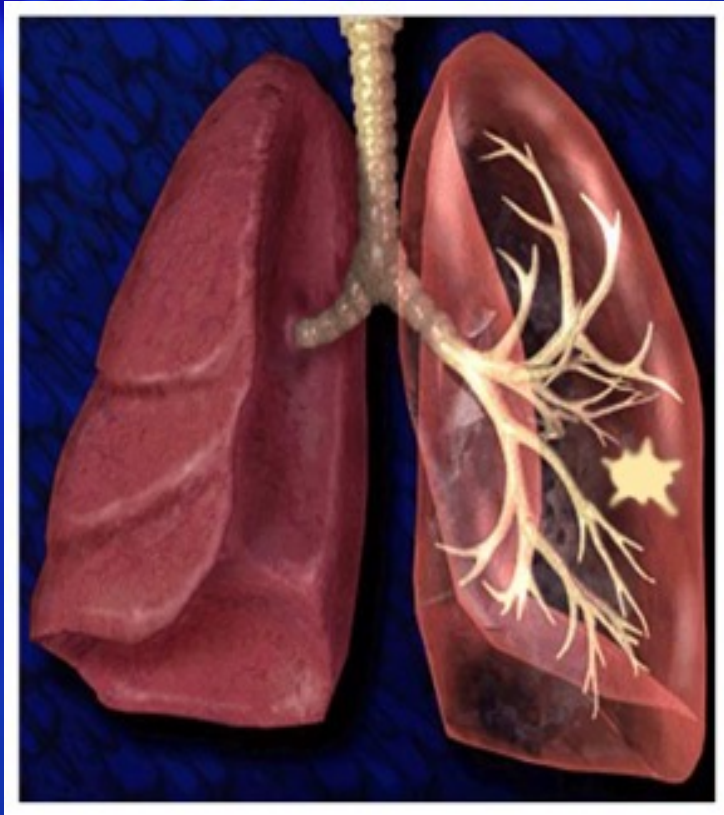


Lung Cancer

Clinical and Biological Considerations



Chumy Nwogu, MD, PhD
Professor of Oncology and
Surgery
Thoracic Surgery Dept



Outline


- **Epidemiology**
- **Clinical Presentation**
- **Disease staging**
- **Screening**
- **Overview of Treatment**
 - **Targeted therapy**

Histologic Types of Lung Ca


- **Small Cell Ca – 15%**
- **Non-Small Cell Ca – 85%**
 - **Adenocarcinoma**
 - **Squamous Cell Ca**
 - **Large Cell Ca**
 - **Others**
 - **Bronchioloalveolar, Carcinoid, Adenosquamous, etc**

Incidence & Mortality 2016

Estimated New Cases

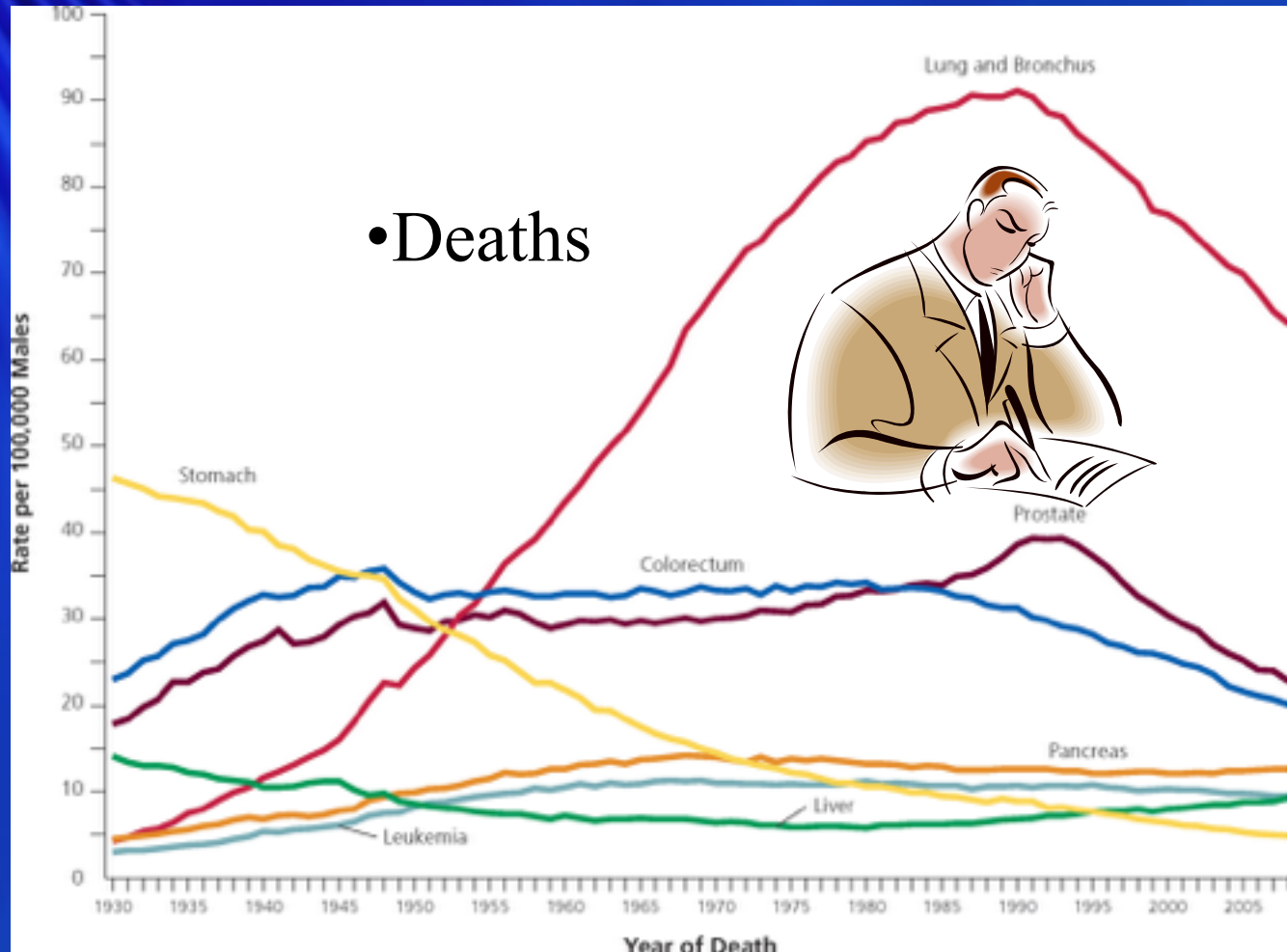
		Males		Females		
Prostate	180,890	21%		Breast	246,660	29%
Lung & bronchus	117,920	14%		Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%		Colon & rectum	63,670	8%
Urinary bladder	58,950	7%		Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%		Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%		Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%		Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%		Leukemia	26,050	3%
Leukemia	34,090	4%		Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%		Kidney & renal pelvis	23,050	3%
All Sites	841,390	100%	All Sites	843,820	100%	

Estimated Deaths

		Males		Females		
Lung & bronchus	85,920	27%		Lung & bronchus	72,160	26%
Prostate	26,120	8%		Breast	40,450	14%
Colon & rectum	26,020	8%		Colon & rectum	23,170	8%
Pancreas	21,450	7%		Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%		Ovary	14,240	5%
Leukemia	14,130	4%		Uterine corpus	10,470	4%
Esophagus	12,720	4%		Leukemia	10,270	4%
Urinary bladder	11,820	4%		Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%		Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%		Brain & other nervous system	6,610	2%
All Sites	314,290	100%	All Sites	281,400	100%	

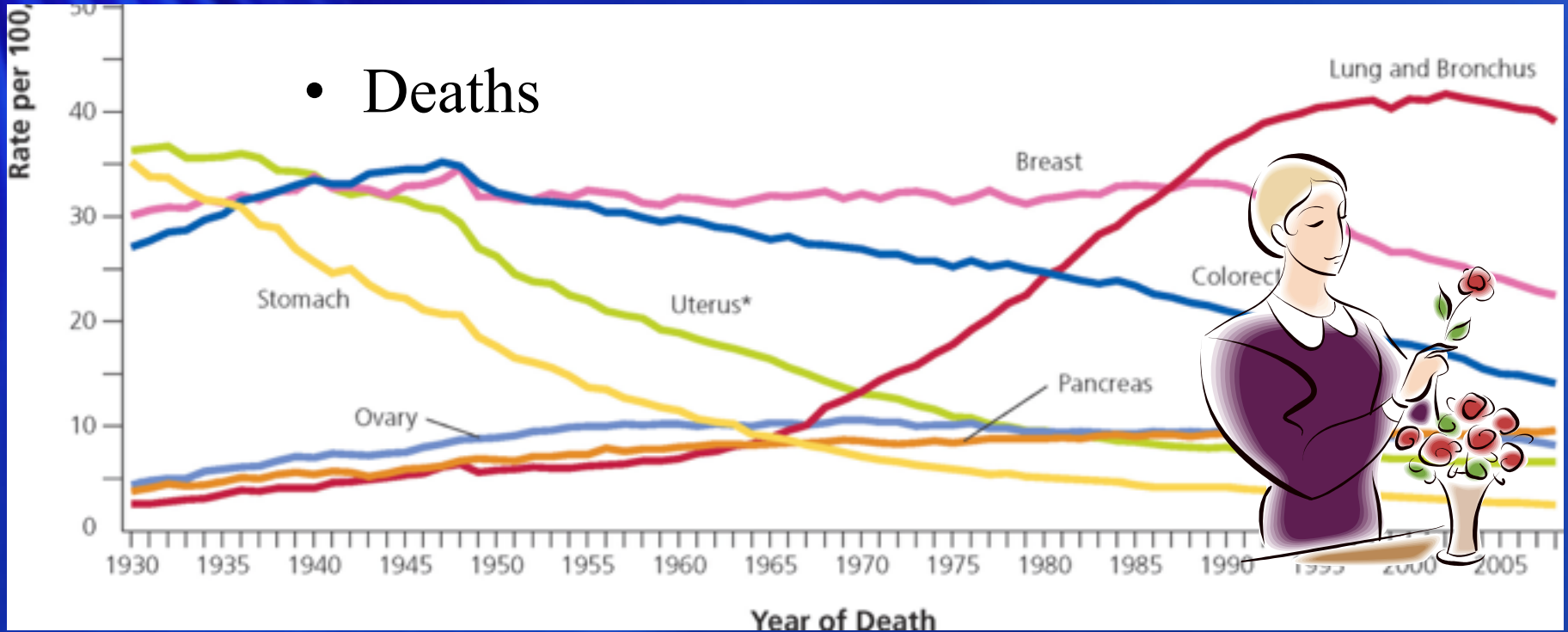
Demographics - Males

- Deaths



Demographics - Females

- Deaths



- 600% rise from 1930 to 1997

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

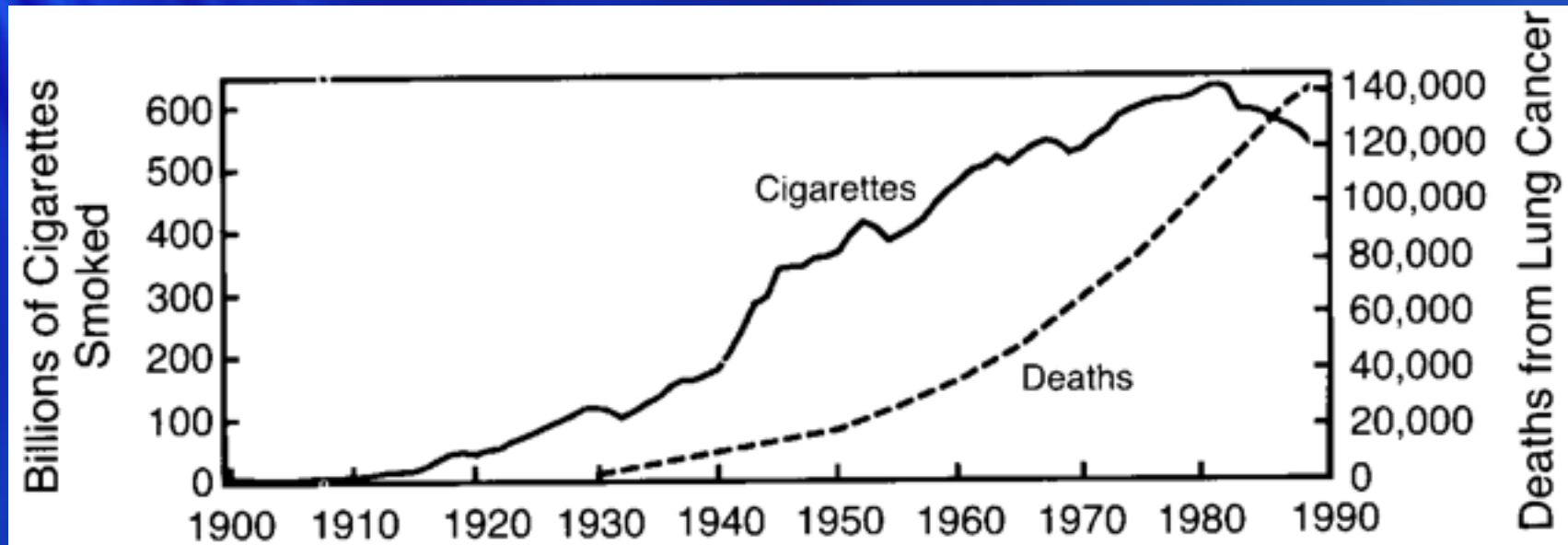
- **Risk Factors**
 - ? **Gender**
 - **Conflicting results**
 - **Race**
 - **↑ risk in African Americans & Native Hawaiians**
 - **Diet**
 - **Fruits & vegetables intake lower the risk**
 - **ID of specific nutritional elements - elusive**
 - **COPD/Pulmonary fibrosis**

Impact of Age

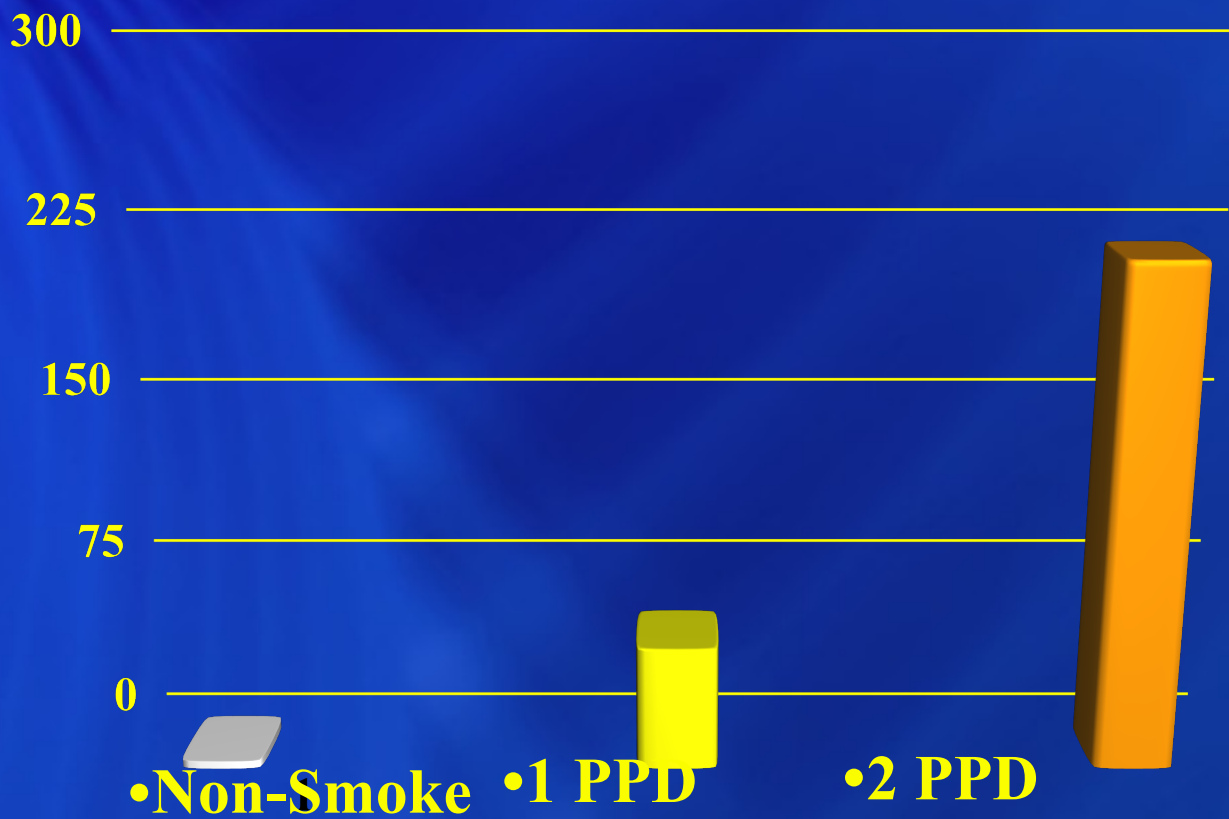
■ **Table 19-5.** INCIDENCE OF MALIGNANCY IN SOLITARY PULMONARY NODULES RELATED TO AGE

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

Smoking and Lung CA



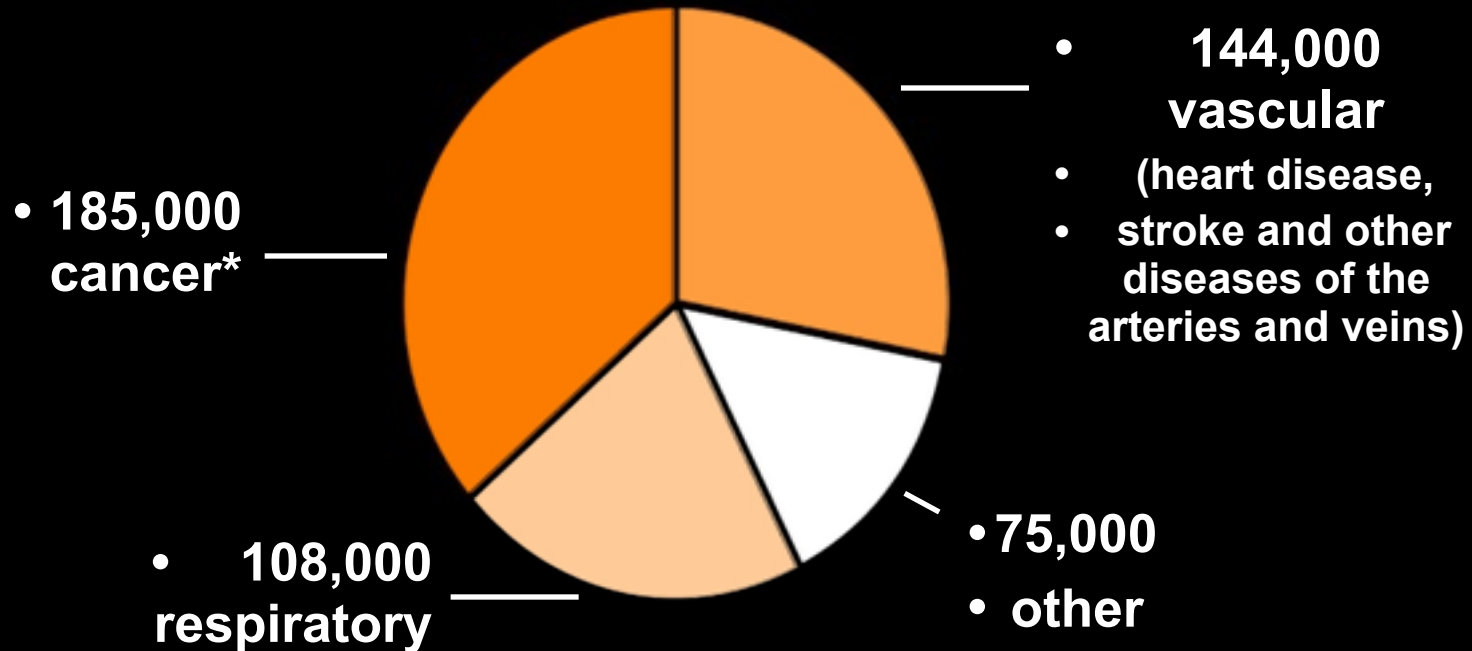
Incidence (per 100,000)





United States, year 2000

Smoking kills 512,000 people a year, from many different diseases



• www.deathsfromsmoking.net

• *includes 138,000 (89%) of the 155,521 lung cancer deaths



About one in three of all cancer deaths is due to smoking

- 185,000 (33%)
- from smoking

- 553,000
- total cancer deaths



- 115,000 (40%)
- from smoking

- 286,000
- male



- 70,000 (26%)
- from smoking

- 267,000
- female





United States, year 2000

Smoking causes about three times as many deaths as all non-medical causes put together

• **512,000
smoking**



• **151,268*
non-medical**

- Murder / assault
- Suicide
- Road accidents
- Plane crashes
- Train crashes
- Accidents at work
- Accidents at home
- Falls
- Drowning
- Poisoning
- Fires
- Floods / storms
- Other natural disasters
- Other accidents

*in year 2000

Low Smoking Exposure

- **Mutations TK domain of EGFR**
- **Adenocarcinomas**
- **Well Differentiated**
- **Women > Men**
- **Non-smokers**

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

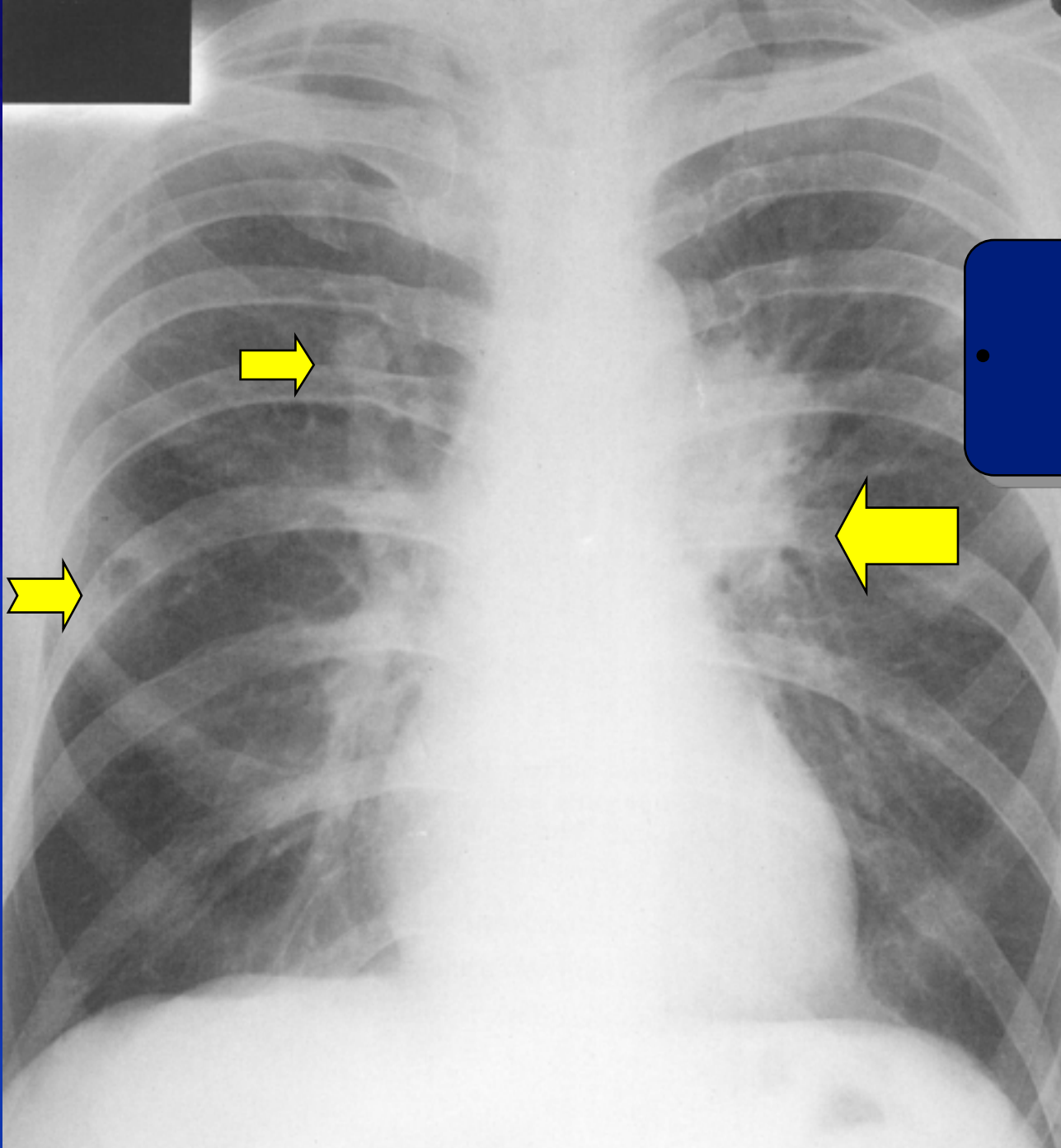
- **Will depend on extent of disease**
- **Cachexia**
- **Lymphadenopathy**
- **Clubbing**
- **Pulmonary findings**
- **Manifestations of metastases**

Laboratory

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

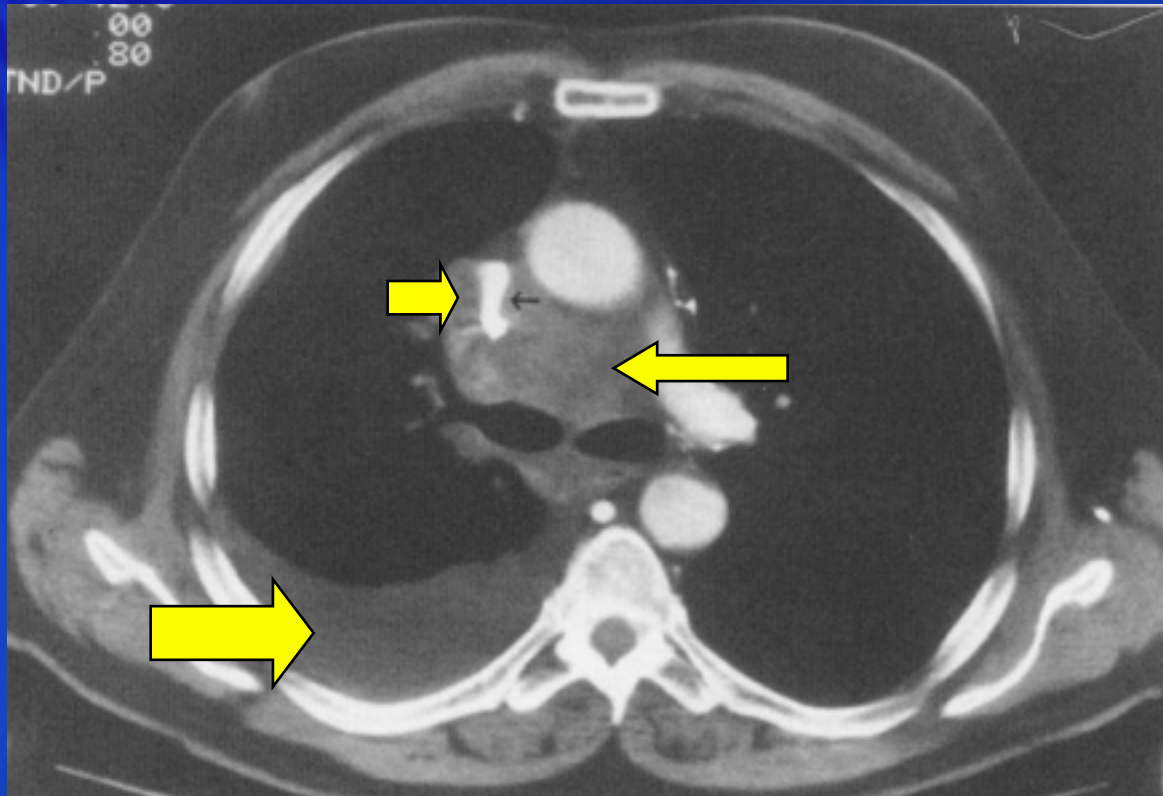
Imaging

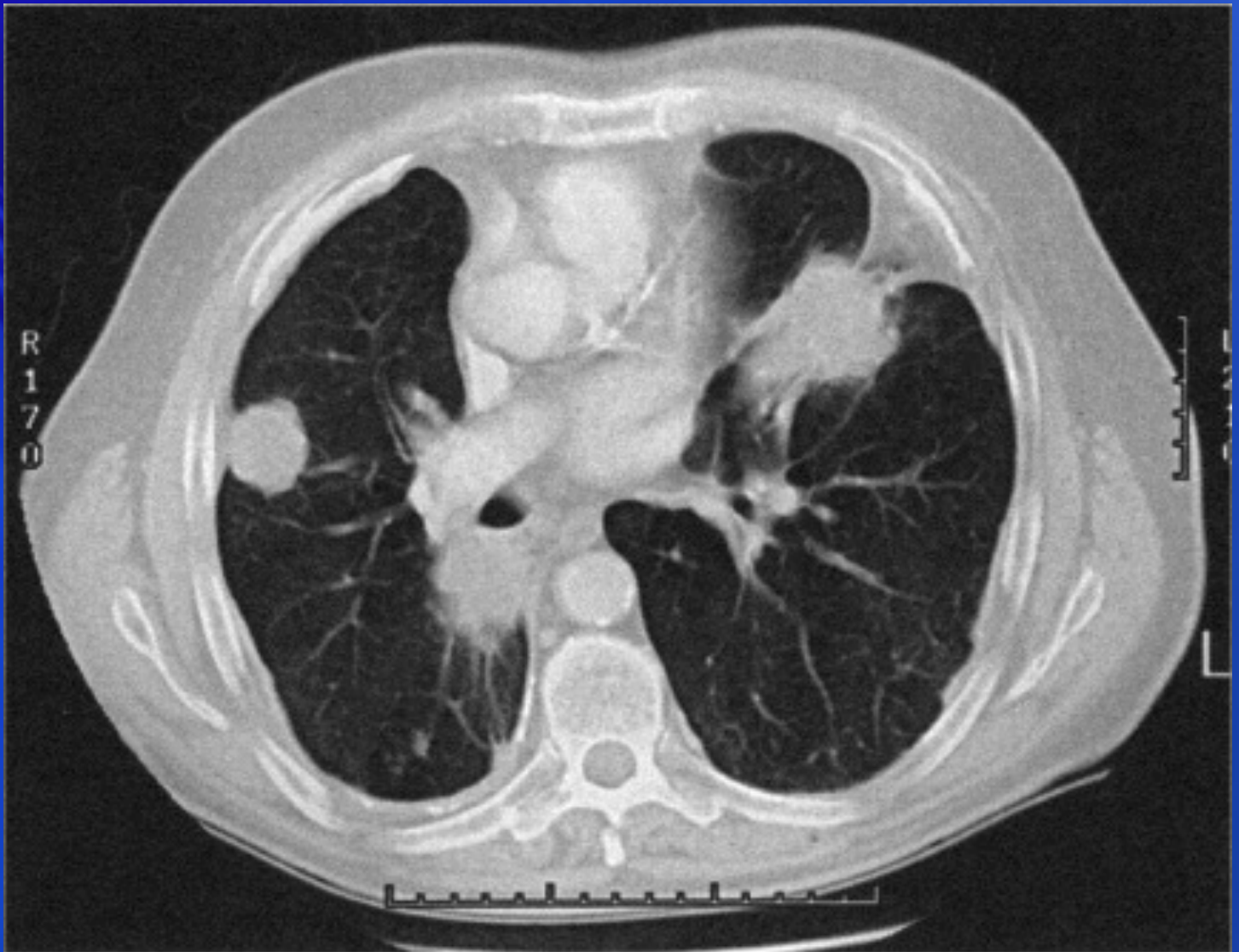
- **CXR (OLD FILMS!)**
- **CT Scan**
- **MRI**
- **Bone Scan**
- **PET Scan**



• CXR

CT Scan





B

Copyright © 2005 by Elsevier Inc.

PET Scan Imaging



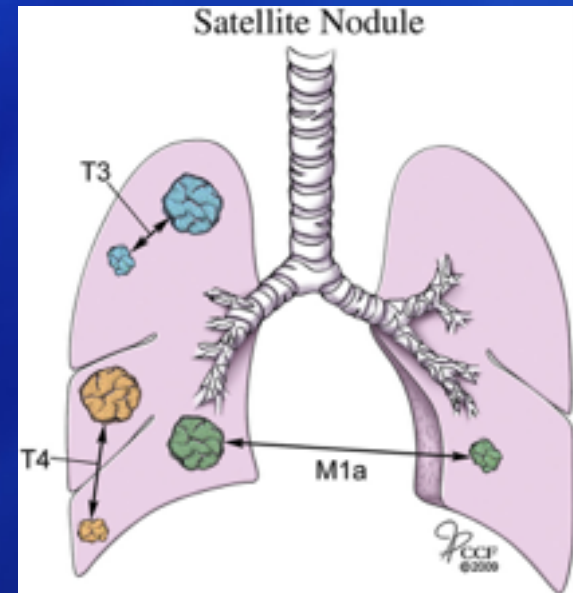
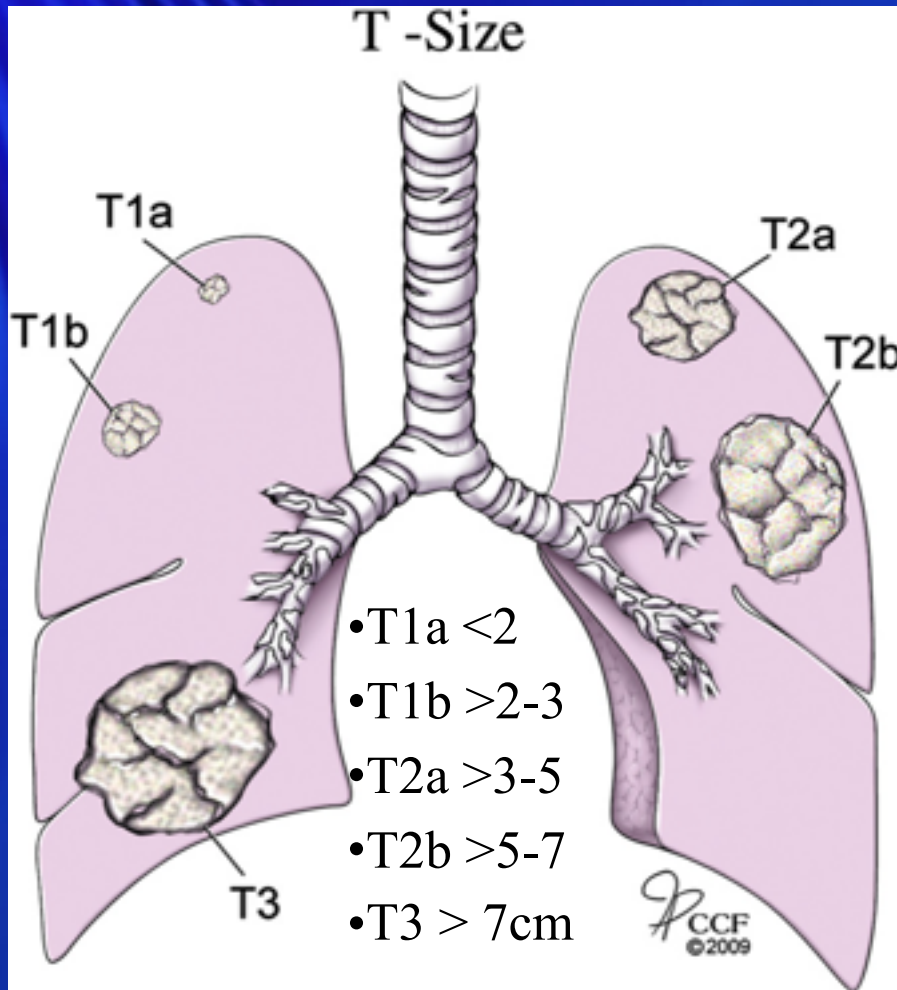
- 97% Sensitive
- 78% Specific
- > 1 cm

Disease Staging

TNM Staging – 7th edition

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	T3 _{>7}	IIb	IIIa	IIIa	IIIb
	T3 _{Inv}	IIb	IIIa	IIIa	IIIb
	T3 _{Satell}	IIb	IIIa	IIIa	IIIb
T4	T4 _{Inv}	IIIa	IIIa	IIIb	IIIb
	T4 _{Ipsi Nod}	IIIa	IIIa	IIIb	IIIb
M1	M1a _{Contra Nod}	IV	IV	IV	IV
	M1a _{PI Disem}	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

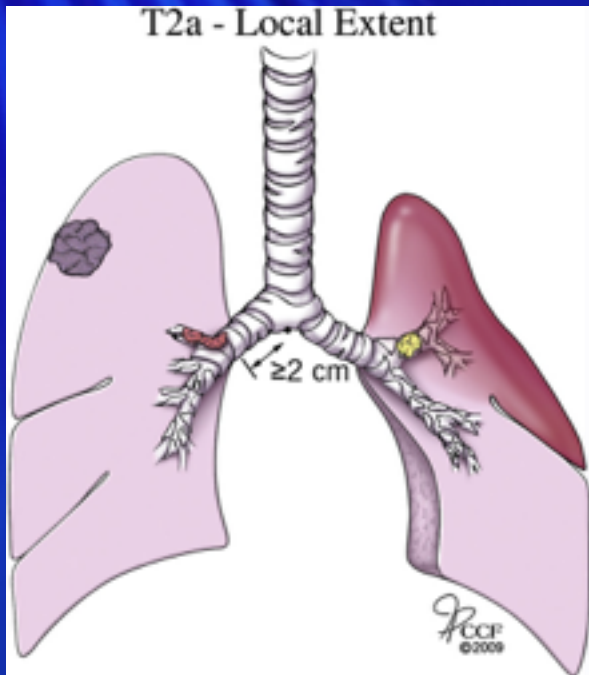
T Status



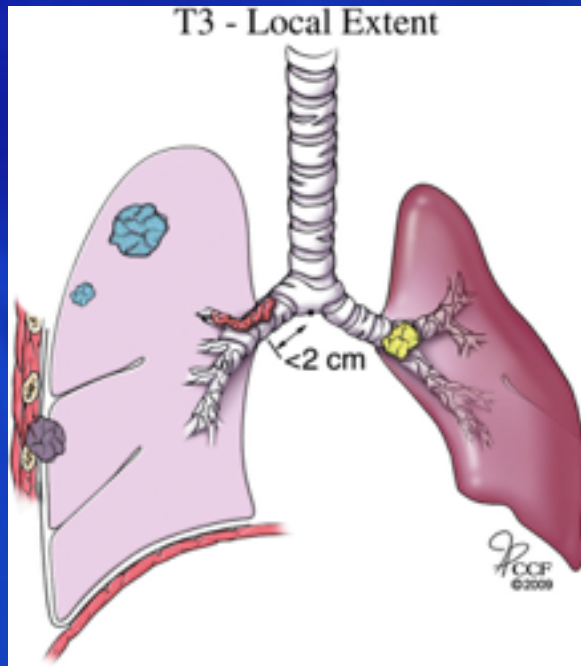
- TX Primary tumor cannot be assessed, eg sputum positive
- T0 No evidence of primary tumour
- Tis Carcinoma in situ

T Status

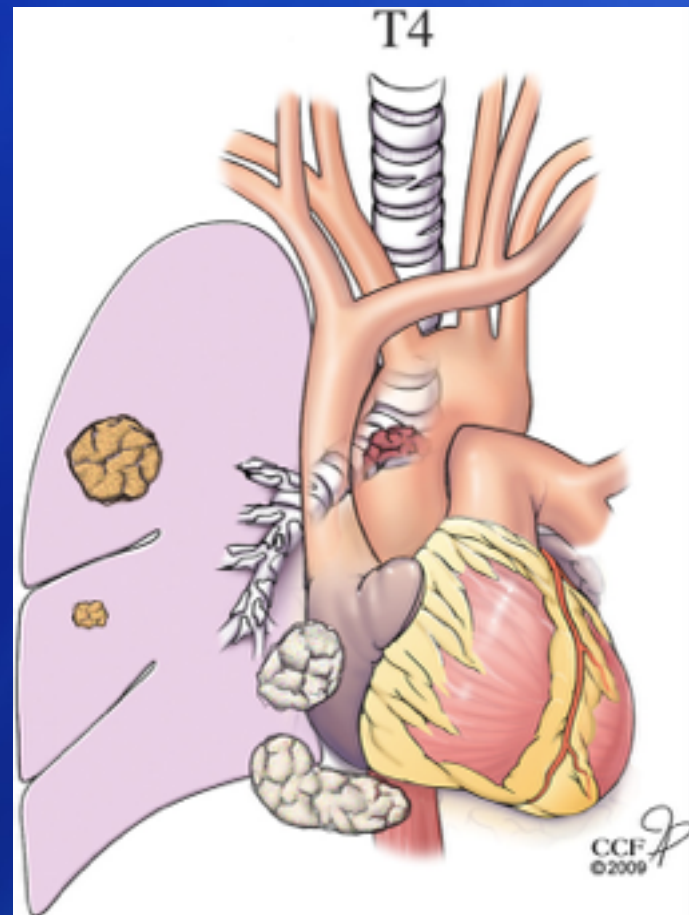
T2a - Local Extent



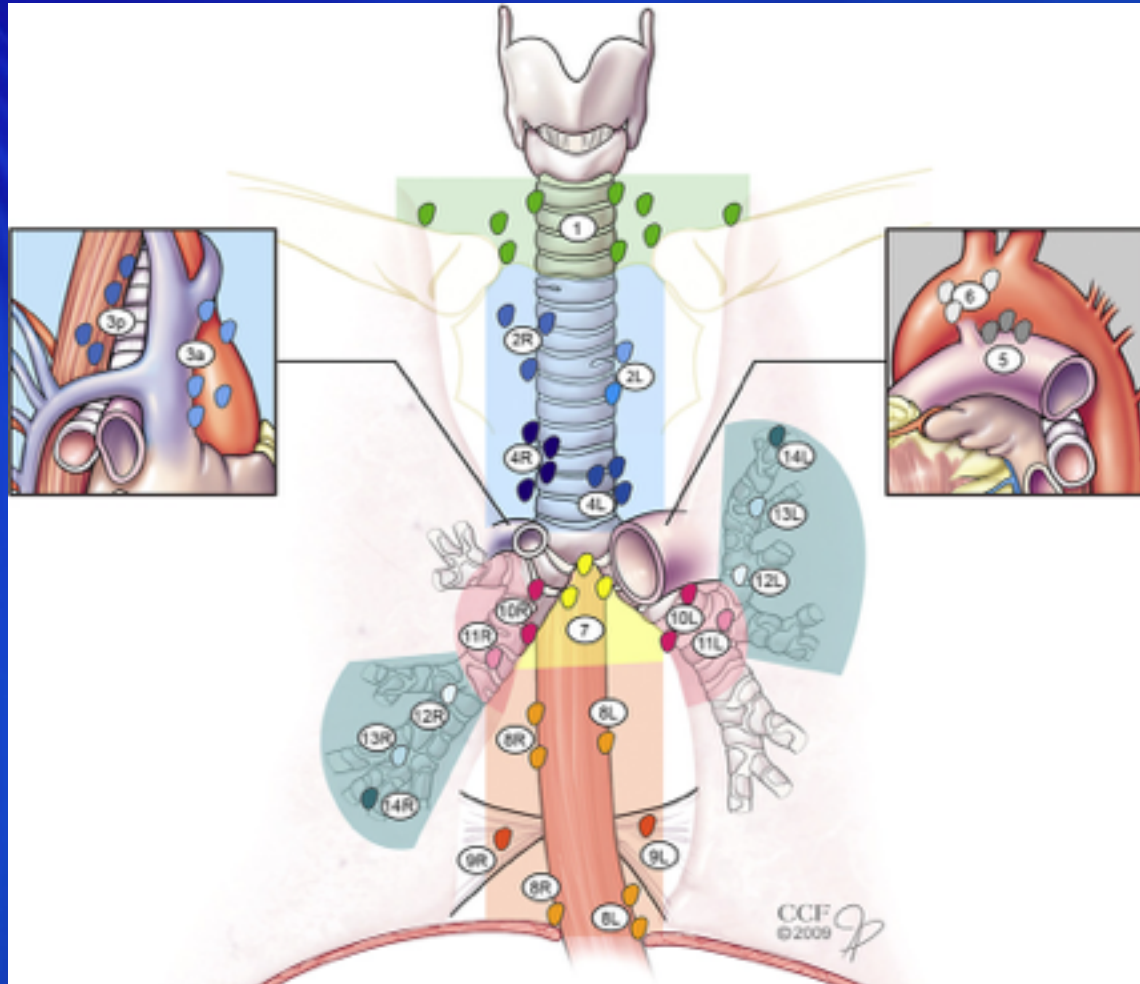
T3 - Local Extent



T4

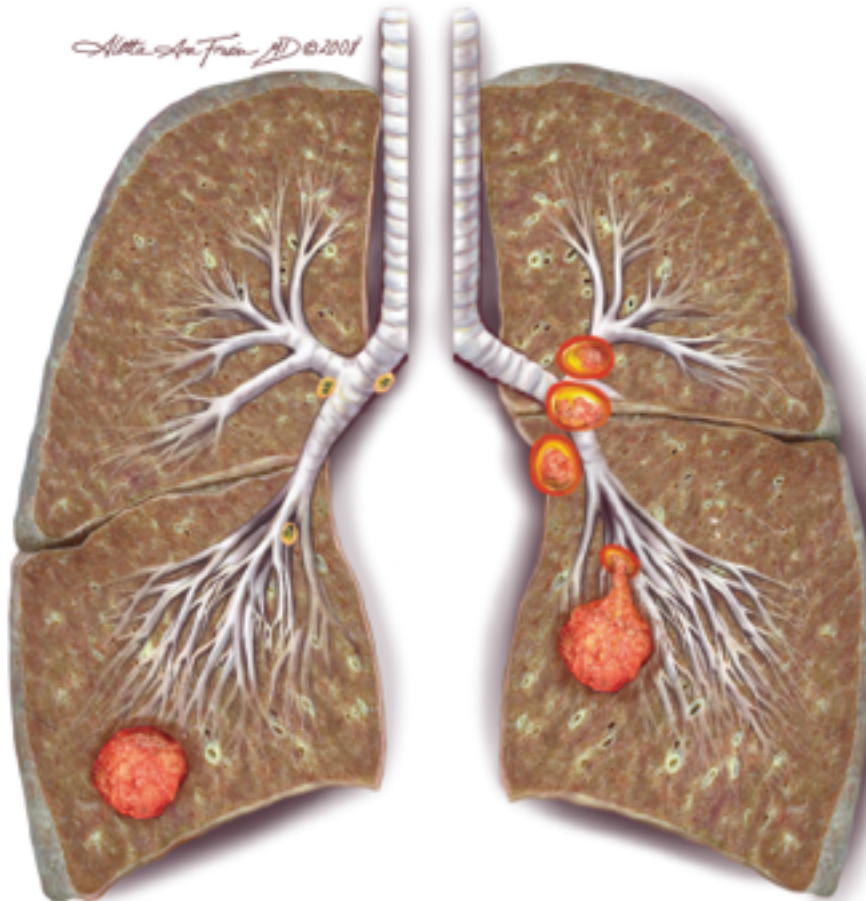


N Status



No

N1



No regional lymph node metastases

Metastasis in ipsilateral intrapulmonary/peribronchial/hilar lymph node(s), including nodal involvement by direct extension

Nodal Status

NX- Can't Assess

N0- No regional nodes

N1- Peribronchial

N2- Ipsilateral mediastinal

N3- Contralateral mediastinal

N2



Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s), including "skip" metastasis without N1 involvement

Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) associated with N1 disease

Nodal Status

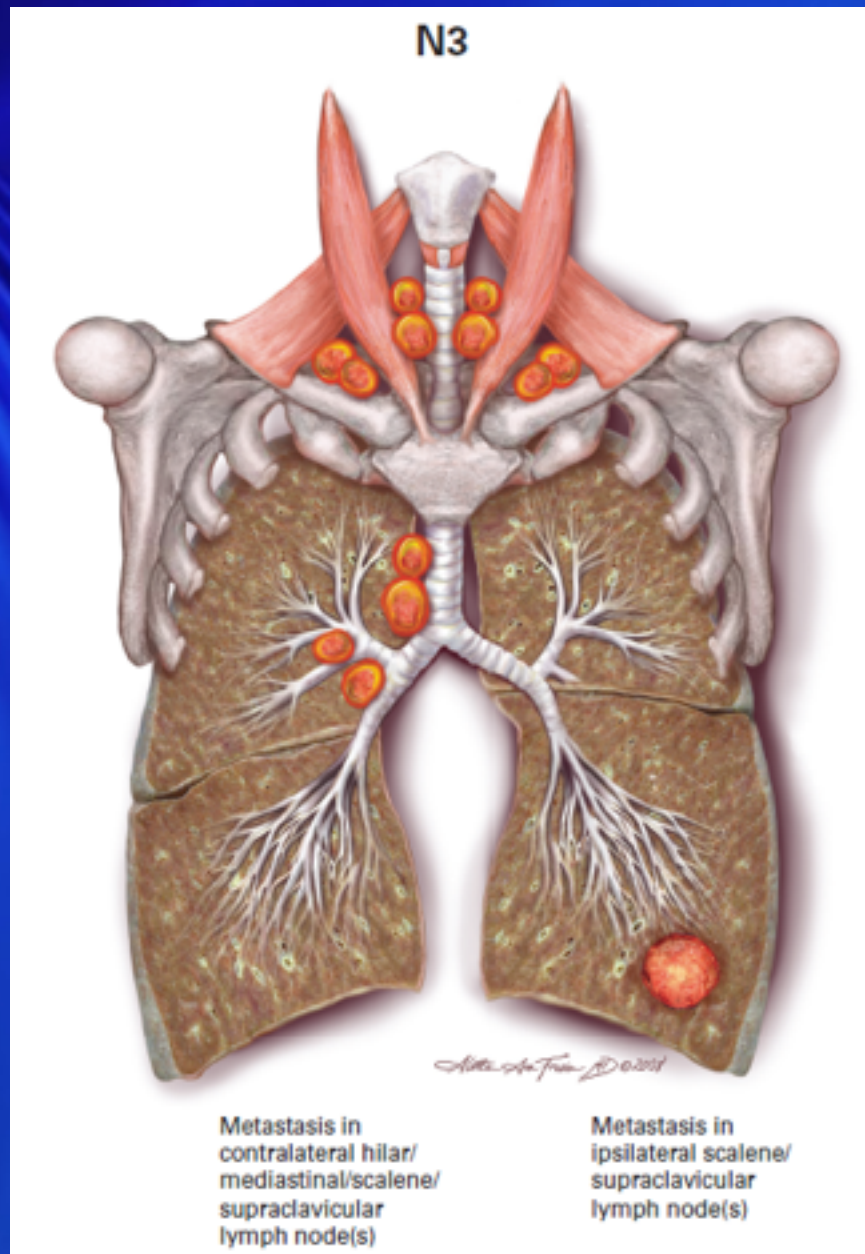
NX- Can't Assess

N0- No regional nodes

N1- Peribronchial

N2- Ipsilateral mediastinal

N3- Contralateral mediastinal



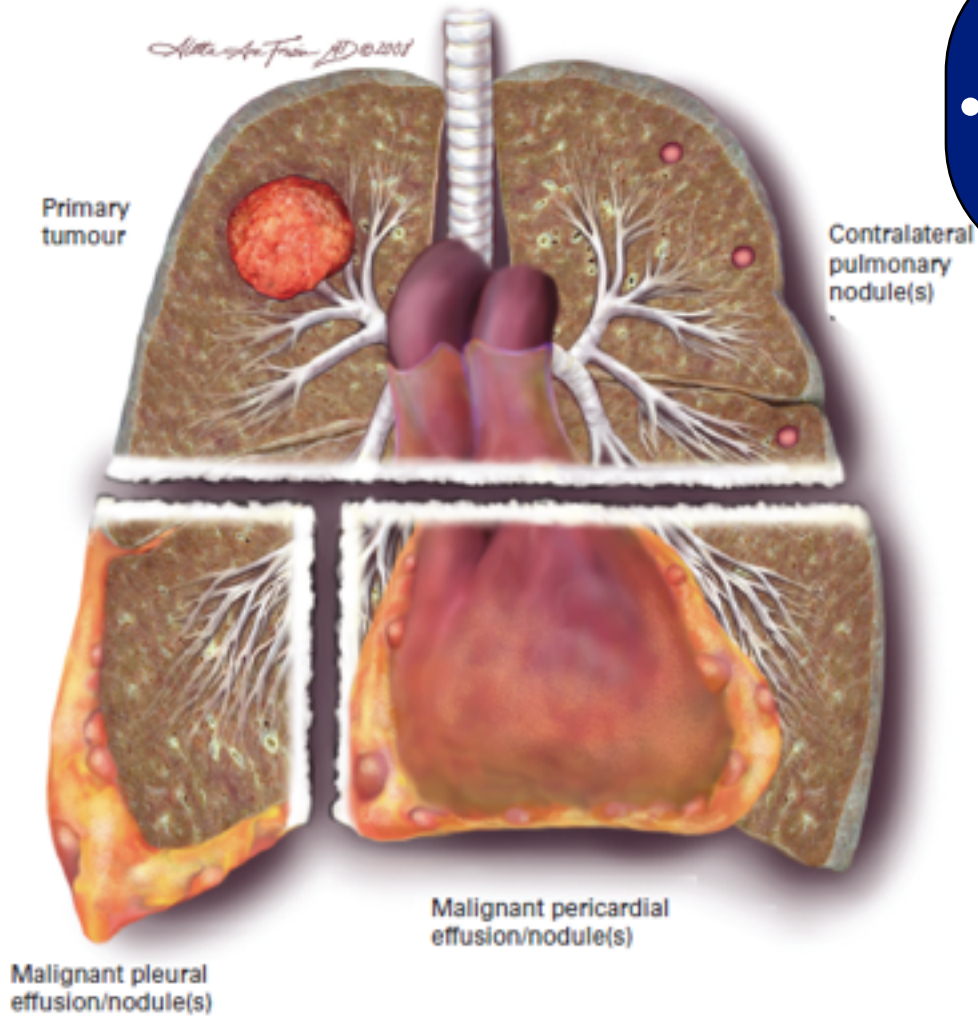
Nodal Status

- NX-** **Can't Assess**
- N0-** **No regional nodes**
- N1-** **Peribronchial**
- N2-** **Ipsilateral mediastinal**
- N3-** **Contralateral
mediastinal**

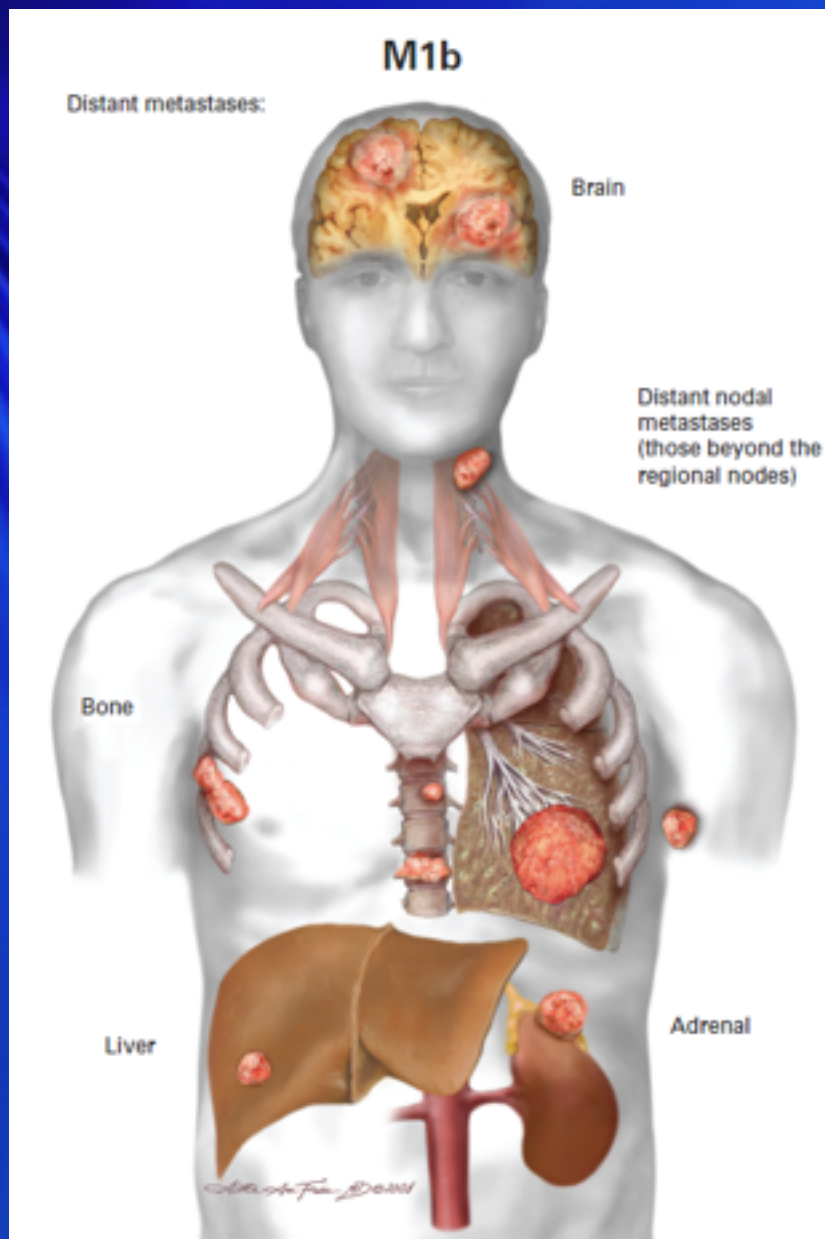
M Status

- M0 No distant metastasis
- M1 Distant metastasis
 - M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusions
 - M1b Distant metastasis

M1a



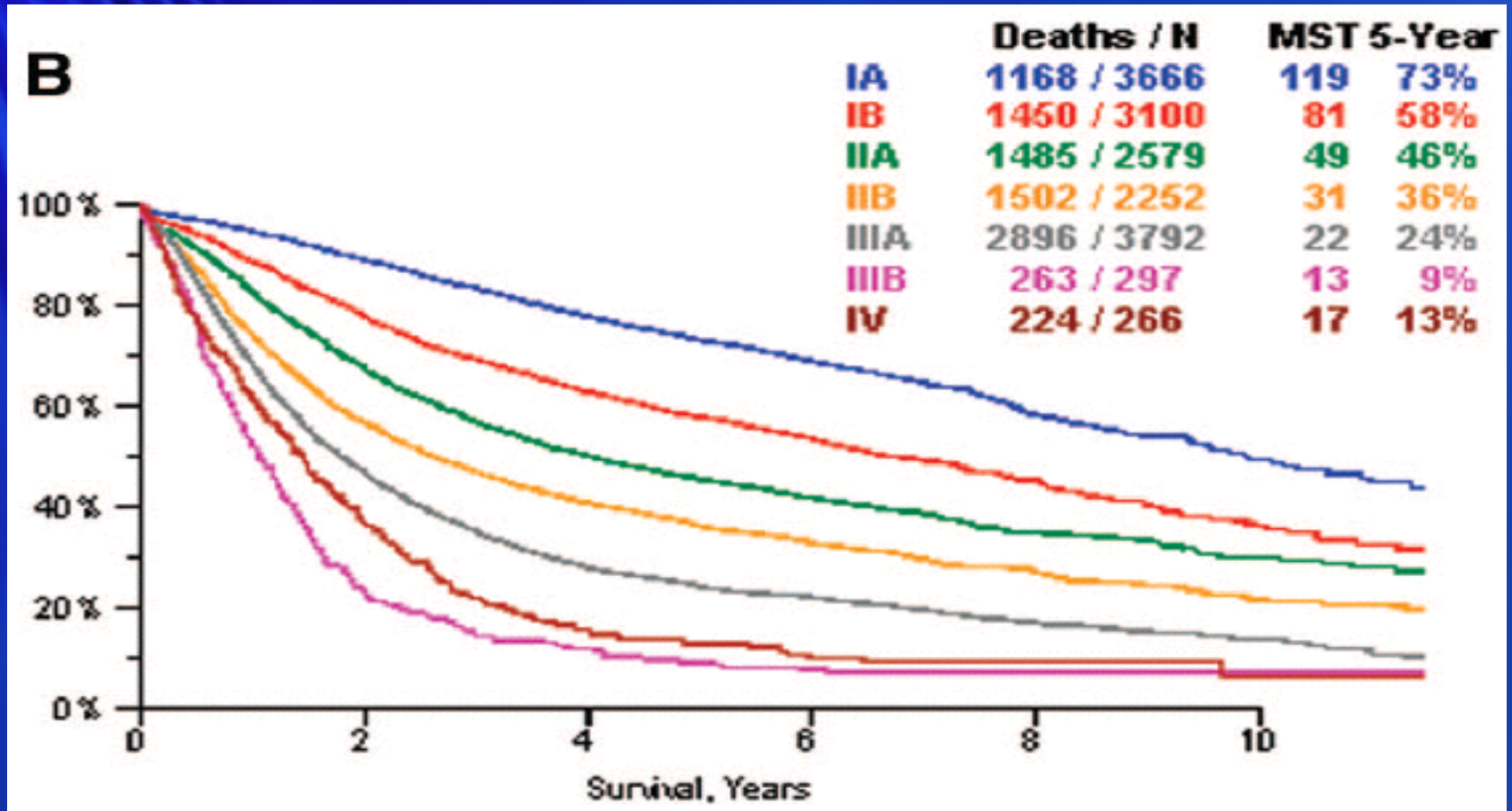
Lung Staging



Lung Staging - Mets

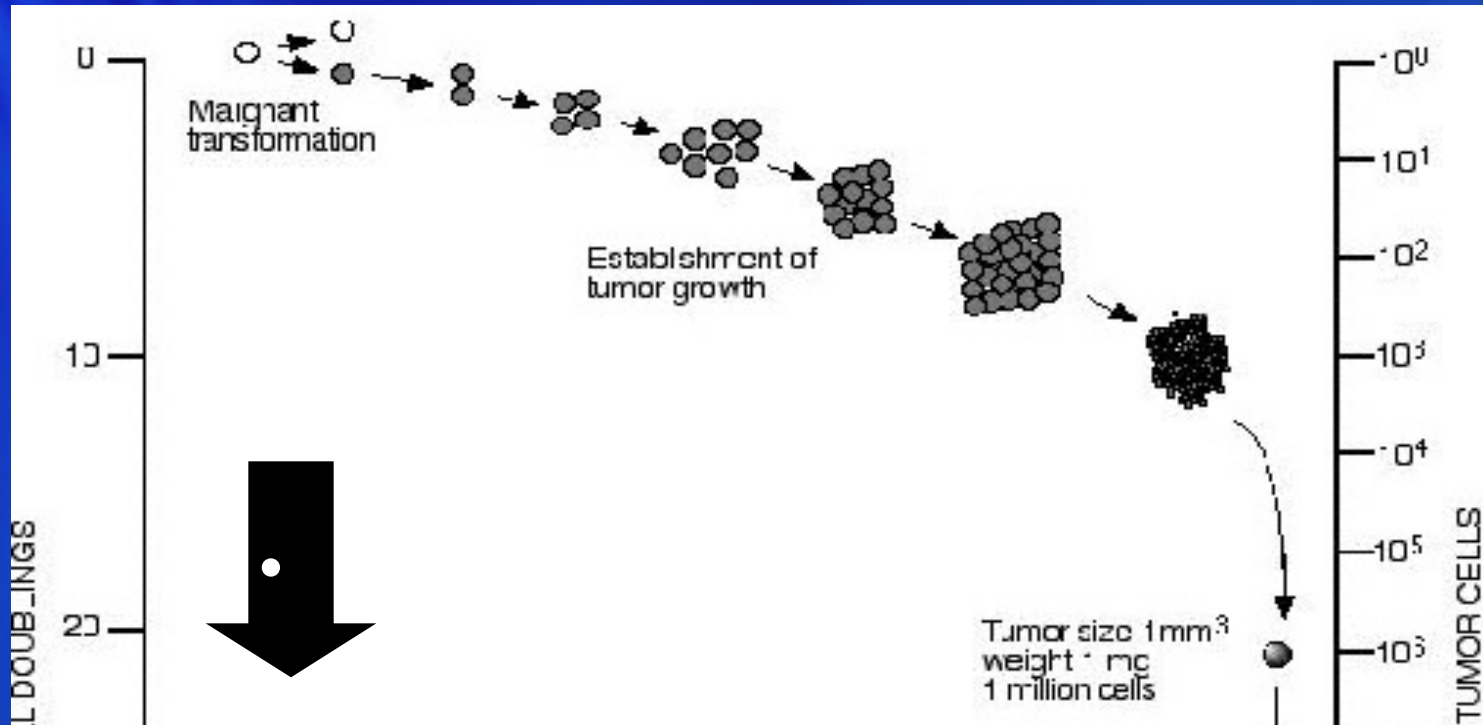
- **Lymph Nodes** 96%
- **Bones** 48%
- **Adrenals** 40%
- **Liver** 41%
- **Kidneys** 19%
- **Heart** 15%
- **Opposite lung** 13%

Survival by Stages Pathologic



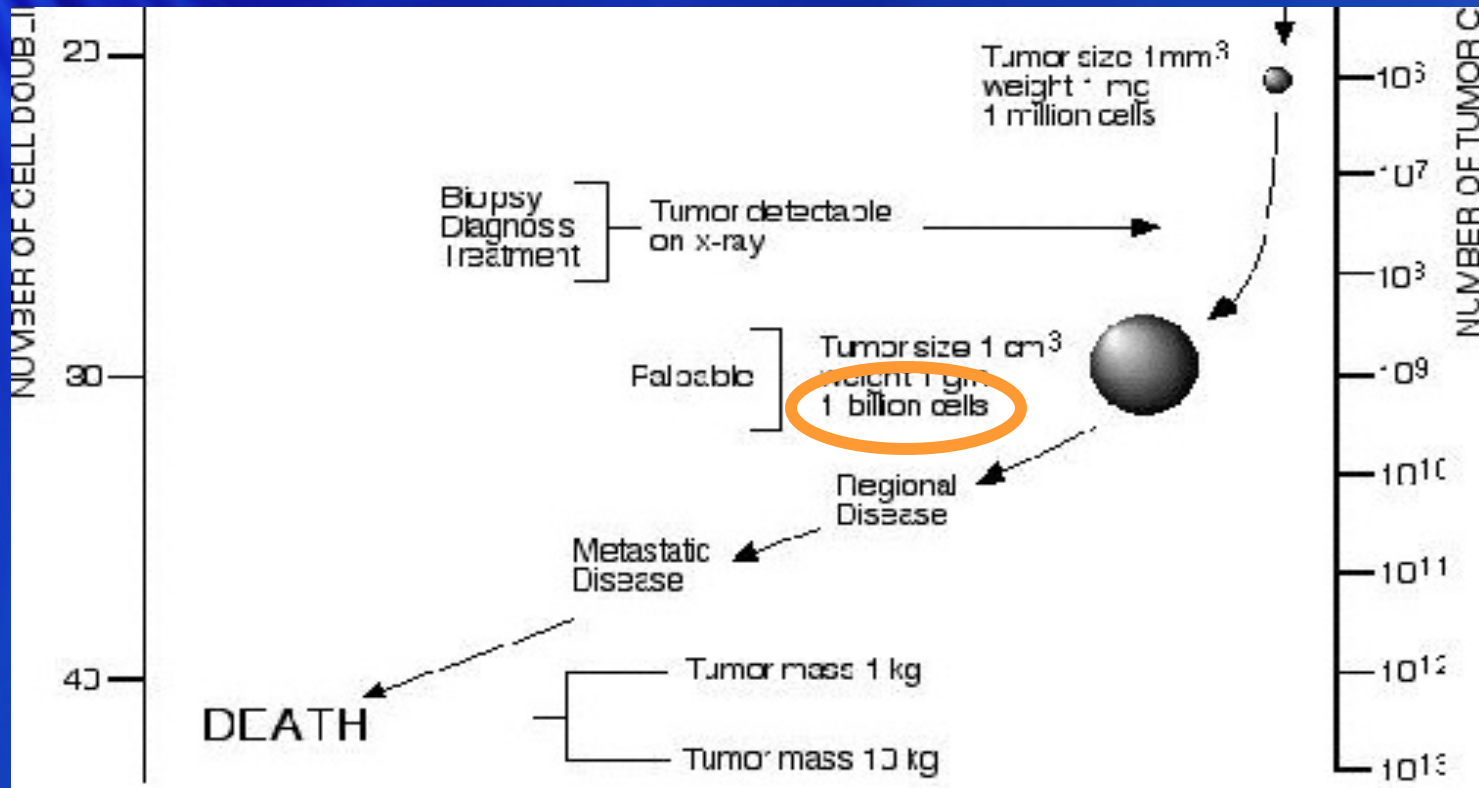
Tumor Growth I

Stepwise Model

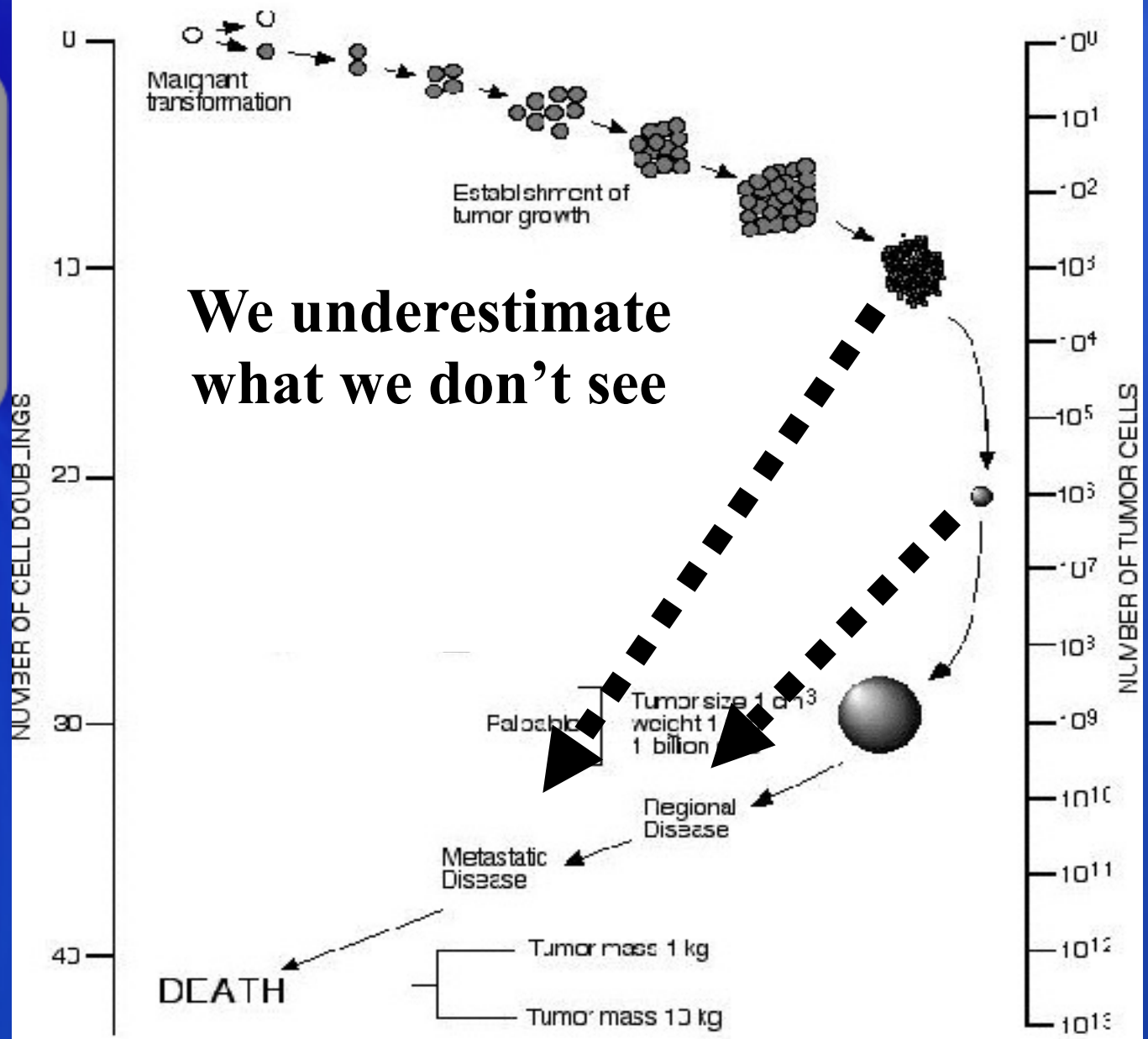


Tumor Growth II

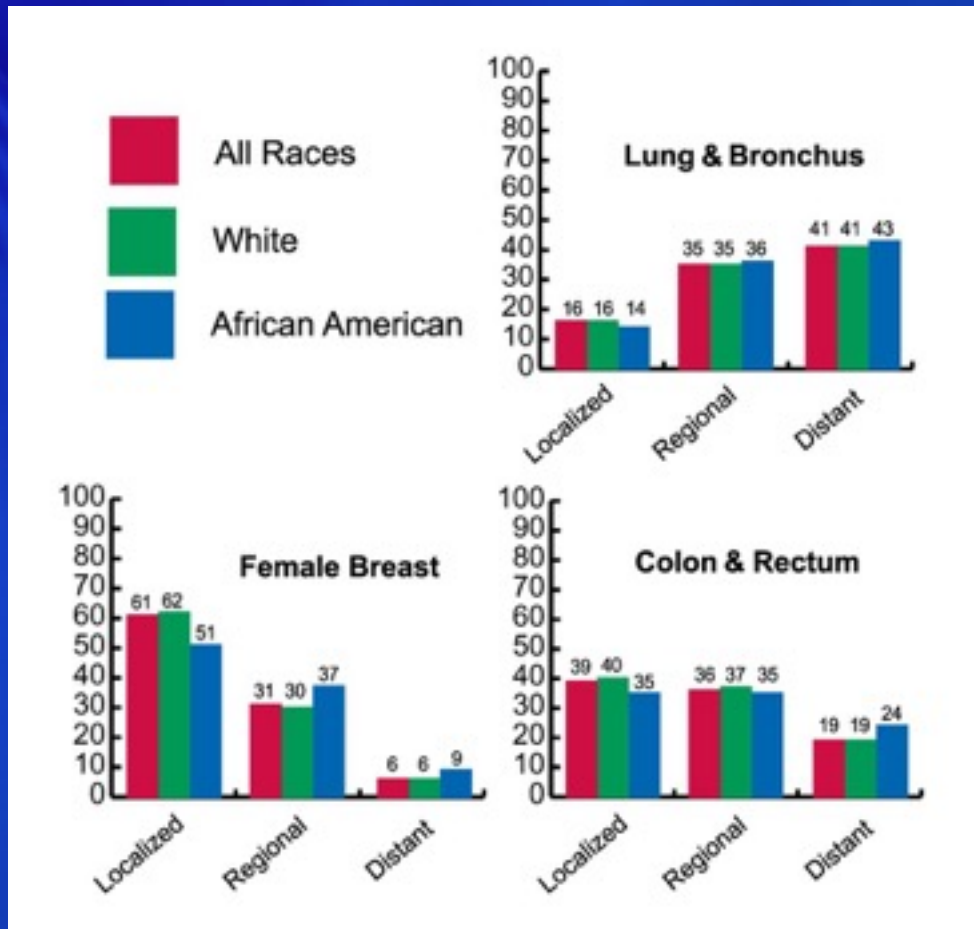
Stepwise model



Alternate Disease Progression

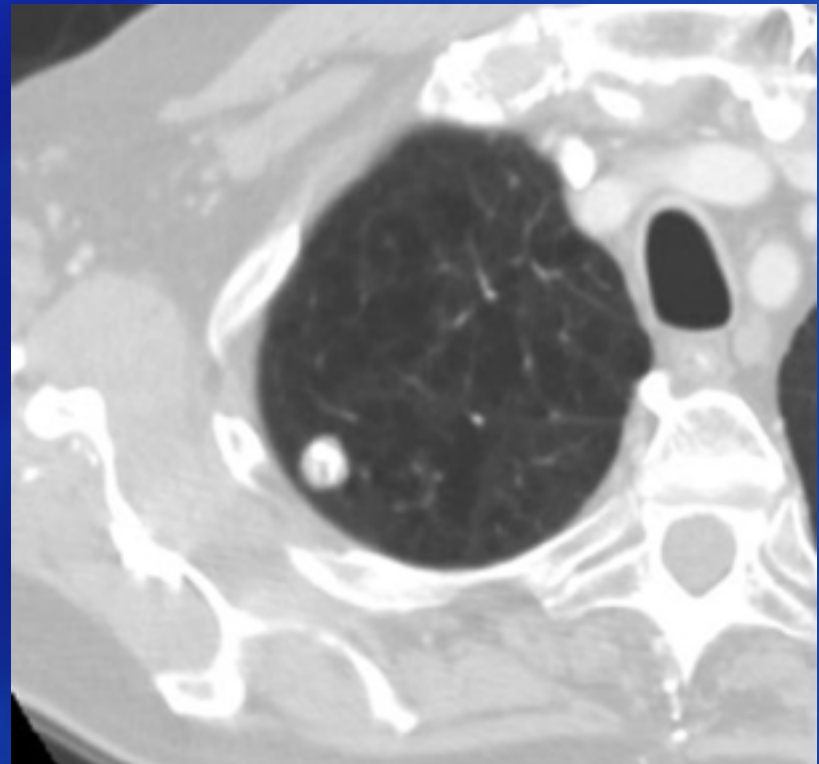


Stage at Presentation

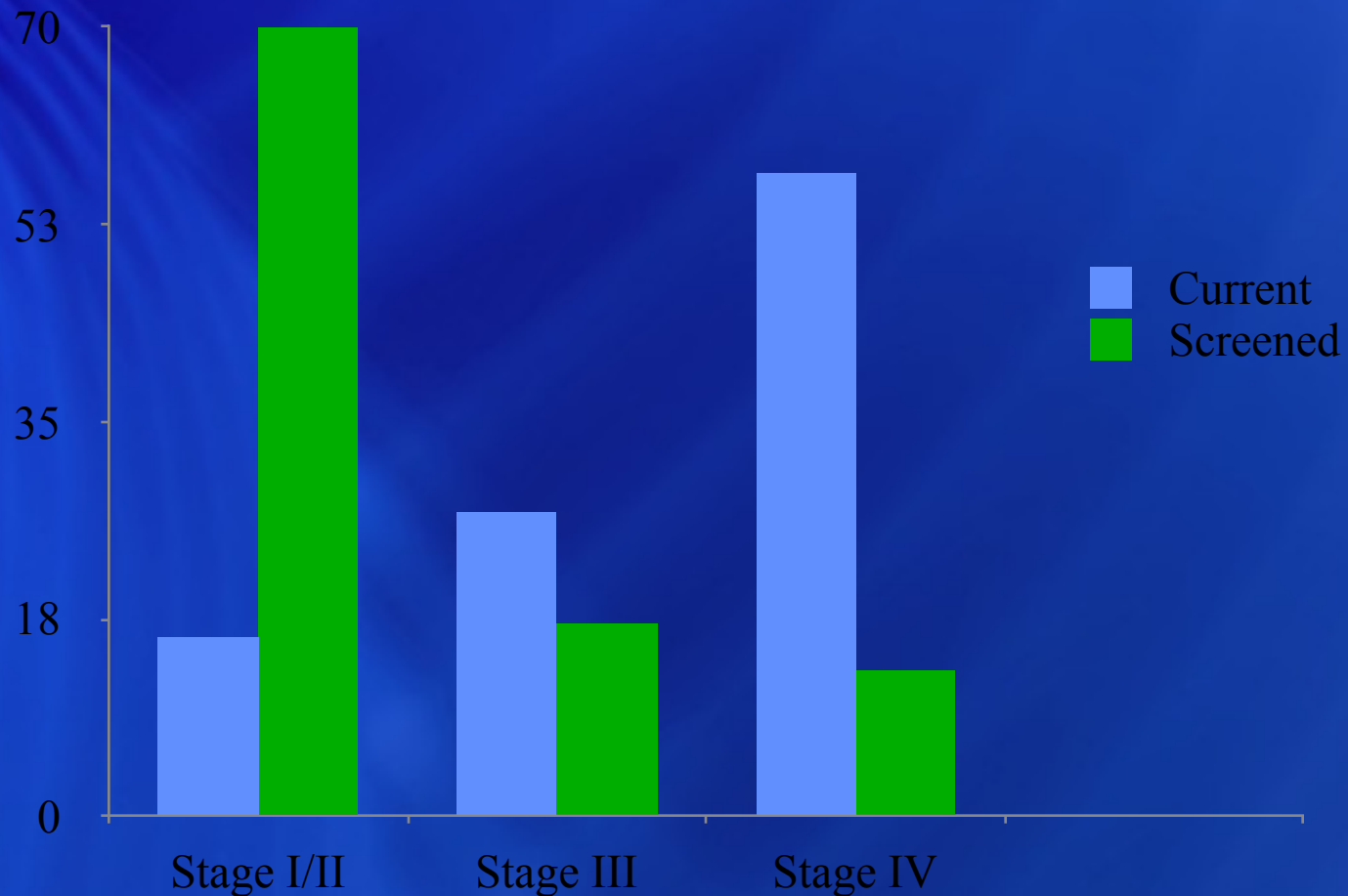


Purpose of Lung Cancer Screening

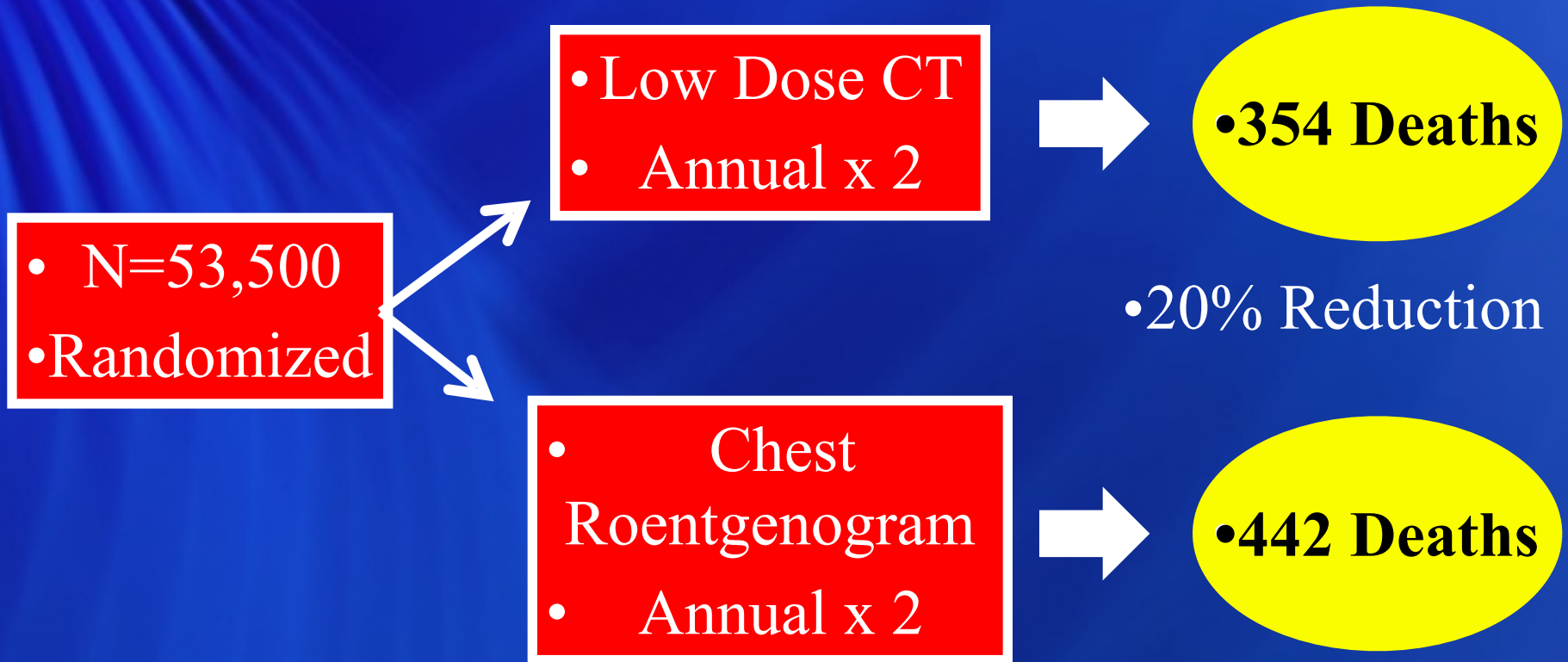
- **Detect asymptomatic, early stage disease that is amenable to curative therapy**
- **Improved outcomes**
 - **Survival**
 - **Quality of Life**



The Shift in Stage of Lung Cancer with LDCT Screening



Schema



Summary of Screening Criteria Presented by Professional Organizations

Organization	Screening Criteria
NCCN	<ul style="list-style-type: none"> • NLST Criteria (55-74 years, 30 Packyear (PY)) • ≥ 50, 20 PY with additional risk factor (Cancer History, COPD, FH, work exposure, pulmonary fibrosis)
ACS	<ul style="list-style-type: none"> • NLST Criteria with Expertise in LDCT • Multidisciplinary Team • Vigorous Smoking Cessation
ALA	<ul style="list-style-type: none"> • NLST Criteria with Expertise in LDCT • Encourage Smoking Cessation • No Chest X-ray • Multidisciplinary Team
ACCP/ASCO	<ul style="list-style-type: none"> • NLST Criteria • Smoking Cessation ≥ 15 Years Ago • Multidisciplinary Team

Summary of Screening Criteria Presented by Professional Organizations

Organization	Screening Criteria
AATS	<ul style="list-style-type: none">• NLST Criteria (55-79 years, 30 PY)• ≥ 50, 20 PY with additional risk factor (Moderate COPD, Cancer History, FH, work exposures)• No suggested limits on numbers of LDCTs• Lifelong surveillance for aerodigestive cancer survivors
AAFP (January 2014)	<ul style="list-style-type: none">• Insufficient evidence to recommend for or against screening for lung cancer• Potential for screening from ages 55-80• Physicians must engage in shared decision making regarding the benefits, potential harms, and costs from screening

Recommendations for Lung Cancer Screening Programs

- **Experienced management of nodule surveillance**
- **Multidisciplinary team**
- **Referral centers with experienced radiologists and pulmonologists**
- **Must be integrated with comprehensive smoking cessation program**

Lung Cancer Multidisciplinary Team

- **Medical Oncology**
- **Pulmonology**
- **Prevention**
- **Radiation Oncology**
- **Nuclear Medicine**
- **Thoracic Surgery**
- **Diagnostic Radiology**
- **Pulmonary Pathology**

Obtaining Tissue for Diagnosis

- **CT guided needle biopsy**
- **Endobronchial biopsy**
- **Endobronchial Ultrasound**
- **Navigational bronchoscopy**
- **Thoracoscopic biopsy**

Treatment Modalities

- **Surgery**
- **Radiotherapy**
- **Chemotherapy**
- **Targeted Therapy**
- **Endobronchial Interventions**
- **Palliative Procedures**

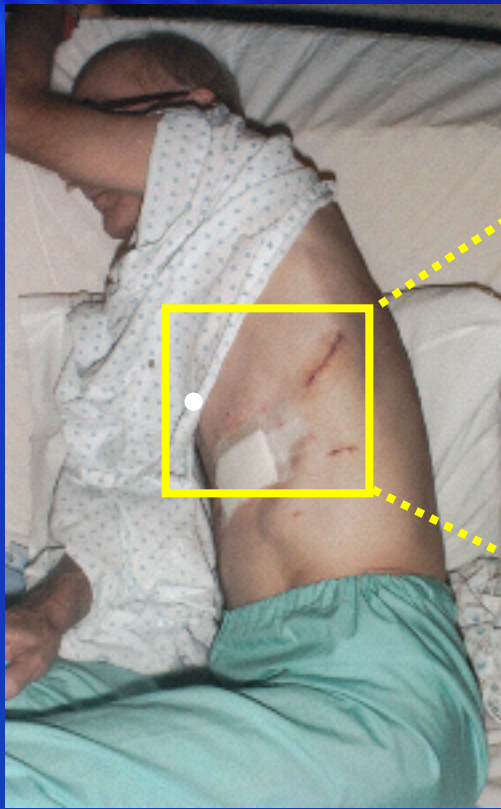
Surgical Management

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

Surgical Management

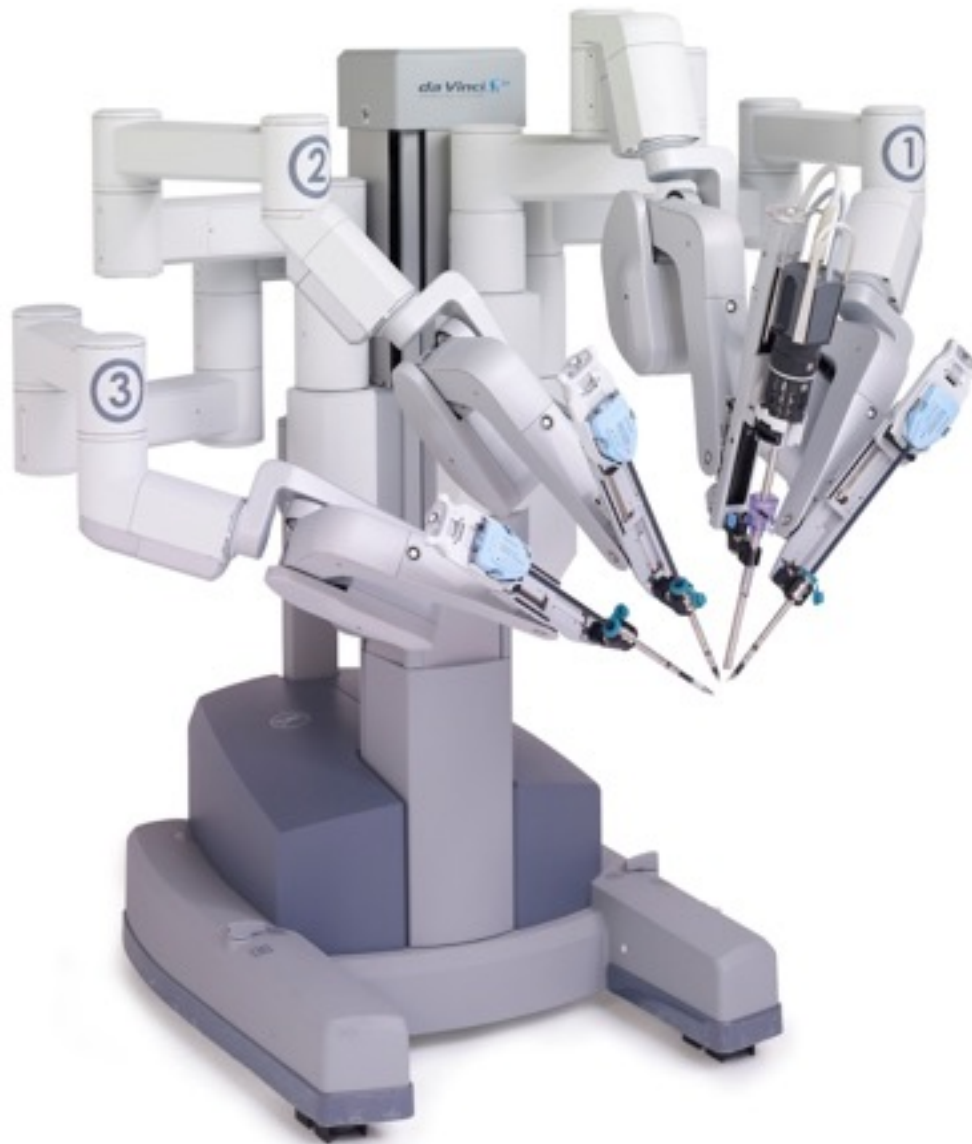
- **Lobectomy (+ lymphadenectomy)**
- **Larger resections**
 - **Bilobectomy, Pneumonectomy**
- **Lesser resections**
 - **Segmentectomy, wedge resection**

Minimally Invasive Lobectomy



Robot-Assisted Lobectomy





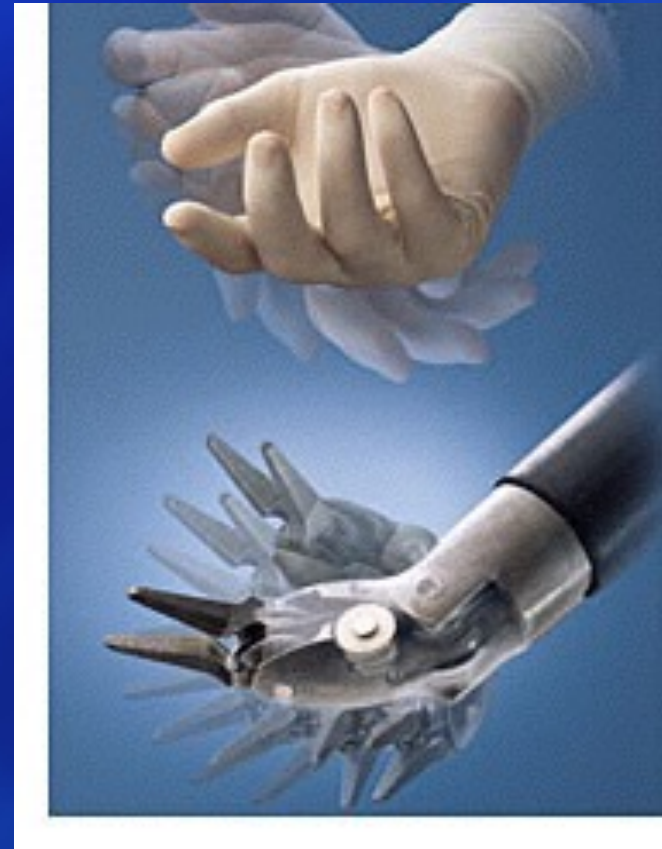
The da Vinci SI Surgical Robot (bedside cart)

The da Vinci Robot



Features

- *EndoWrist*
Instruments provide enhanced dexterity, precision and control:
 - 7 degrees of freedom
 - 90 degrees of articulation
 - *Intuitive* motion and finger-tip control
 - Motion scaling and tremor reduction



Surgical Contraindications

- **Inadequate cardiopulmonary reserve**
- **Malignant pleural effusion**
- **Recurrent laryngeal nerve paralysis**
- **Small cell carcinoma**
- **Contralateral lymph node mets**
- **Distant mets**

Non-Surgical Therapies

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

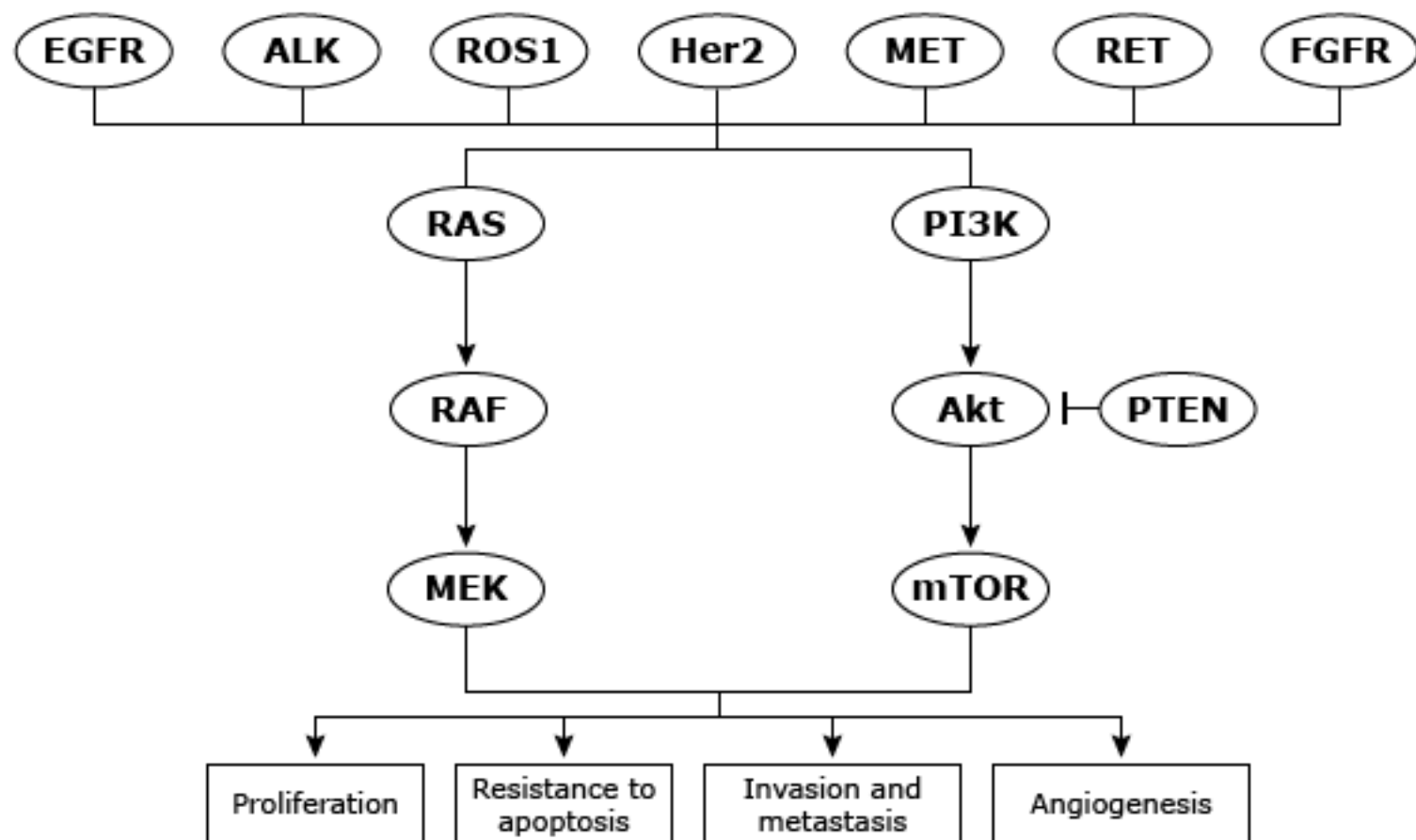
Chemotherapy

- **Traditional chemotherapeutic agents are systemic cytotoxic drugs**
- **Platin-based therapy**
 - **Cisplatin**
 - **Carboplatin**
- **Typically a doublet**
 - **Combination of 2 chemotherapeutic agents**

Targeted Therapy

- **Markedly improved understanding of molecular pathways in NSCLC**
- **Identification of “Driver Mutations”**
- **Design of small molecules to interfere with the products of these mutated genes**
- **Often more effective & less toxic than traditional chemotherapy**

Molecular targets in non-small cell lung cancer

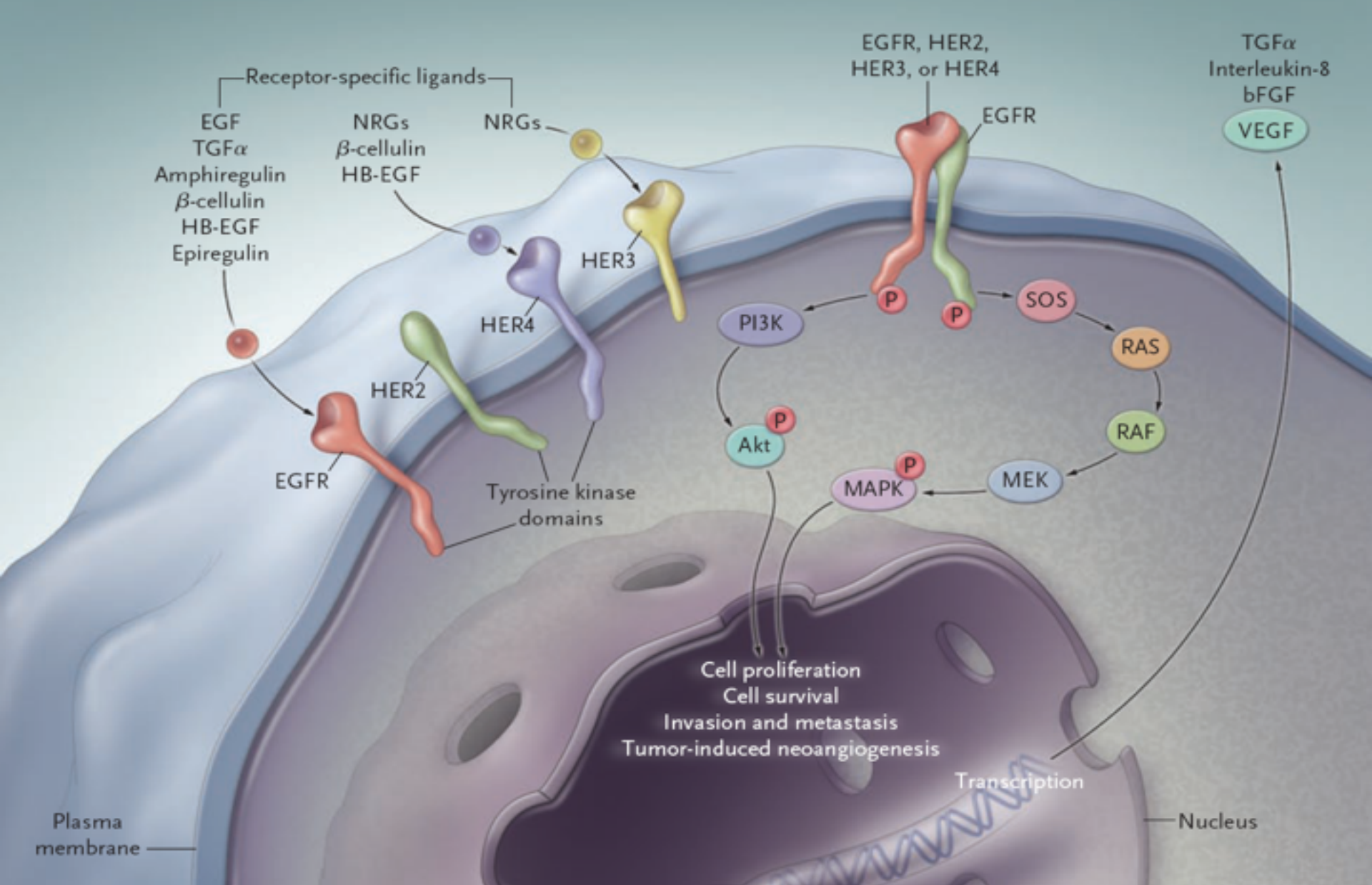


Pathways for molecularly targeted therapy in non-small cell lung cancer.

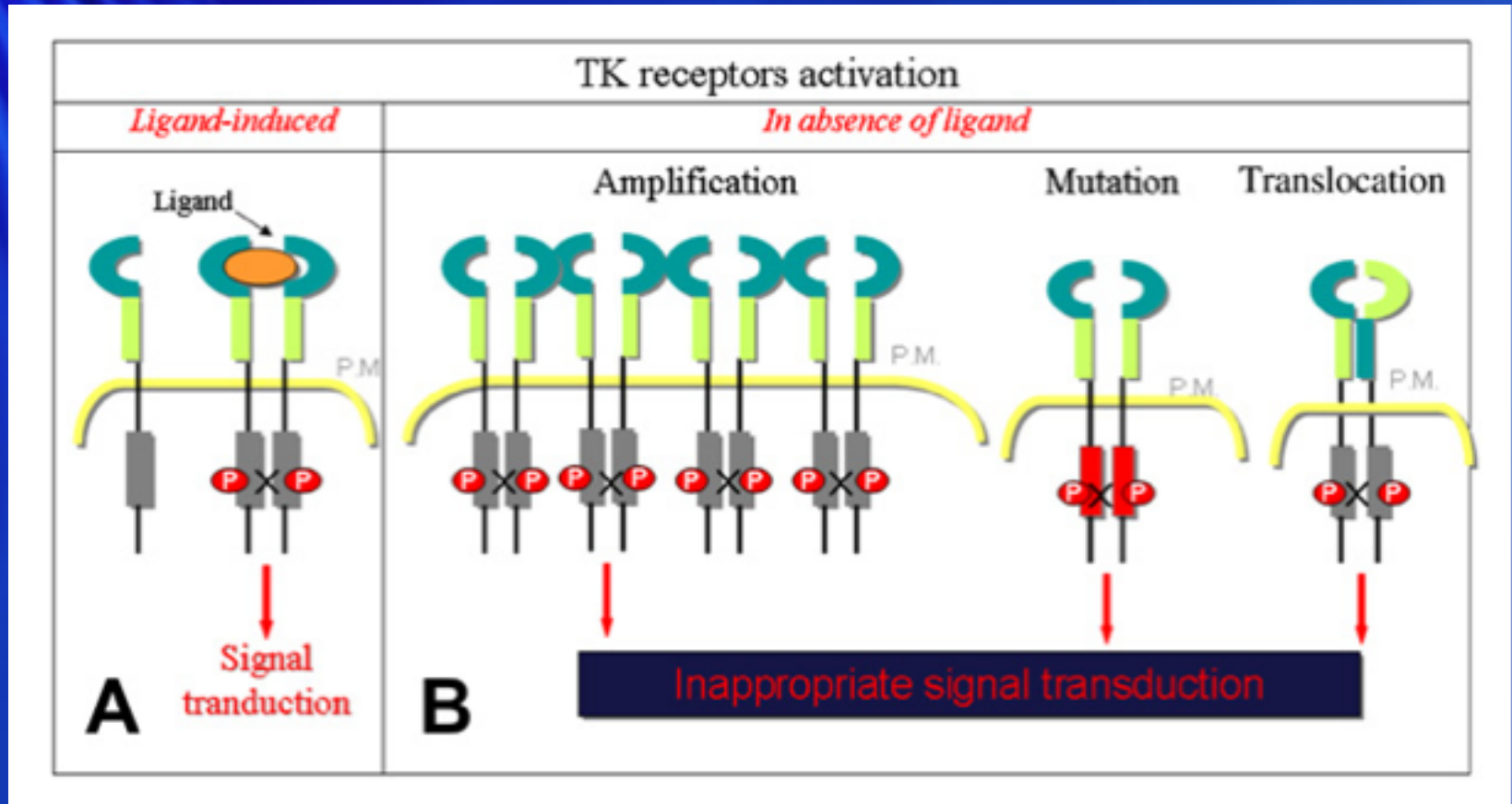
Original, courtesy of Dr. Joel Neal.

Background

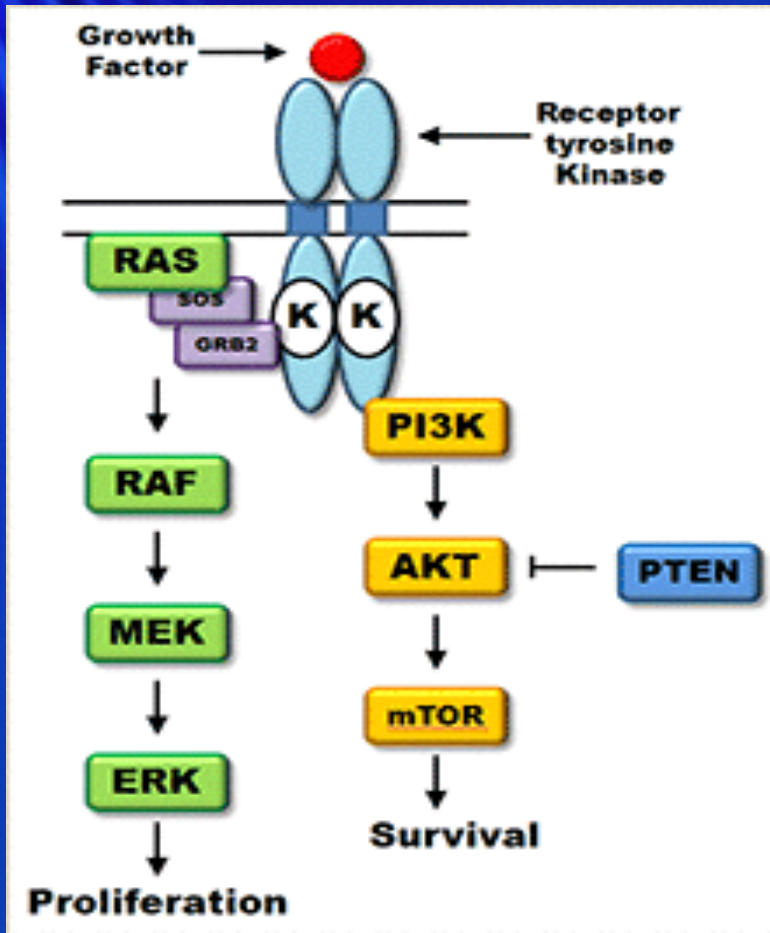
- **The EGFR family**
 - EGFR (ErbB1, HER1)
 - ErbB2 (HER2, neu)
 - ErbB3 (HER3)
 - ErbB4 (HER4)
- **Binding of soluble extracellular ligand → dimerization → intracellular TK domain activation/ phosphorylation → downstream signaling → promotion of cell proliferation, motility and invasion**
- **EGFR mutated in ~10% of NSCLC in the US and 35% in East Asia (overall 26%)**
- **Confers poor prognosis**



Receptor Tyrosine Kinases (RTKs) Activation

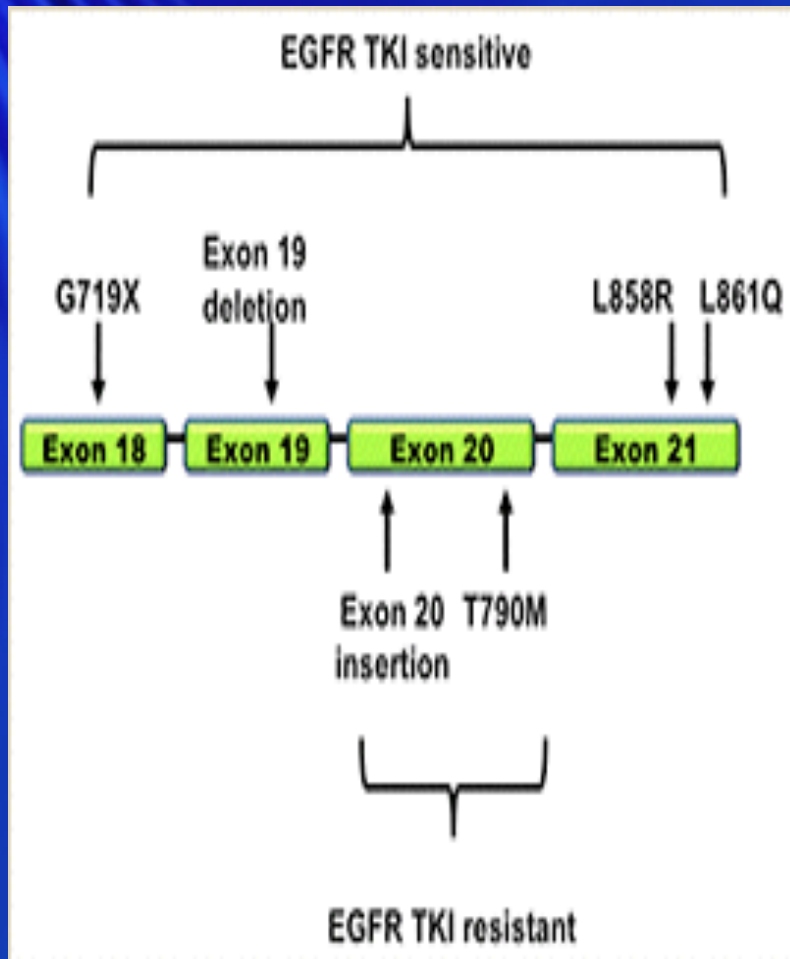


EGFR Signaling



• Growth factor binding to EGFR results in activation of the MAPK signaling pathway (RAS-RAF-MEK-ERK) and the PI3K pathway (PI3K-AKT-mTOR).

EGFR Mutations



Mutations above the schematic are associated with sensitivity to EGFR TKIs

Mutations listed below the schematic are associated with EGFR TKI resistance

EGFR Mutations

- **More often occur in adenocarcinomas in female never-smokers**
- **Typically, non-overlapping with other oncogenic mutations found in NSCLC (i.e. KRAS mutations, ALK rearrangements, etc.)**
- **Both prognostic and predictive**
- **Identifies the subset of patients responsive to TKIs**

Pharmacologic targeting of the EGFR signaling pathway

- **Two basic approaches**
 - **Anti-EGFR monoclonal antibodies (mAbs)**
 - **Small molecule Tyrosine Kinase Inhibitors (TKIs)**
- **Limited efficacy in unselected NSCLC**

Anti-EGFR mAbs

- **Bind to the extracellular domain of EGFR**
- **Competitive occlusion of the ligand binding region**
- **Inhibit ligand-induced phosphorylation of the catalytic region**
- **Blocks the intracellular signaling cascade**
- **Cetuximab (Erbitux[®]) & Panitumumab (Vectibix[®])**
 - **Effective in combination with chemotherapy**
 - **No validated predictive biomarker**

Small molecule TKIs

- **Response is predictable based on activating EGFR somatic mutations**
- **Gefinitib (Iressa[®]) and Erlotinib (Tarceva[®])**
 - **Reversible inhibitors of the EGFR kinase**
 - **Bind to the ATP-binding site thus preventing phosphorylation and downstream signaling**
 - **Superior to chemotherapy in pts with tumors that bear activating EGFR mutations**
 - **EGFR amplification (detected by FISH in 20-40% of NSCLCs) adds to the response rates**

Small molecule TKIs

- **A small proportion of pts show a radiographic response with no detectable EGFR mutation**
 - **Need for new biomarkers**

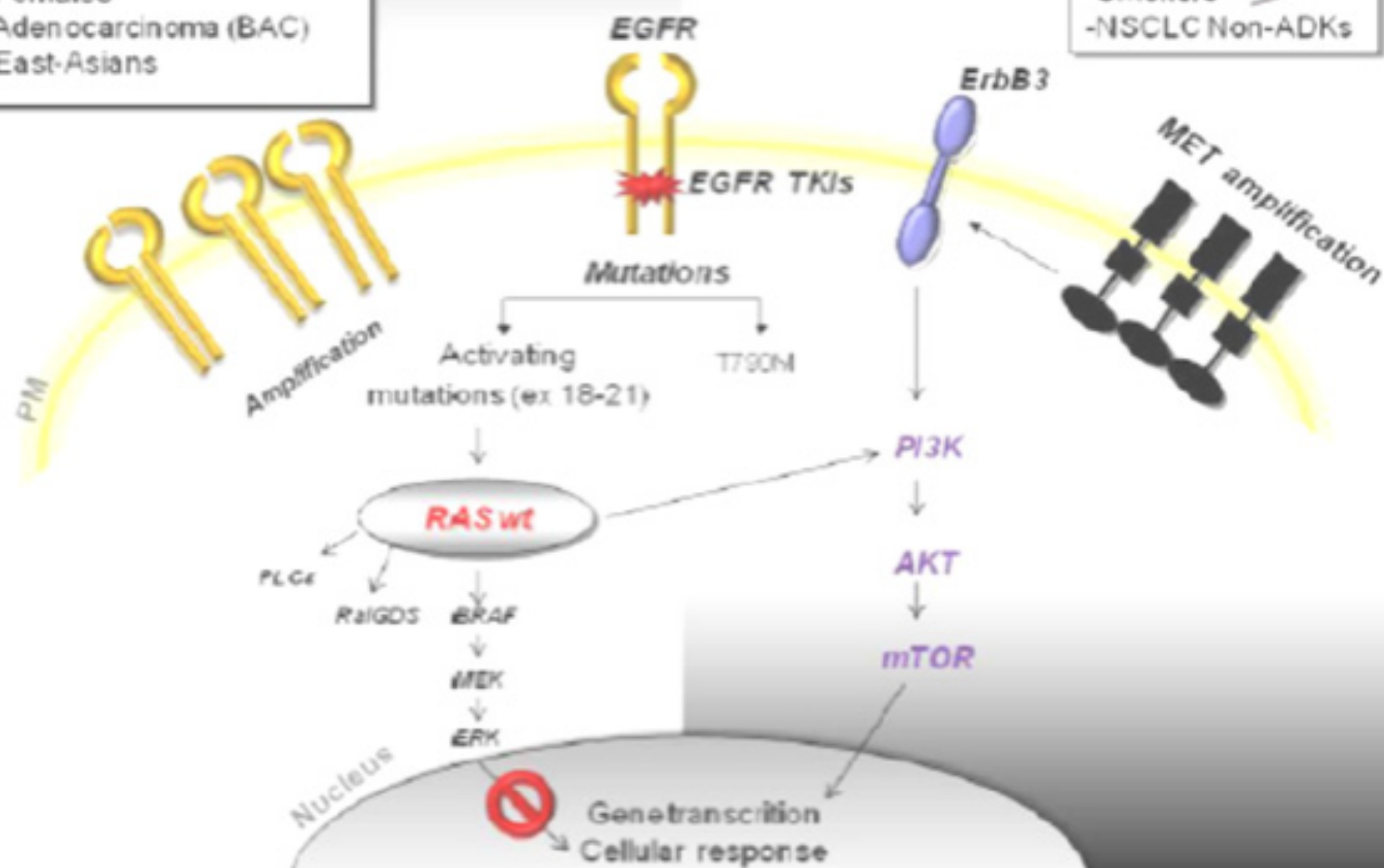
NSCLC Patients selection for EGFR TKIs

POSITIVE SELECTION

- Never smokers
- Females
- Adenocarcinoma (BAC)
- East-Asians

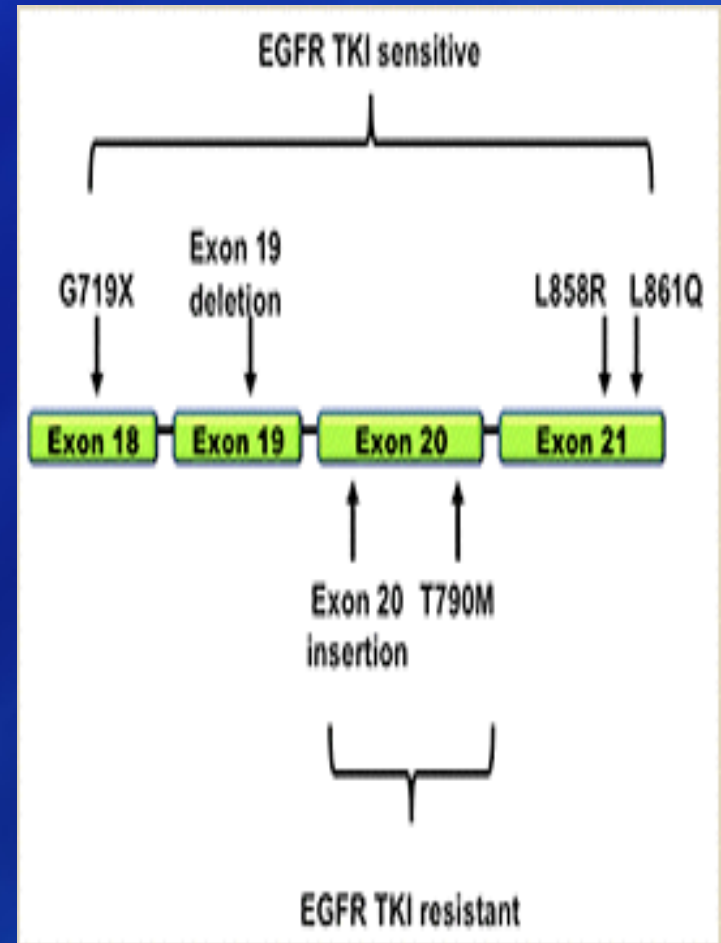
NEGATIVE SELECTION

- Smokers
- NSCLC Non-ADKs



Mechanisms of Resistance

- 2 types
 - Primary or *de novo* resistance
 - Secondary or acquired
- Both types related to EGFR mutations
 - mainly affecting exon 20 - Small insertions or duplication; T790M mutation



Mechanisms of Resistance

- **Newer irreversible EGFR inhibitors (pan-Erb inhibitors) may overcome T790M-mediated resistance**
- **Other genomic alterations can coexist with EGFR mutations**
 - **Mutations of PIK3CA**
 - **Loss of function of the inhibitor PTEN**
 - **Altered IGF1R signaling**

Mechanisms of Resistance

- **In EGFR wild type tumors, downstream genetic lesions may cause TKI resistance**
 - **KRAS mutations; 17% of NSCLC**
 - **BRAF mutations; rare (2%)**
 - **PIK3CA mutations (3%)**
 - **Loss of PTEN expression**
 - **Activating mutations of the AKT gene**
 - **Amplified MET mediates PIK3CA activation via ErbB3 activation**

Mechanisms of Resistance

- **T790M mutation and MET amplification account for 70% of acquired resistance to EGFR inhibitors in NSCLC**
- **Strong rationale for combination anti-EGFR /anti-MET approach**
- **EML4-AKT fusion protein**
 - **Product of gene translocation**
 - **Induces constitutive dimerization & activation of the ALK kinase domain**

Conclusion

- **NSCLC is extremely heterogenous**
 - **As an entity**
 - **Even within an individual patient**
- **Targeted therapy results are mixed and not fully understood**
- **Current biomarkers seem inadequate**
- **Modest improvements in survival have been achieved**
- **The holy grail of markedly effective, personalized NSCLC therapy is still elusive**

Radiotherapy

- **Therapy using ionizing radiation to control or kill malignant cells**
 - **3D Conformal RT**
 - **Intensity-modulated radiation therapy (IMRT)**
 - **SBRT**

SBRT

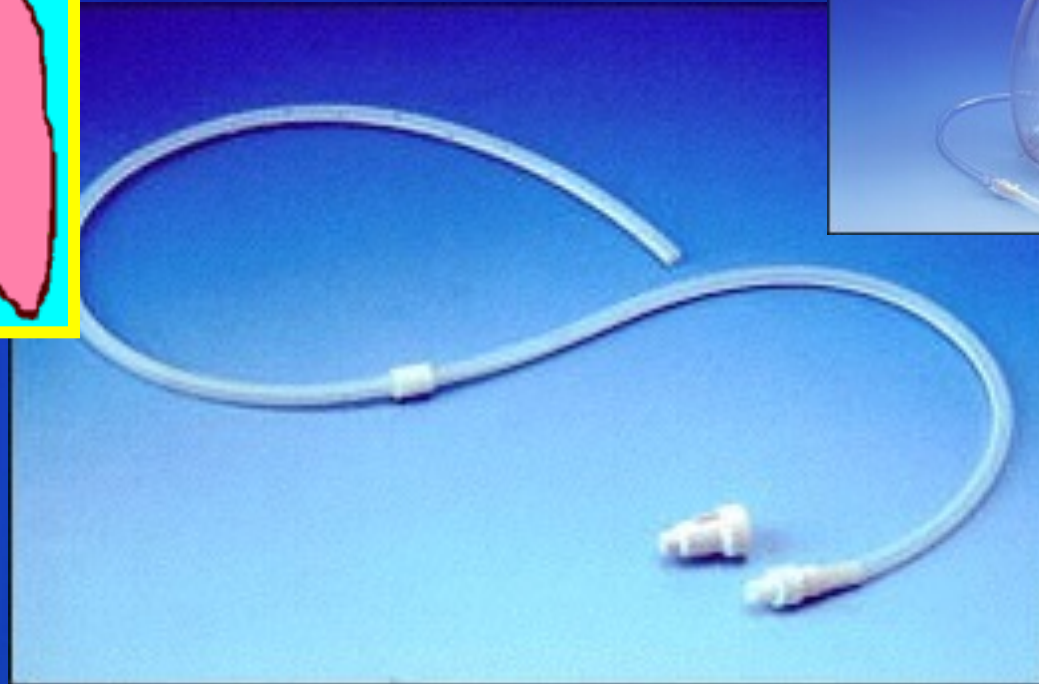
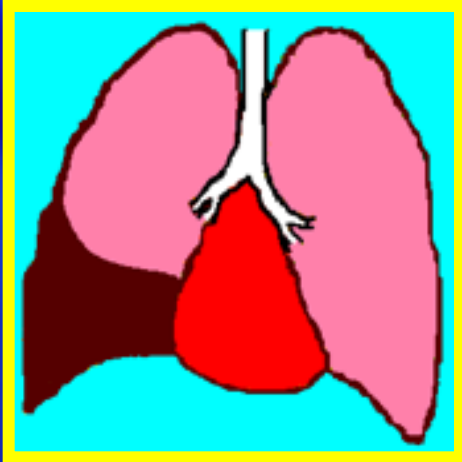
Stereotactic Body Radiation Therapy



Endobronchial Therapy

- **Interventions within the airway via flexible or rigid bronchoscopy**
- **Used for very early (non-invasive) or obstructive disease**
 - **Laser fulguration**
 - **Photodynamic therapy**
 - **Cryotherapy**
 - **Stent insertions**

PleurX Catheter



PleurX Catheter



Management of Advanced Lung Cancer

- **Platin-based combination chemotherapy**
- **Conformal 3-D radiotherapy**
- **Molecularly targeted therapy**
- **Airway obstruction relief – Lasers, PDT, stents**
- **Management of Pleural Effusions**
- **Pain Control & other aspects of Palliative care – dyspnea, psychosocial problems, etc**

Long-term Care

- **Surveillance**
- **Survivorship – Fertility, Cognitive challenges, other disabilities**
- **End of Life Planning – Proxy, Hospice (home or institutional), Intubation or not, DNR (Do Not Resuscitate), etc**

