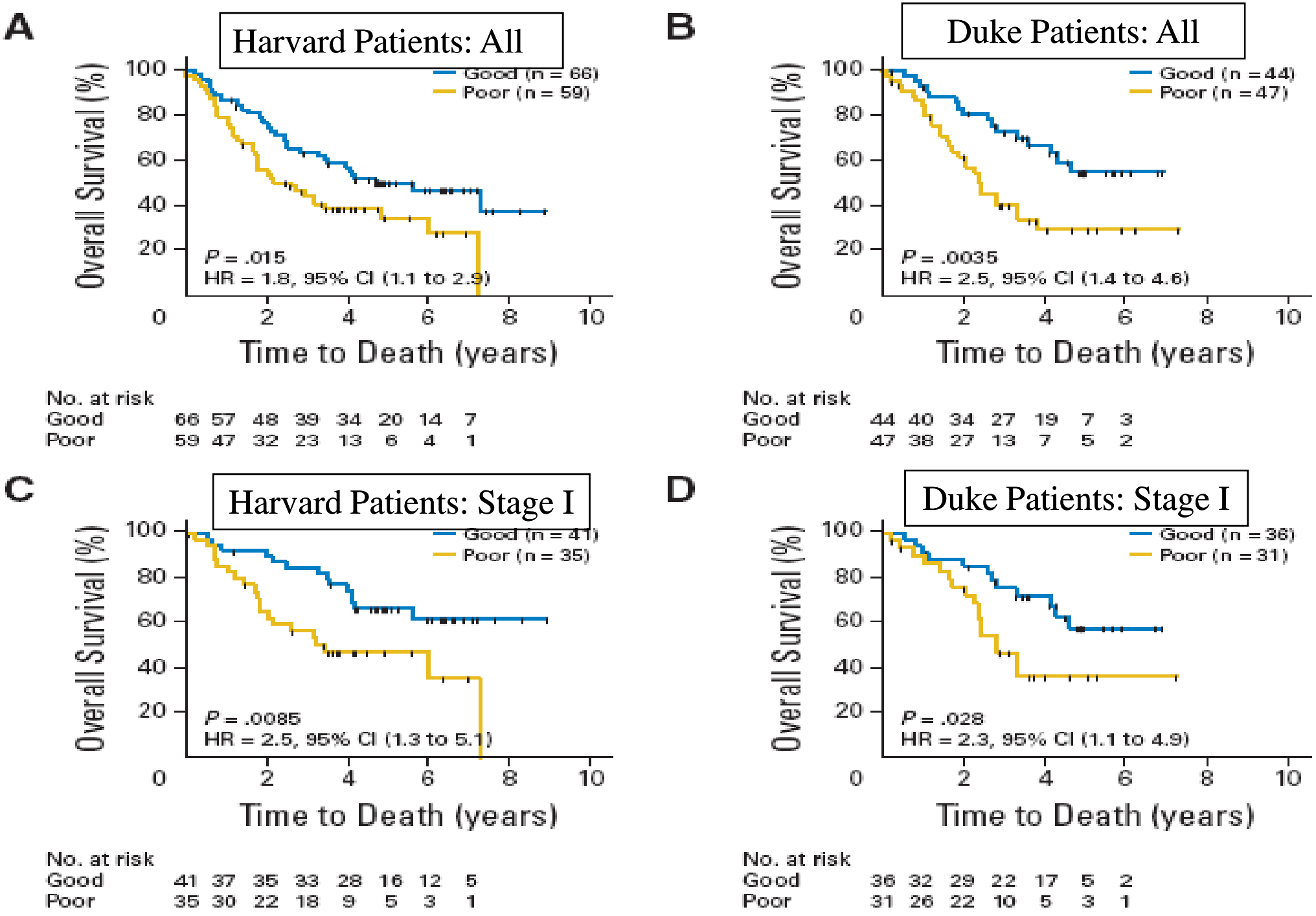


Lung Cancer Staging

3-Gene Prognostic Classifier for Early-Stage NSCLC

Lau et al. J Clin Oncol 2007; 25: 5562-5569

- 158 prognostic genes identified in previous microarray studies analyzed by RT-PCR (n=147)
- Concordance indices and risk scores used to identify a set of genes for risk stratification
- 3-gene classifier (*STX1A*, *HIF1A*, *CCR7*) developed (hazard ratio = 3.8; $P < .001$) to stratify stage I and II patients


A
Harvard Patients: All
Overall Survival (%)
100
80
60
40
20
0
2
4
6
8
10
Time to Death (years)
Good (n = 66)
Poor (n = 59)
P = .015
HR = 1.8, 95% CI (1.1 to 2.9)
No. at risk
Good 66 57 48 39 34 20 14 7
Poor 59 47 32 23 13 6 4 1
B
Duke Patients: All
Overall Survival (%)
Time to Death (years)
Good (n = 44)
Poor (n = 47)
P = .0035
HR = 2.5, 95% CI (1.4 to 4.6)
No. at risk
Good 44 40 34 27 19 7 3
Poor 47 38 27 13 7 5 2
C
Harvard Patients: Stage I
Overall Survival (%)
Time to Death (years)
Good (n = 41)
Poor (n = 35)
P = .0085
HR = 2.5, 95% CI (1.3 to 5.1)
No. at risk
Good 41 37 35 33 28 16 12 5
Poor 35 30 22 18 9 5 3 1
D
Duke Patients: Stage I
Overall Survival (%)
Time to Death (years)
Good (n = 36)
Poor (n = 31)
P = .028
HR = 2.3, 95% CI (1.1 to 4.9)
No. at risk
Good 36 32 29 22 17 5 2
Poor 31 26 22 10 5 3 1

A Multigene Assay Is Prognostic of Survival in Patients with Early-Stage Lung Adenocarcinoma

Raz et al *Clinical Cancer Research* 14, 5565-5570

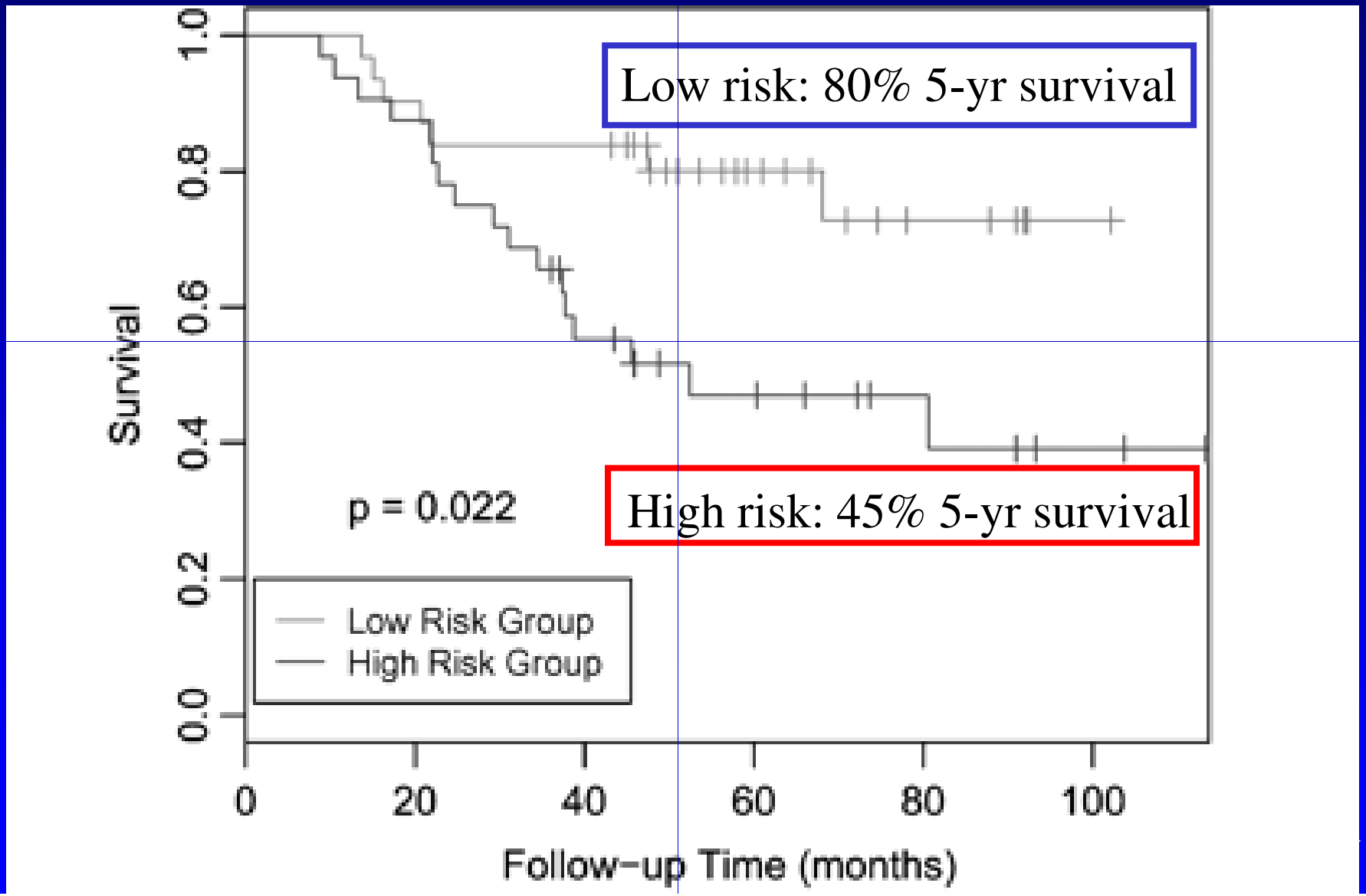
- 107 patients with adenocarcinoma, RT-PCR
- 4-gene model: *WNT3a, ERBB3, LCK, RND3*
- Predicted mortality better than clinical stage or tumor size (hazard ratio 6.7; $P = 0.001$)
- 5-year survival in 70 pts with stage I:

  87% with low-risk scores

  38% with high-risk scores ($P = 0.0002$)

A Five-gene Signature In NSCLC

Chen et al N Engl J Med 2007;356:11–20

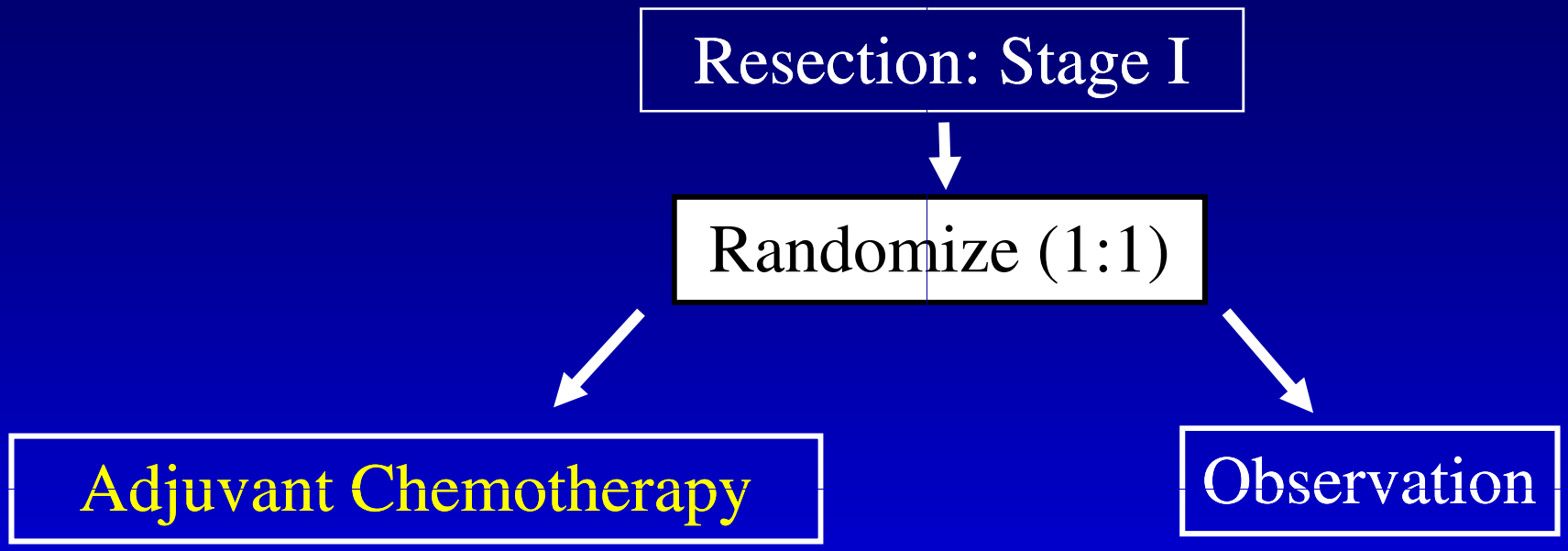


Selecting Patients Who Need No Further Therapy

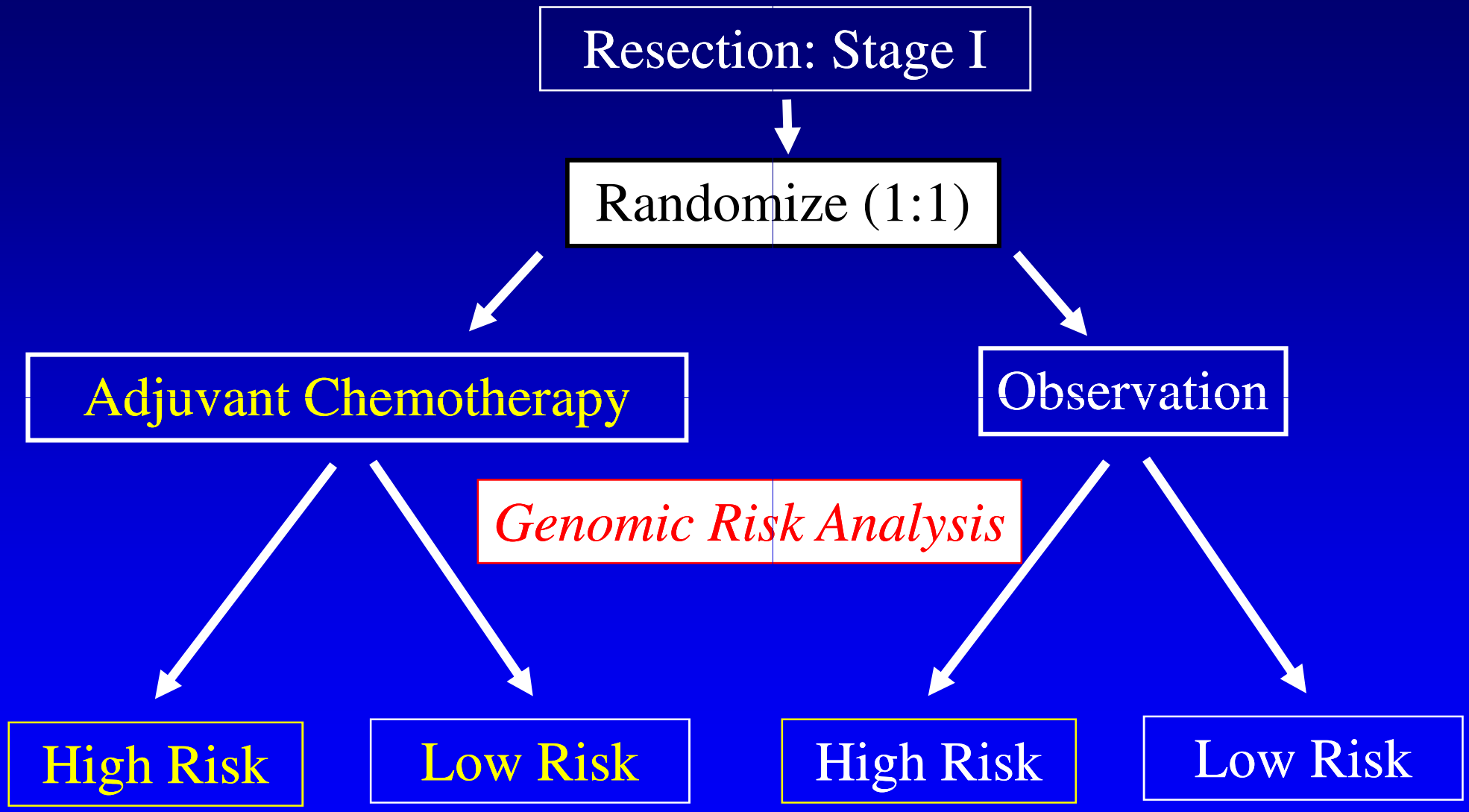
- Gene expression profiling and PCR techniques successfully stratify patients with early stage lung cancer into low-risk and high-risk sub-groups (at least 5 studies)

- The efficacy of adjuvant therapy in “high-risk” early-stage patients has not been tested

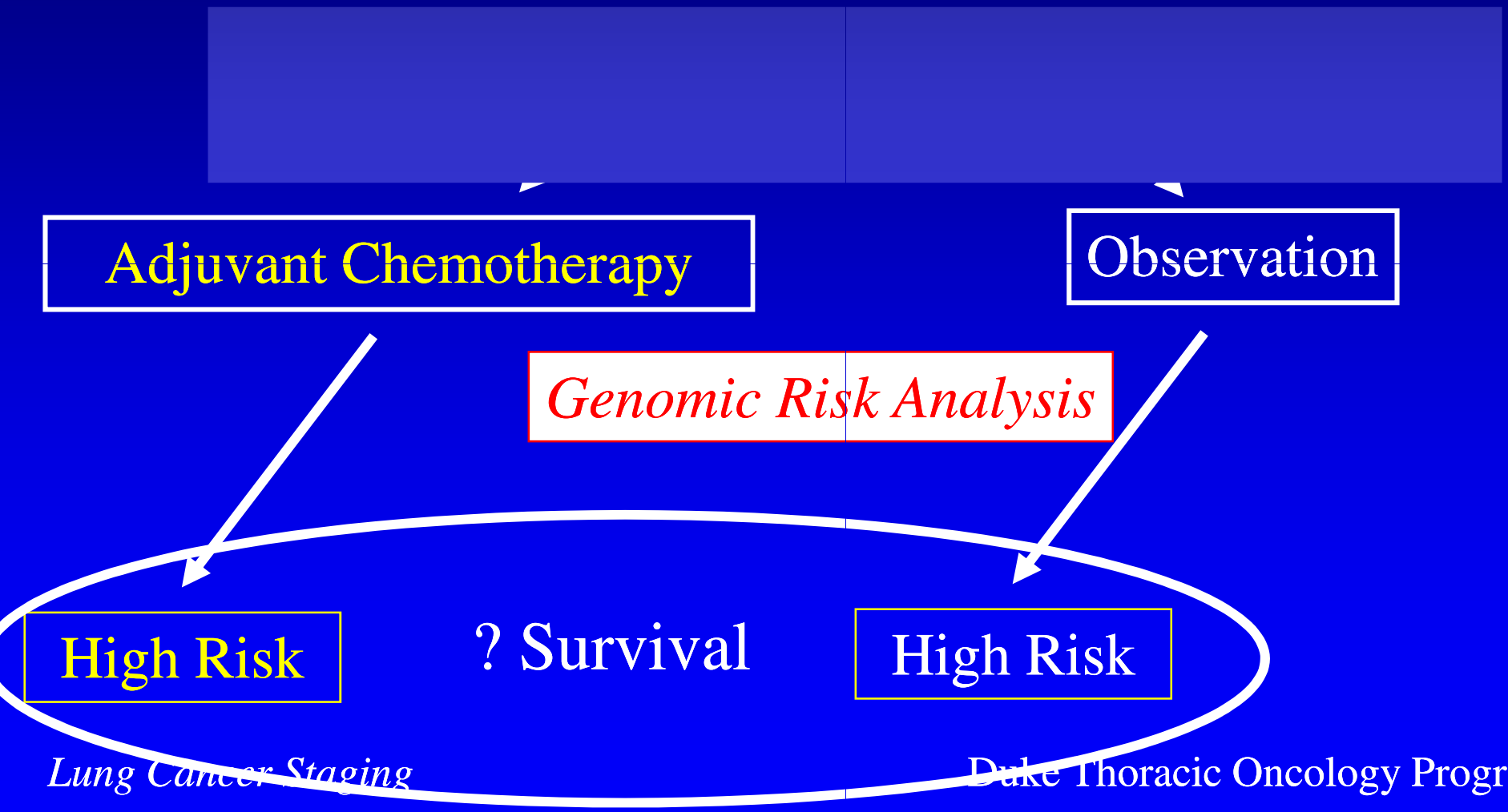
CALGB 30506


Resection: Stage I
Randomize (1:1)
Adjuvant Chemotherapy
Observation

CALGB 30506


Resection: Stage I
Randomize (1:1)
Adjuvant Chemotherapy
Observation
Genomic Risk Analysis
High Risk
Low Risk
High Risk
Low Risk

Does adjuvant chemotherapy improve the survival of high-risk patients identified by gene expression profiling?

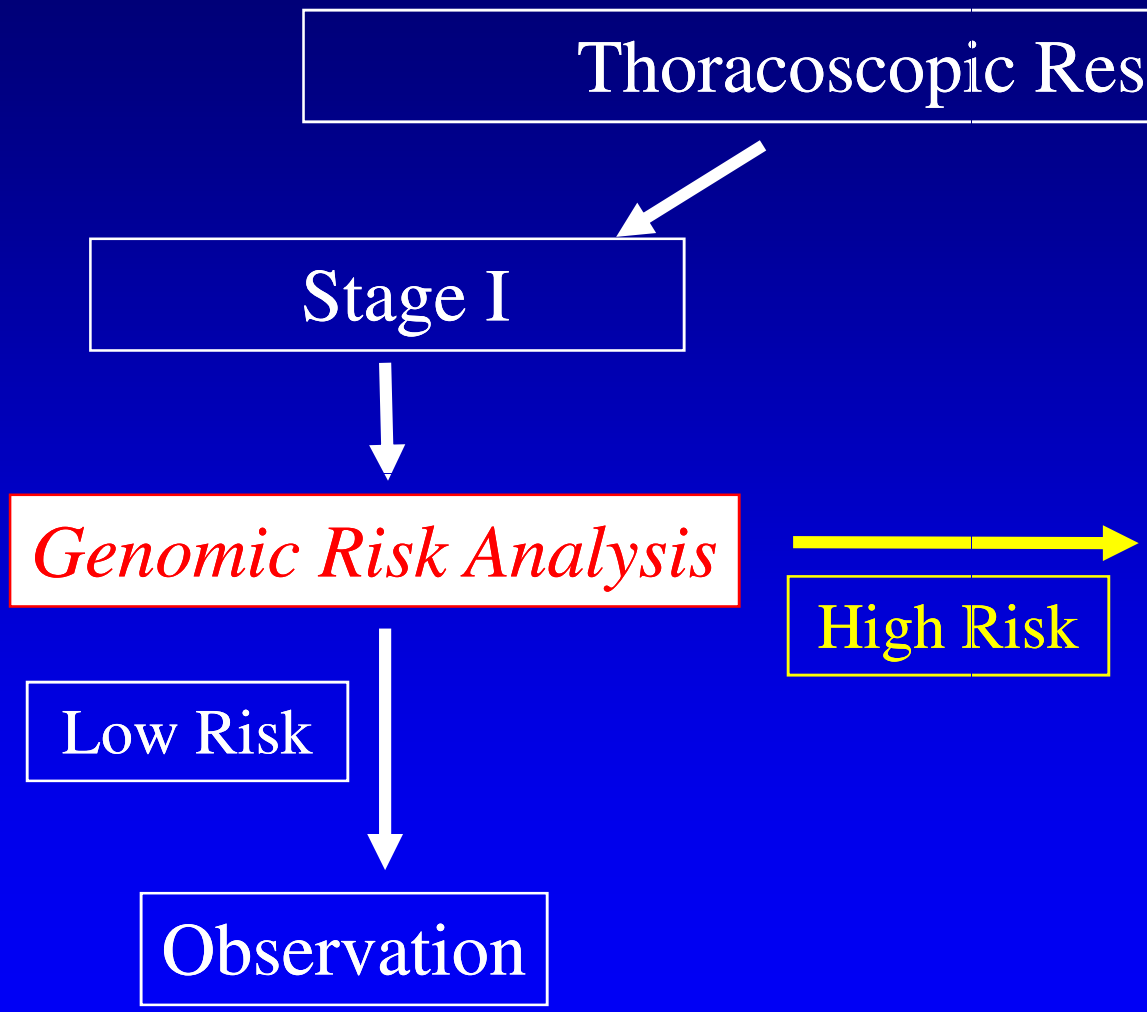


Biologic Staging: Summary

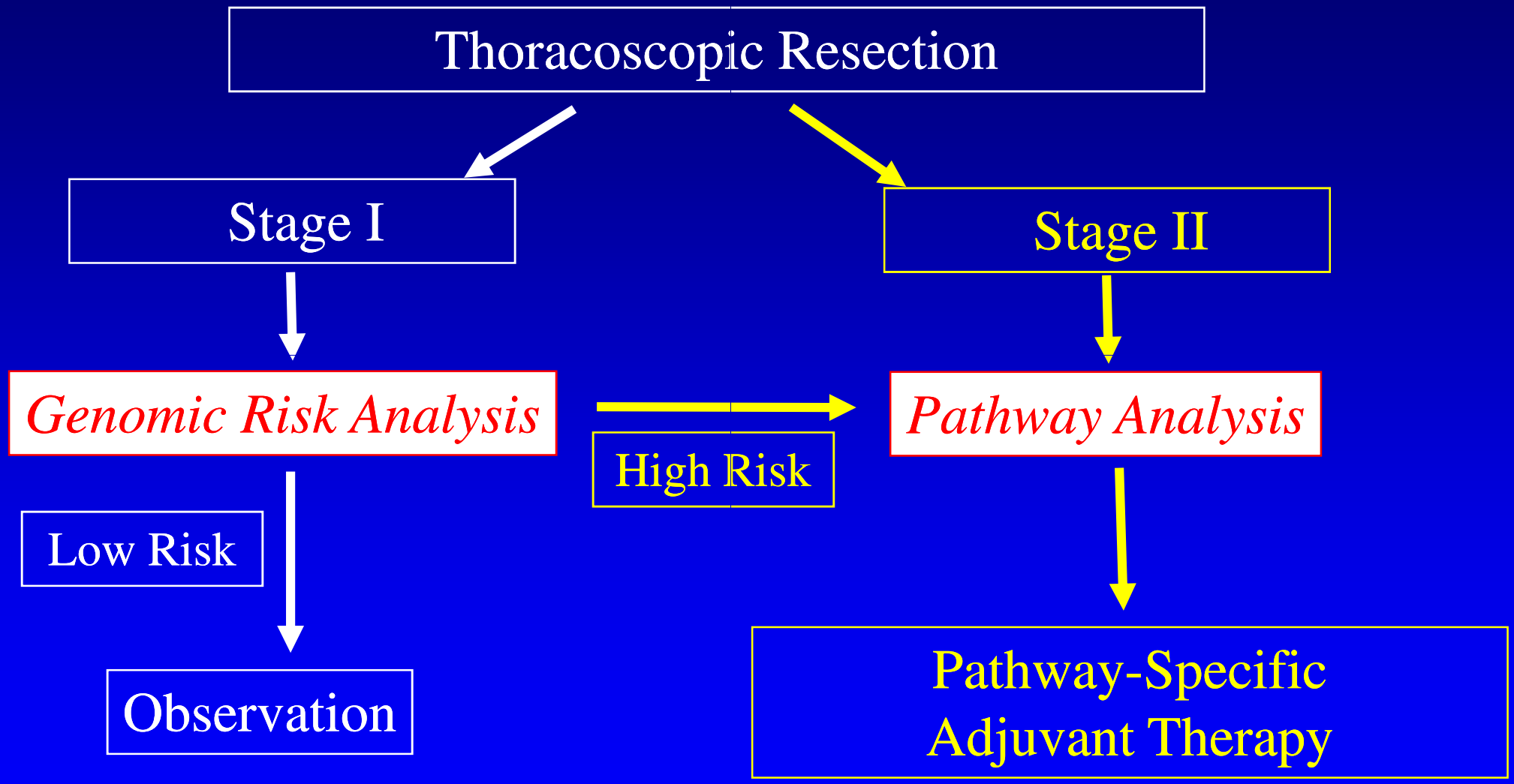
Genomic strategies will *improve outcomes:*

- More accurate risk stratification
- Better patient selection for surgery and adjuvant therapy
- Better selection of specific chemotherapy agents based on sensitivity pathways

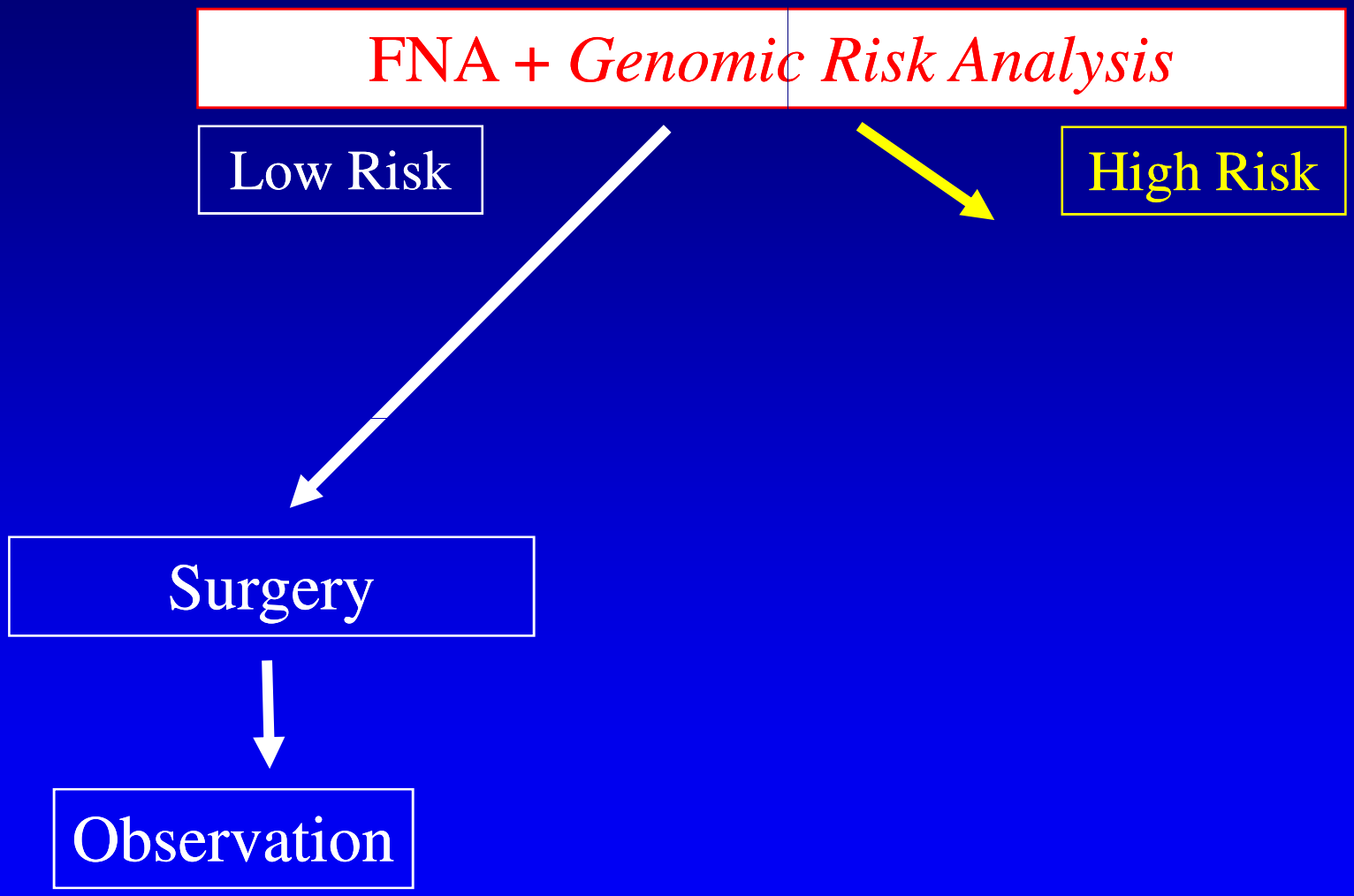
Management of Early Stage Lung Cancer



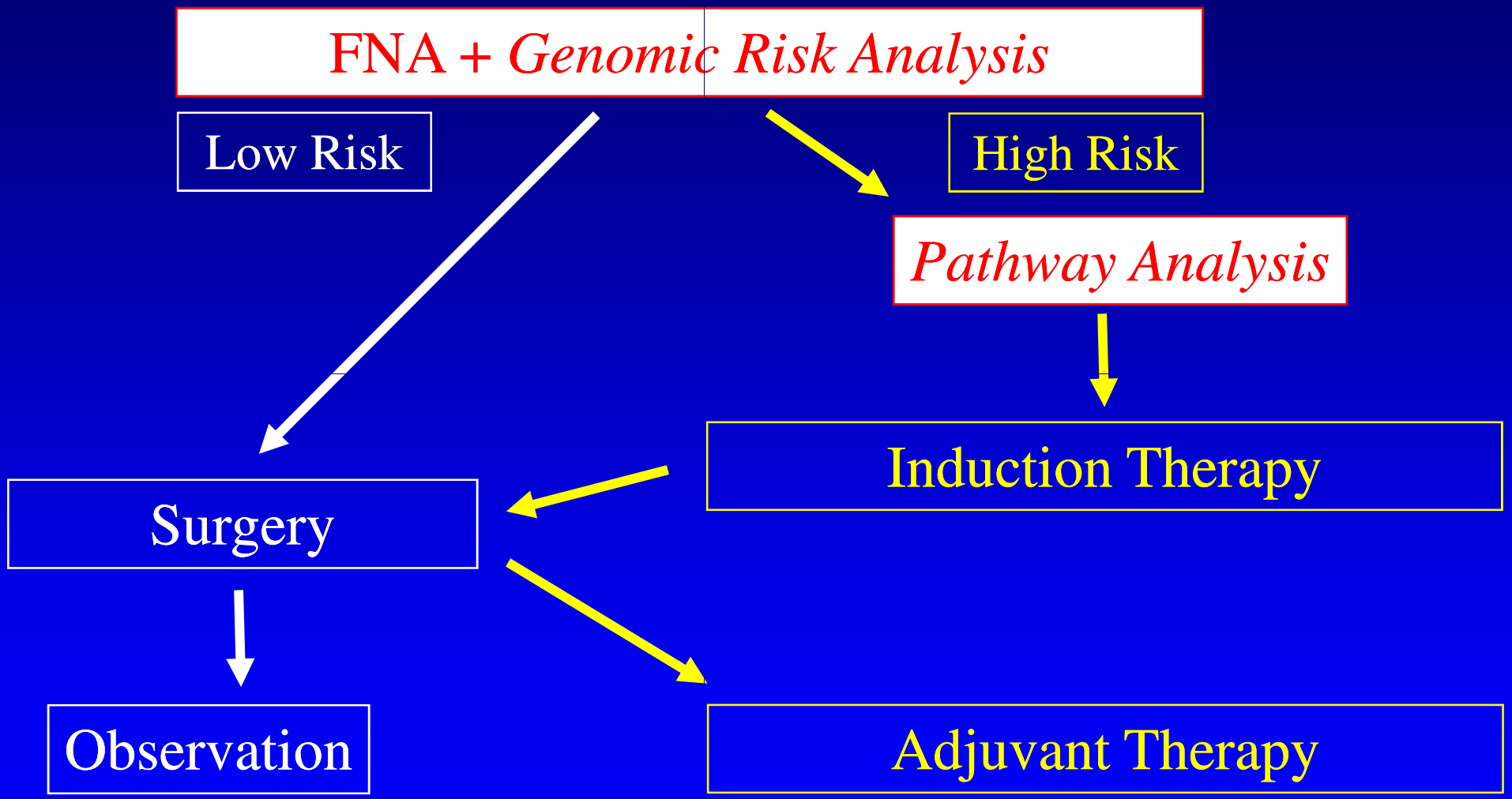
Management of Early Stage Lung Cancer



Management of Early Stage Lung Cancer



Management of Early Stage Lung Cancer



Future

- Condensing genomic analysis of tissue for widespread use
- Integration of biologic variables in the TNM system

13th World Conference on Lung Cancer

July 31 - August 4, 2009 San Francisco, CA