Non Surgical NSCLC - Overcoming barriers to care – Diagnosis and Referrals

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Webinar Series: Continuum of Care for Non-Resectable NSCLC

-Today is the first of a 3-part webinar series focused on the multidisciplinary care of non-resectable lung cancer patients and focuses on the ***workup and referral*** of the suspected and newly diagnosed lung cancer patient

Webinar 2: July 21 at 6:00 p.m. ET - Non Surgical NSCLC - Best Practices for the Continuum of Care: A Multidisciplinary Approach

Webinar 3: August 16 at 6:00 p.m. ET - Non Surgical NSCLC - Challenging Cases

Overview

Lung cancer screening
Patient Evaluation and Workup
Diagnostic Procedures for Lung Cancer
Molecular Markers in NSCLC
Multidisciplinary Team Care
    -Surgical Evaluation
    -Evaluation for SBRT
    -Locally Advanced NSCLC: Standard treatment and clinical trials
Discussion and audience questions

Goals of the Webinar

-Overcome barriers to timely and appropriate care for lung cancer patients

-Ensure appropriate assessments and staging are obtained for suspected and newly diagnosed lung cancer patients

-Review role of the multidisciplinary team in the workup and management of lung cancer patients

LUNG CANCER SCREENING

Michael Simoff, MD

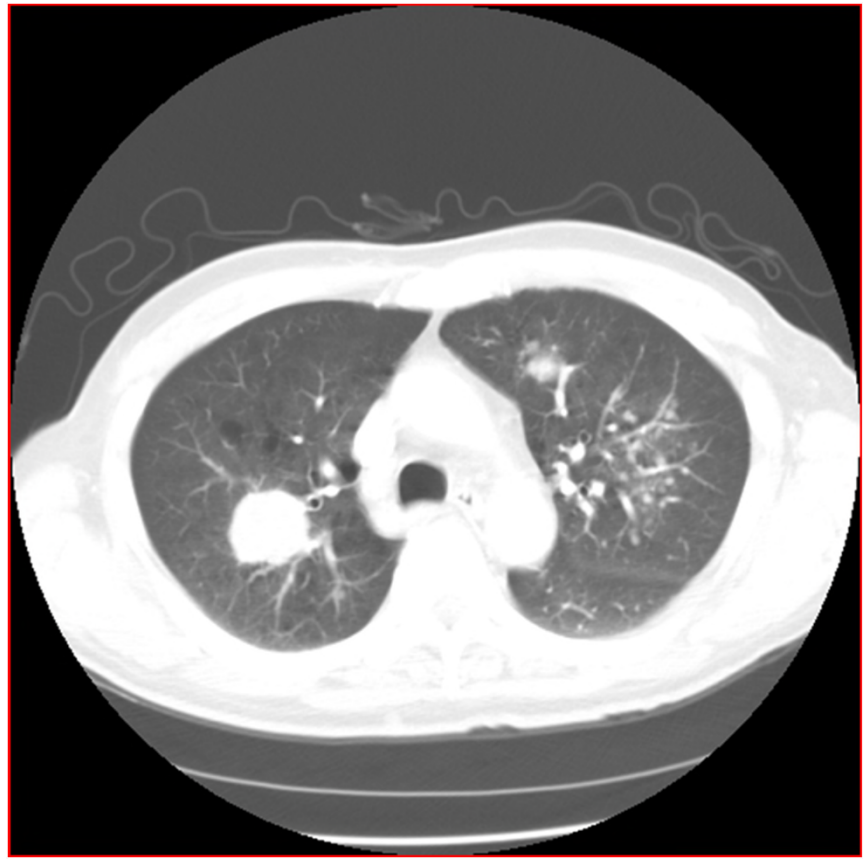
Lung Cancer:
Newly Diagnosed

- Current Smokers: 35%
- Former Smokers: 50%
- Never Smokers: 15%

Lung Cancer: Prevention

1. Primary: Smoking Cessation
    a. Decrease overall lung cancer deaths
    b. Most people who die from lung cancer are FORMER SMOKERS

2. Secondary: Lung Cancer Screening
    a. Find early stage cancer
    b. Decrease mortality, not incidence



History Of Lung Cancer Screening

Biannual CXR

- NW London Mass Radiography Service (1968)

CXR – Sputum

- Memorial Sloan Kettering (1984)
- Johns Hopkins Study (1984)
- Mayo Lung Project (1986)
- Czechoslovakian Study (1986)

LDCT vs CXR

- Keneko et al. (1996)
- Sone et al. (1998)
- ELCAP (1999)

Annual LDCT

- Germany (2002)
- Japan (2002)
- Italy (2003)
- Lung Screening Study (2004)
- Mayo Clinic LDCT study (2005)

National Lung Screening Trial (NLST)

N Engl J Med 2011; 365:395-409august 4, 2011

- NLST was a NCI and ACRIN sponsored controlled trial
  - 53,000 high-risk subjects randomized to either
  - 3 annual chest radiographs (CXR) or
  - 3 annual low-dose chest CT (LDCT) exams

- Inclusion criteria included:
  - Aged 55-74
  - Current or former smokers (quit within the past 15 years)
  - >30 pack-year smoking history.

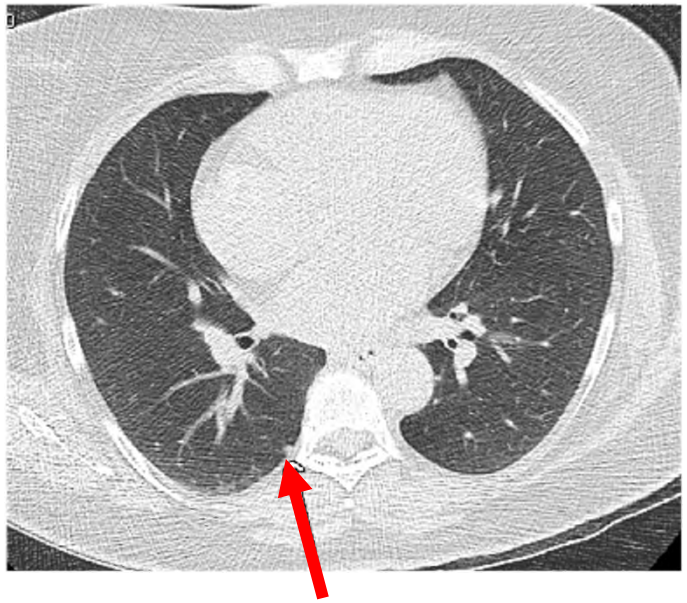
The study was halted early (11/2010) due to attainment of 20% mortality benefit goal in LDCT group.

NLST And Stage Shifting In Lung Cancer Diagnosis

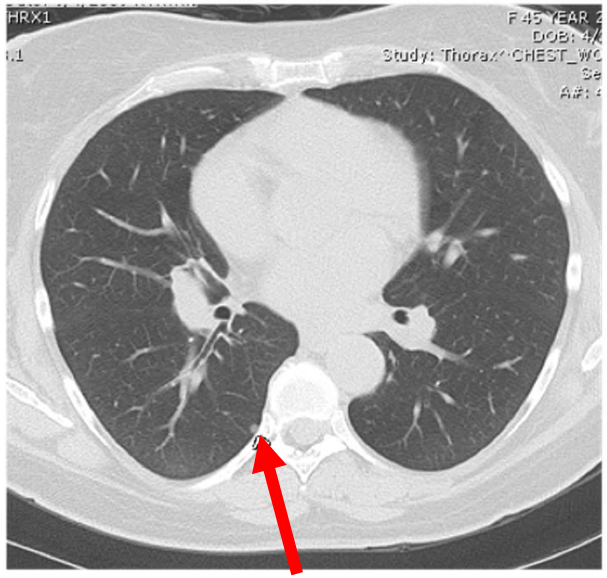
Stage	AJCC - NSCLC	Positive Lung Cancer Screen
I	24%	63%
II	6%	7%
IIIA /IIIB	23%	8-9%
IV	44%	13%
Early Stage (I-II)	30%	70%
Late Stage (III-IV)	70%	30%

Low Dose CT Scanning

- Multidetector computed tomography (MDCT) resolution allows for dose reduction
- Most LDCT <1mSv / Mammography 0.7mSv



1 mSv



10 mSv

Chest CT Interpretation and Lung Cancer Screening

- Fleischner Society Criteria:
  - Used to categorize incidental findings on lung CT scans
  - Have subsequently developed screening recommendations
- LungRADS (ACR)
  - Purpose: Establish a standardized quality assurance tool to mirror the tool widely utilized in Mammography (BI-RADS)
  - Developed to interpret screening studies of the chest to decrease false positive rate
  - Objectives:
    - Standardize terminology
    - Organized reporting and assessment structure
    - Data collection tool to facilitate outcome monitoring

Re-evaluation with LungRADS

	Through May 2014 (JACR publication)	Positive Thresholds: NLST Fleischner		Positive Thresholds: LungRADS	
Clinical Follow-up (n=1603)	Negative/Benign (LungRADS 1 & 2)	1185	73.9%	1435	89.5%
	Positive (LungRADS 3&4)	**26.1%**		**10.5%**	
	Probably Benign (LungRADS 3)	352	22.0%	102	6.4%
	Suspicious (LungRADS 4)	66	4.1%	66	4.1%
	Diagnosed lung cancer • Positive exam result • Includes 3 cases of presumed malignancy[1]	29 (1.8%)		29 (1.8%)	
	Positive Predictive Value	**6.9%**		**17.3%**	
	Biopsy-proven lung cancer • Positive exam result • Excludes 3 cases of presumed malignancy[1]	26 (1.6%)		26 (1.6%)	
	Positive Predictive Value	**6.2%**		**15.5%**	

Screening for Lung Cancer:
US Preventive Services Task Force Recommendation Statement
December 30, 2013

- Recommendation: The **USPSTF** recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to curative lung surgery. (B-recommendation)
- B-recommendations from **USPSTF** qualifies a screening study to be covered by insurance with no deductible

CMS and Lung Cancer Screening

- Initially rejected by CMS but was later accepted with modified patient population:
  - Age 55-77 years (USPSTF recommendation 55-80 years)
  - Asymptomatic (no signs or symptoms of lung disease)
  - Tobacco smoking history of at least 30 pack-years
    - One pack-year = smoking one pack per day for one year;
    - 1 pack = 20 cigarettes
  - Current smoker or one who has quit smoking within the last 15 years

JDM: Joint Decision-Making Appointment (Must be documented in note)

- Age eligibility
- No signs or symptoms
- Specific calculation of years
- Former smoker, years since quitting
- Use of one or more d
  - Benefits and harr
  - Follow-up diagnostic testing potentially needed
  - Define:
    - Over-diagnosis
    - False positive rate
  - Explain total radiation exposure and risks

Time required to complete: 20-25 minutes with an organized PowerPoint presentation by trained personnel

Code G0296
Physician Office Billing: $28.64

- Counseling on the importance of:
  - lung cancer LDCT
  - ties on testing and
  - Ability or willingness to undergo diagnosis
  - portance of
  - Maintaining cigarette smoking abstinence if former smoker;
  - Or the importance of smoking cessation if current smoker
    - Tobacco cessation discussion/referral
  - Data to be uploaded to national database (ACR)

Lung Cancer Screening Programs

Centralized

- Organized from single office for entire health system
- Administrative and medical structure
- Centralized databasing
- JDM structure
- Pipeline to advanced testing or diagnostic procedures

Decentralized

- Independent physicians must perform JDM as part of visits
- Order screening CTs
- Review screening CTs and follow recommendations
- Consult appropriate specialists pending results

Lung Cancer Screening At HFH: Centralized Program

Year	Screening CT Complete	Lung Cancer
2011	3	
2012	12	
2013	28	
2014	569	1
2015	222	1
2016	754	9
2017	131	30
2018*	2164	32
2019	3314	57
2020	3495	65
Total	11992	195

- 2011: Out of pocket - $350
- 2013: Out of pocket to $99 in last quarter
  - 22 scans in last quarter
- 2014: Marketing of $99 scans
- 2015: CMS covers LCS CT scans
- 2018: Became centralized program

HFH Data 2019 & 2020

2019	
Screening CTs	
Initial	2470
Subseq	844
Total Scans	3314
New Cancers	57
Smoking cessation referrals	1106

2020	
Screening CTs	
Initial	1766
Subseq	1715
Total Scans	3495
New Cancers	65
Smoking cessation referrals	896

Number Needed to Screen

NNS

[Patients screened to prevent one cancer death]:

Cancer	NNS
• Lung	320
• Breast	233-746 (various subgroups)
• Colorectal	1176
• Prostate (PSA)	1254

HFH NNS LCS:

- 2018 55
- 2019 58
- 2020 53

Concluding Remarks

- 450 Americans die per day due to lung cancer
  - Lung cancer screening can begin to reduce this number
- Screening is based on excellent data
- Primary care physicians do not have the time to perform actual JDM
- Research needs to be supported for further evaluation of:
  - Additional high-risk populations
  - The use of concurrent liquid or exhaled markers of risk
  - How to maximize integration and follow-up
  - The influence of S-modifiers to further evaluation and management of patients
- Education of the entire medical community is needed
- Screening must be developed as a system-wide program or a centralized structure needs to be constructed at regional or the state level to manage LCS programs
- Newest USPSTF Guidelines will improve screening opportunities

LUNG CANCER PATIENT EVALUATION AND WORKUP

Janani Reisenauer, MD

Cognitive Processes

Clinical Processes

History & Physical Exam
CXR, CT, labs
Assess patient values
Functional status

⇨

Evaluate for Paraneoplastic syndromes
Presumptive initial clinical diagnosis
Presumptive initial clinical stage

⇨

Treat paraneoplastic syndrome
Evaluate co-morbidities, Physilogic status
Confirm clinical stage
Confirm clinical diagnosis

⇨

Establish final treatment plan

Clinical Approach to Lung CA

Initial Evaluation—History

- **Risk Factors**
  - Smoking, Age, Prior Cancer, Occupational exposure
- **Pulmonary symptoms**
  - Cough, dyspnea, wheeze, hemoptysis
- **Extrapulmonary symptoms**
  - Local compression
    - Pain, dysphagia, voice changes, hoarseness
  - Distant metastases & Paraneoplastic syndromes
    - Weight loss, fatigue, anorexia
    - Headache, nausea, weakness
- **Functional Status assessment**

Initial Evaluation—Symptoms

FIGURE 3. [Section 2.0] Range of frequencies of initial symptoms and signs of lung cancer.

Symptoms and Signs	Frequency, %
Cough	8-75
Weight loss	0-68
Dyspnea	3-60
Chest pain	20-49
Hemoptysis	6-35
Bone pain	6-25
Clubbing	0-20
Fever	0-20
Weakness	0-10
SVC obstruction	0-4
Dysphagia	0-2
Wheezing and stridor	0-2

Initial Evaluation—Paraneoplastic

FIGURE 5. [Section 3.0] Paraneoplastic syndromes in patients with lung cancer.

Endocrine syndromes	SIADH	Hypoglycemia
	Nonmetastatic hypercalcemia	Hyperthyroidism
	Cushing syndrome	Carcinoid syndrome
	Gynecomastia	Hypercalcitonemia
	Elevated levels of LH and FSH	
Neurologic syndromes	Subacute sensory neuropathy	Encephalomyelitis
	Intestinal pseudoobstruction	Necrotizing myelopathy
	Lambert-Eaton myasthenia syndrome	Mononeuritis multiplex
	Cancer associated retinopathy	
Skeletal syndromes	Hypertrophic osteoarthropathy	Clubbing
Renal syndromes	Glomerulonephritis	Lactic acidosis
	Nephrotic syndrome	Hypouricemia
	Metabolic syndromes	
Systemic syndromes	Anorexia and cachexia	Fever
Collagen-vascular syndromes	Dermatomyositis	Vasculitis
	Systemic lupus erythematosus	Polymyositis
Cutaneous syndromes	Acquired hypertrichosis languinosa	Exfoliative dermatitis
	Erythema gyratum repens	*Acanthosis nigricans*
	Erythema multiforme	Sweet's syndrome
	Tylosis	Pruritus and urticaria
	Erythroderma	
Hematologic	Leucocytosis and eosinophilia	Anemia
	Leukemoid reactions	Thrombocytosis
	Thrombocytopenic purpura	
Coagulopathies	Disseminated intravascular coagulation	Thromboembolism

Initial Evaluation—Metastasis

FIGURE 1. [Section 2.0, 3.0] Clinical findings suggesting metastatic disease.

Component	Findings
Symptoms elicited in history	Constitutional: weight loss (>10 lb), anorexia, fatigue Musculoskeletal: focal skeletal pain Neurological: headaches, syncope, seizures, extremity weakness, recent changes in mental status
Signs found on physical examination	Supraclavicular lymphadenopathy (>1 cm) Hoarseness, superior vena cava syndrome Bone tenderness Hepatomegaly (>13-cm span) Focal neurologic signs, papilledema Soft-tissue mass
Routine laboratory tests	Hematocrit <40% in men, <35% in women Elevated alkaline phosphatase, GGT, AST, or calcium levels

Imaging Studies

- **CT scan**
  - Tumor size
  - Satellite nodules
  - Atelectasis
  - Local Invasion
  - Mediastinal adenopathy
- **MRI chest**
  - Pancoast tumors
  - Evaluation of chest wall involvement
  - Mediastinal and vessel involvement

PET Scan

Provides information on
- Primary tumor
- Mediastinal LN
- Distant metastases
- Metabolic activity of the tumor
- Response to therapy
- Planning radiation treatment

Limitations
- Tumour size ≤8mm
- Carcinoid tumors
- GGO
- Mucinous tumors
- FP → inflammatory, infectious, post-obstructive

Extrathoracic Staging

- PET/CT more accurate than CT or PET alone
  - Anatomic details + metabolic function merged

- Prediction of T-stage
  - PET/CT → 86%
  - PET → 46%
  - CT → 68%

De Wever W, et al. Eur Respir J. 2009; 33:201-21
De Wever W, et al. Eur Radiol. 2007;17: 23-32

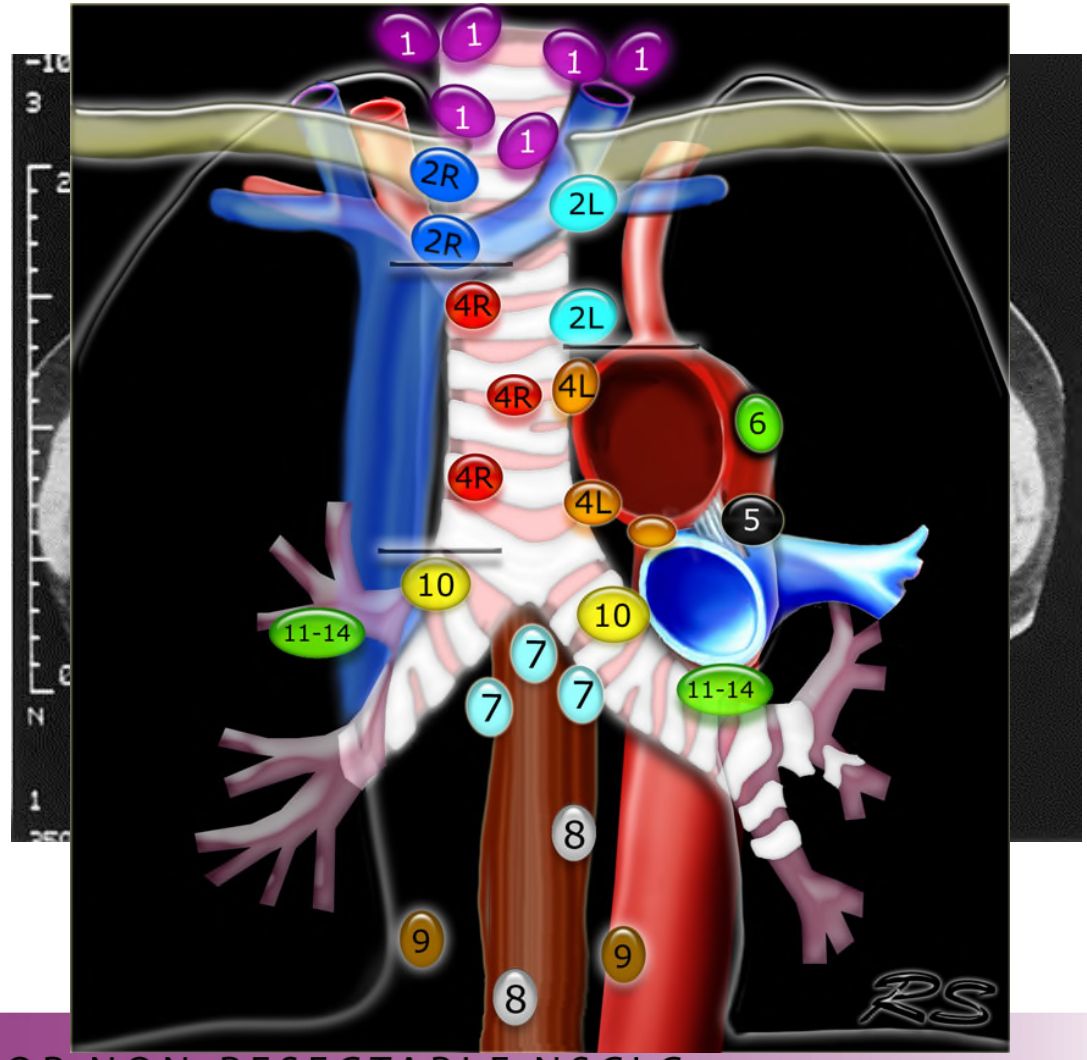
DIAGNOSTIC PROCEDURES FOR LUNG CANCER

Michael Simoff, MD

DIAGNOSTIC PROCEDURES FOR LUNG CANCER

Peripheral nodules

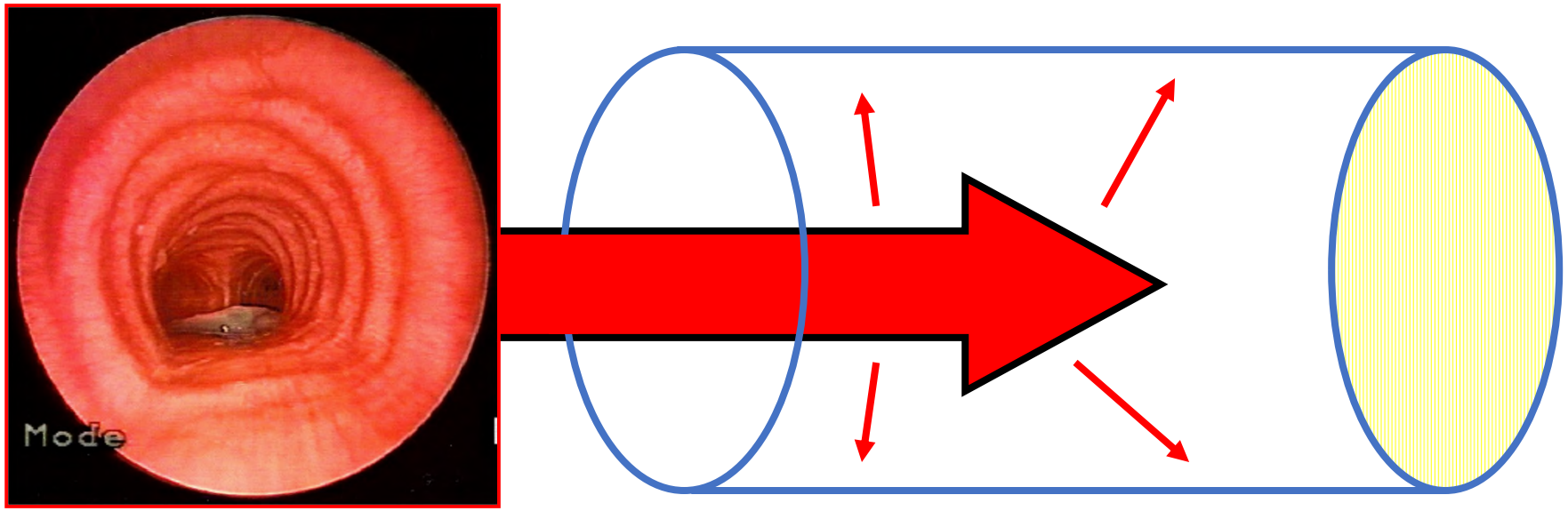
Mediastinal staging



THE HUMAN LUNG

- 22-24 generations
- >100,000 bronchi, bronchioles
- 1500 miles of airways
- 300-500 million alveoli
- 0.3mm in diameter
- Surface area 70m^2
- Capillaries - 616 miles end to end

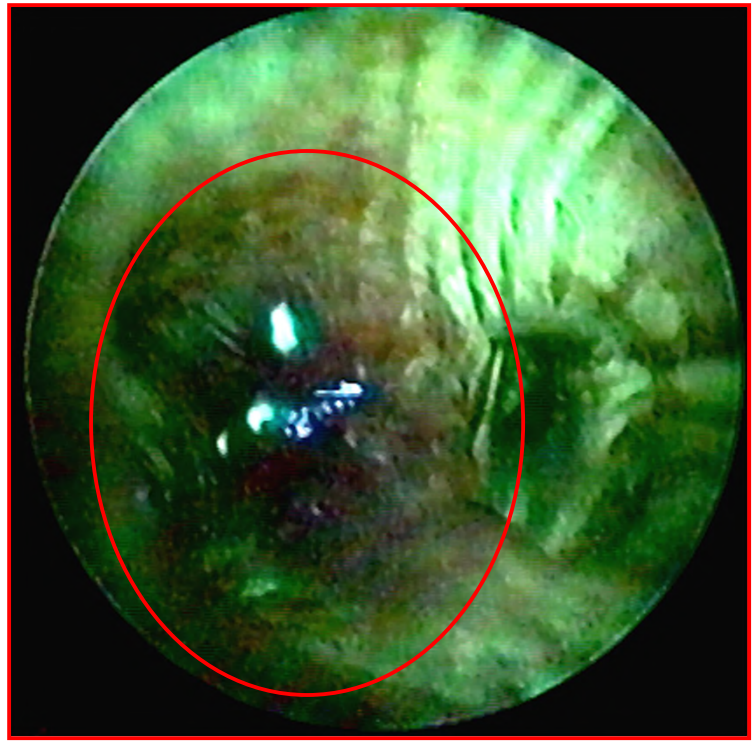
WHITE LIGHT BRONCHOSCOPY



Superficial airway evaluation

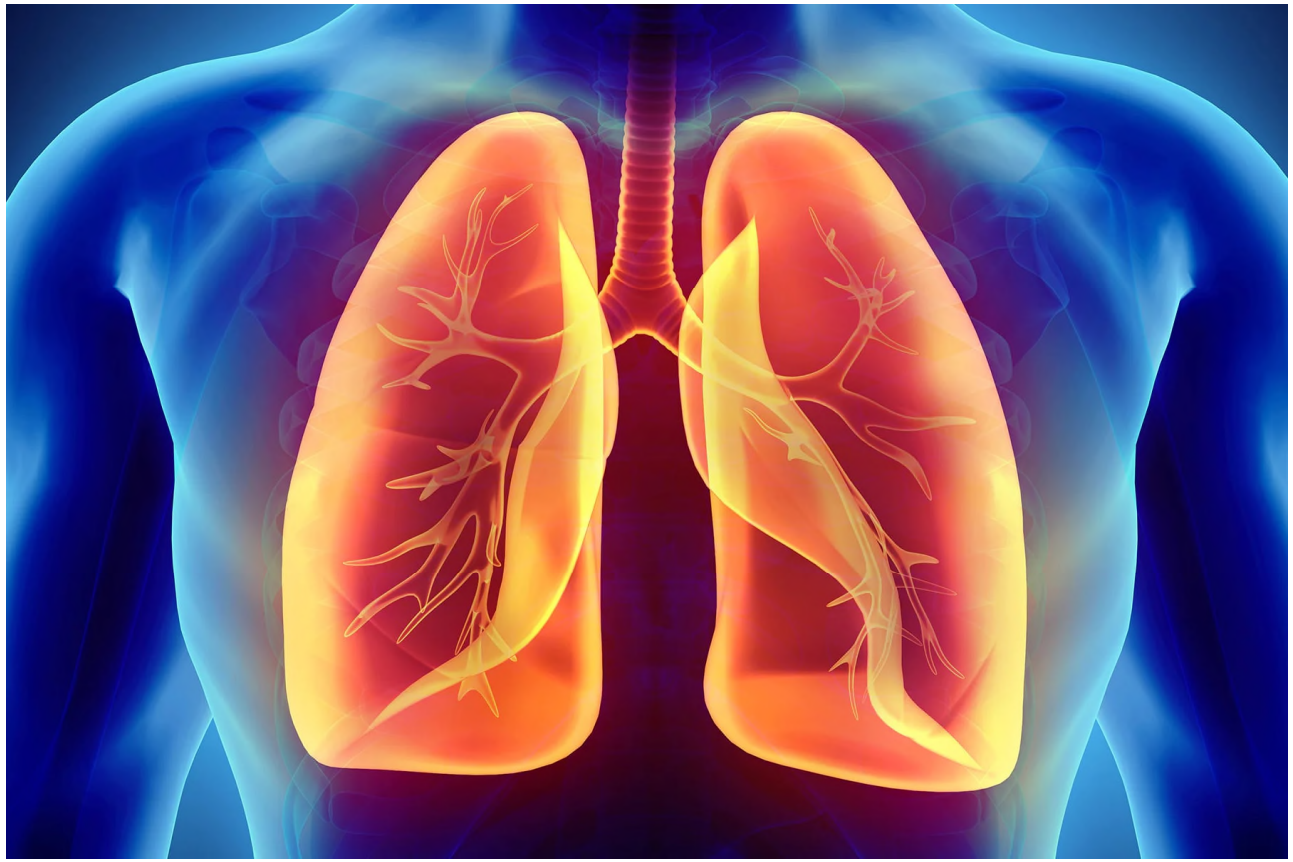
ADVANCED DIAGNOSTIC TECHNIQUES

- Autofluorescence
- Radial Probe Endobronchial Ultrasound
- EBUS - TBNA
- Electromagnetic Navigation
- CT Fluoroscopy / Cone Beam CT Guided Bronchoscopic Biopsies
- Cyrobiopsies
- Robotic Bronchoscopy

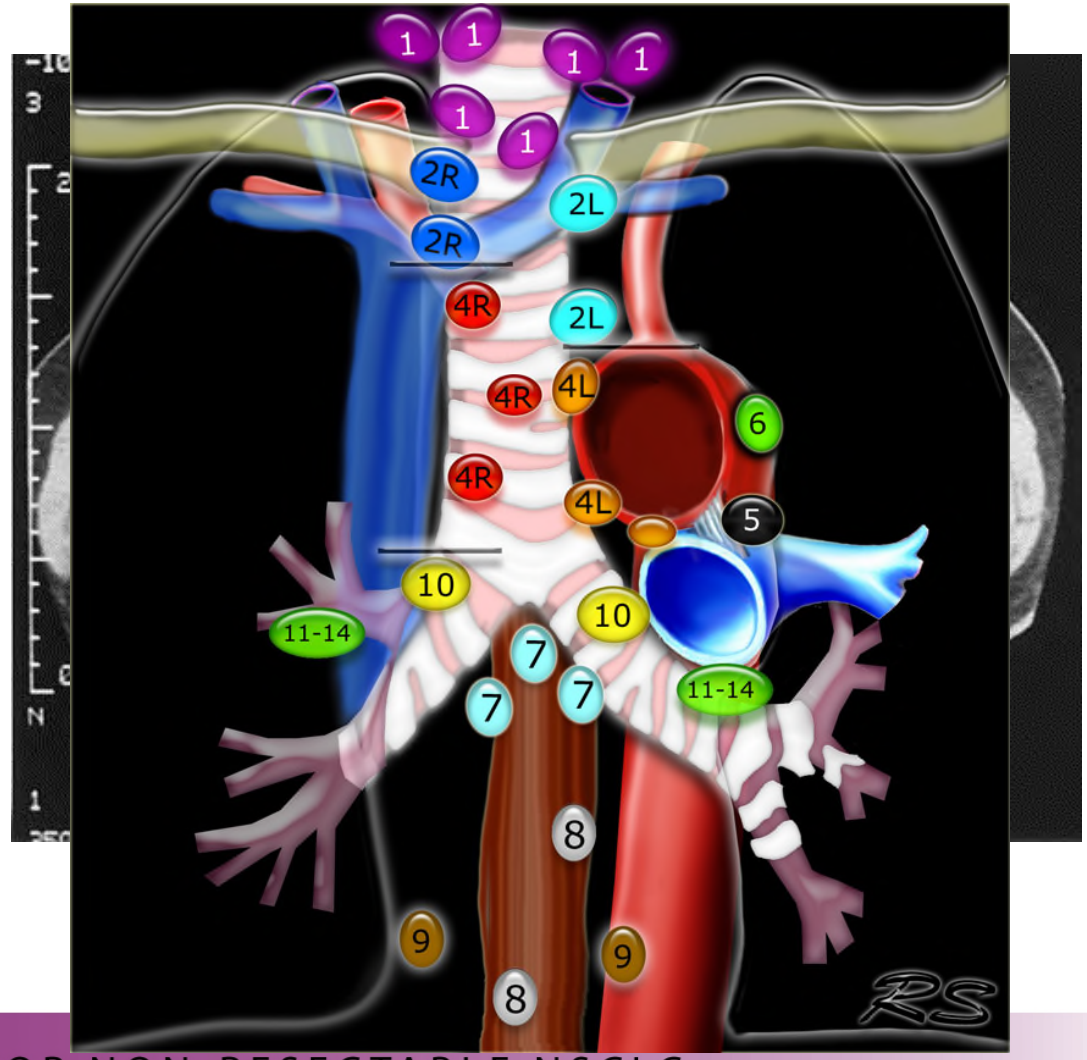


DIAGNOSTIC PROCEDURES FOR LUNG CANCER

Peripheral nodules

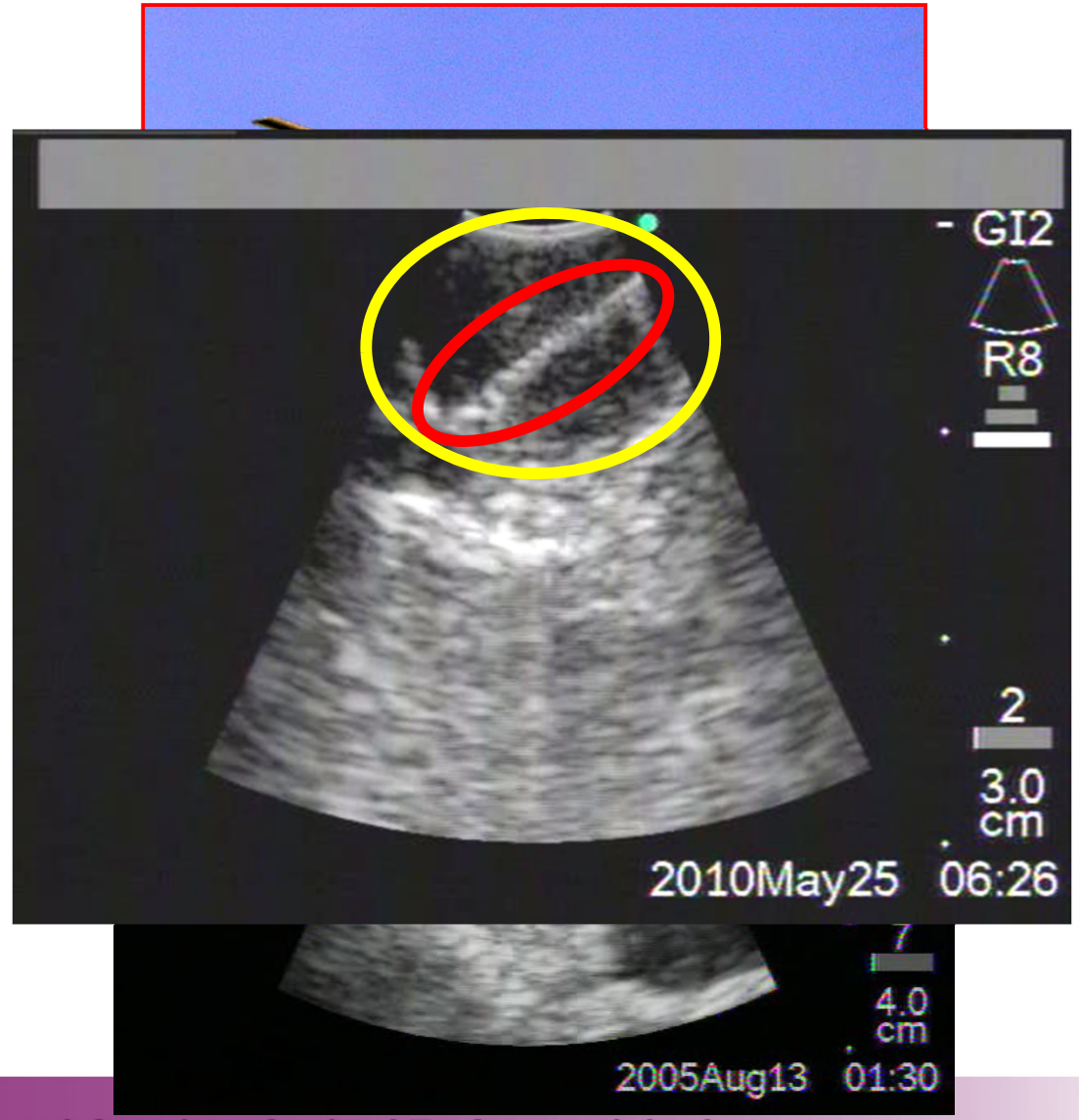


Mediastinal staging

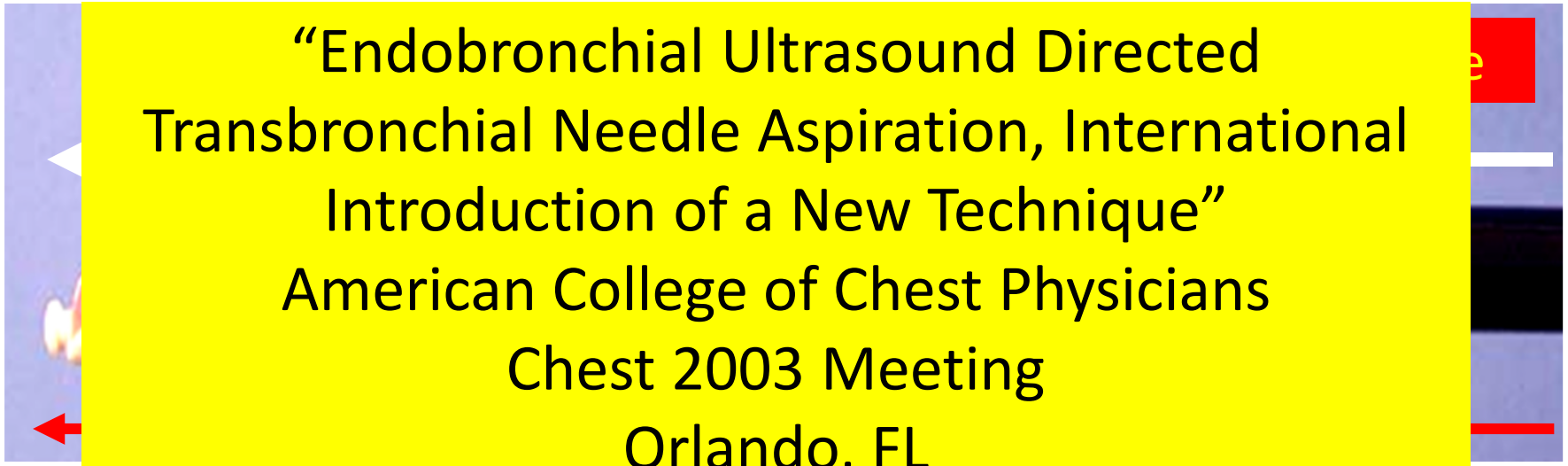


EBUS GUIDED TBNA

- Needle is extended with both visual and ultrasound imaging
- Incorporate a directional ultrasound probe into a bronchoscope
- Real time transbronchial specimens



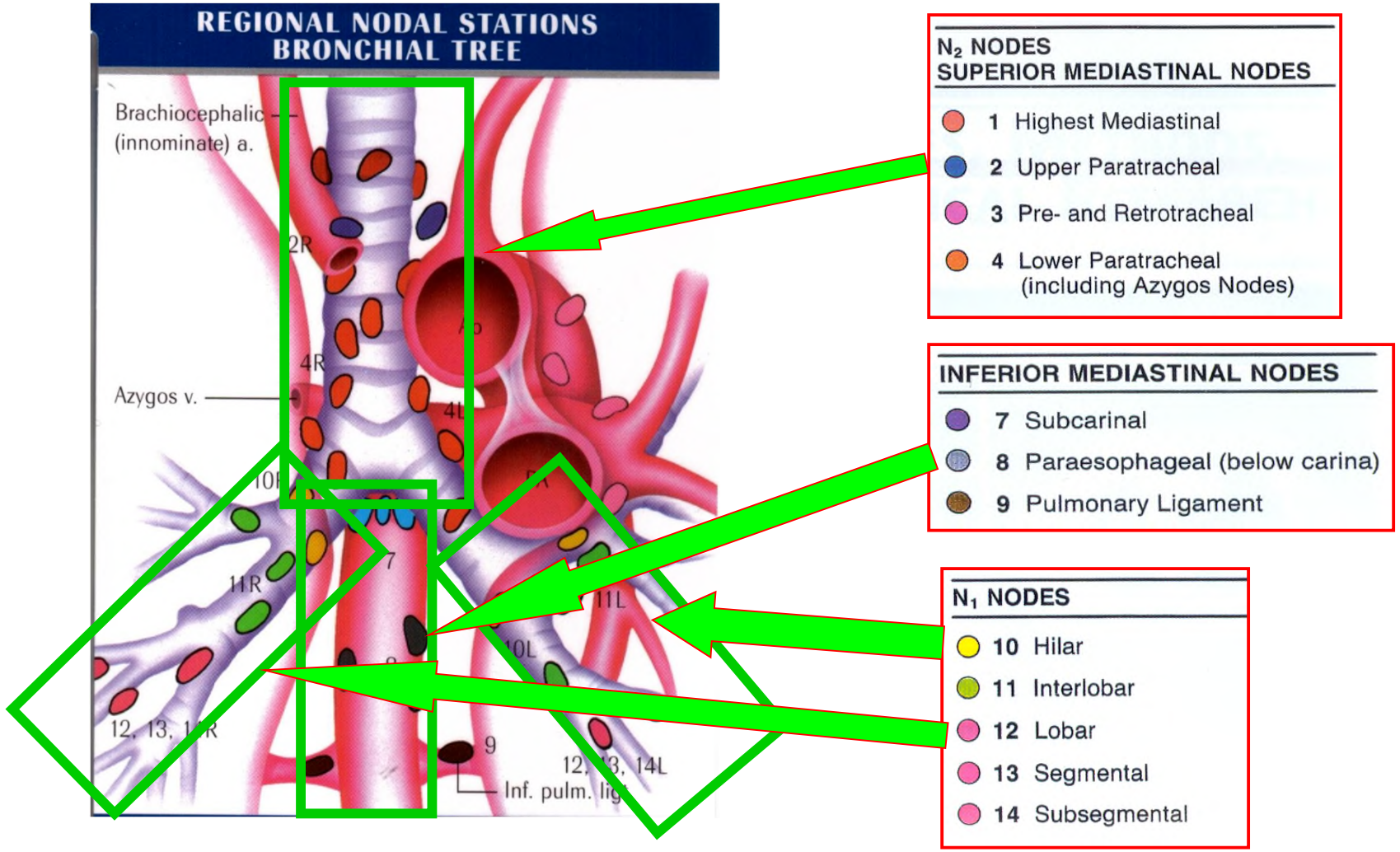
ENDOBRONCHIAL ULTRASOUND GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION



"Endobronchial Ultrasound Directed Transbronchial Needle Aspiration, International Introduction of a New Technique"
American College of Chest Physicians
Chest 2003 Meeting
Orlando, FL
October 2003.

	Fiberscope	Videoscope
Outer Diameter:	6.7mm	6.2mm
Working Length:	550mm	600mm

LYMPH NODE STATIONS



LUNG CANCER AND NEGATIVE CT SCANS

CT negative lymph nodes

- 100 patients, all nodes less than 10mm in short access
- EBUS-TBNA followed by thoracotomy or mediastinoscopy
- Mean diameter 8.1mm
- When appropriate LN are biopsied
  - 22% positive for malignancy
  - 16% had a change in therapy

Herth et al. Eur Resp J 2006

LUNG CANCER AND NEGATIVE PET SCANS

<u>CT & PET negative lymph nodes</u>

- 97 patients negative PET/CT scans
  - Mean diameter 7.9mm
- When appropriate LN are biopsied
  - 8% positive for cancer
  - 6% had a change in therapy

Herth et al. Chest 2008

EBUS vs. MEDIASTINOSCOPY

	Lymph node size in mm: Mean ± SD	EBUS yield (%)	Mediastinoscopy yield (%)	p value*
All Lymph Nodes	15 ± 2.6 (10-21)	109/120 (91)	94/120 (78)	0.007†
LN stations				
2 all	16 ± 3.1 (10-21)	24/25 (96)	22/25 (88)	0.30
2 right	18 ± 1.6 (14-20)	12/13 (92)	11/13 (85)	0.99
2 left	14 ± 3.6 (10-21)	12/12 (100)	11/12 (92)	0.99
4 all	15 ± 2.6 (10-19)	45/54 (83)	40/54 (74)	0.24
4 right	15 ± 2.6 (10-19)	29/34 (85)	24/34 (71)	0.14
4 left	15 ± 2.6 (10-19)	16/20 (80)	16/20 (80)	0.99
7	15 ± 2.4 (10-19)	40/41 (98)	32/41 (78)	0.007†

Ernst A et al., JTO, 2008

“The prospect of cure depends on stage.”

Stefano Gasparini, MD
Heidelberg, Sept. 2002

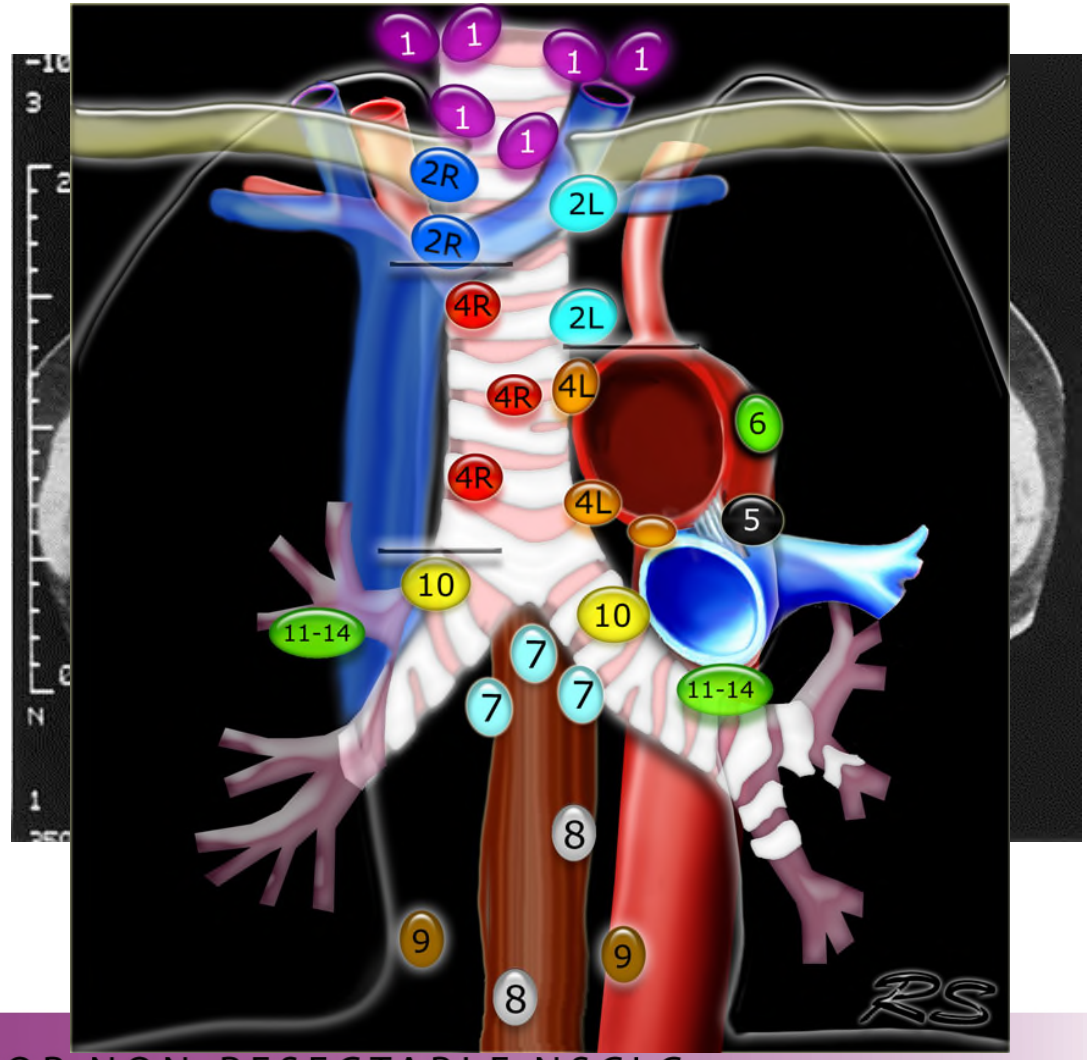
“If you don’t look at lymph nodes, everyone has stage I non-small cell lung cancer.”

Malcome DeCamp, Jr. MD
Beth Israel Deaconess

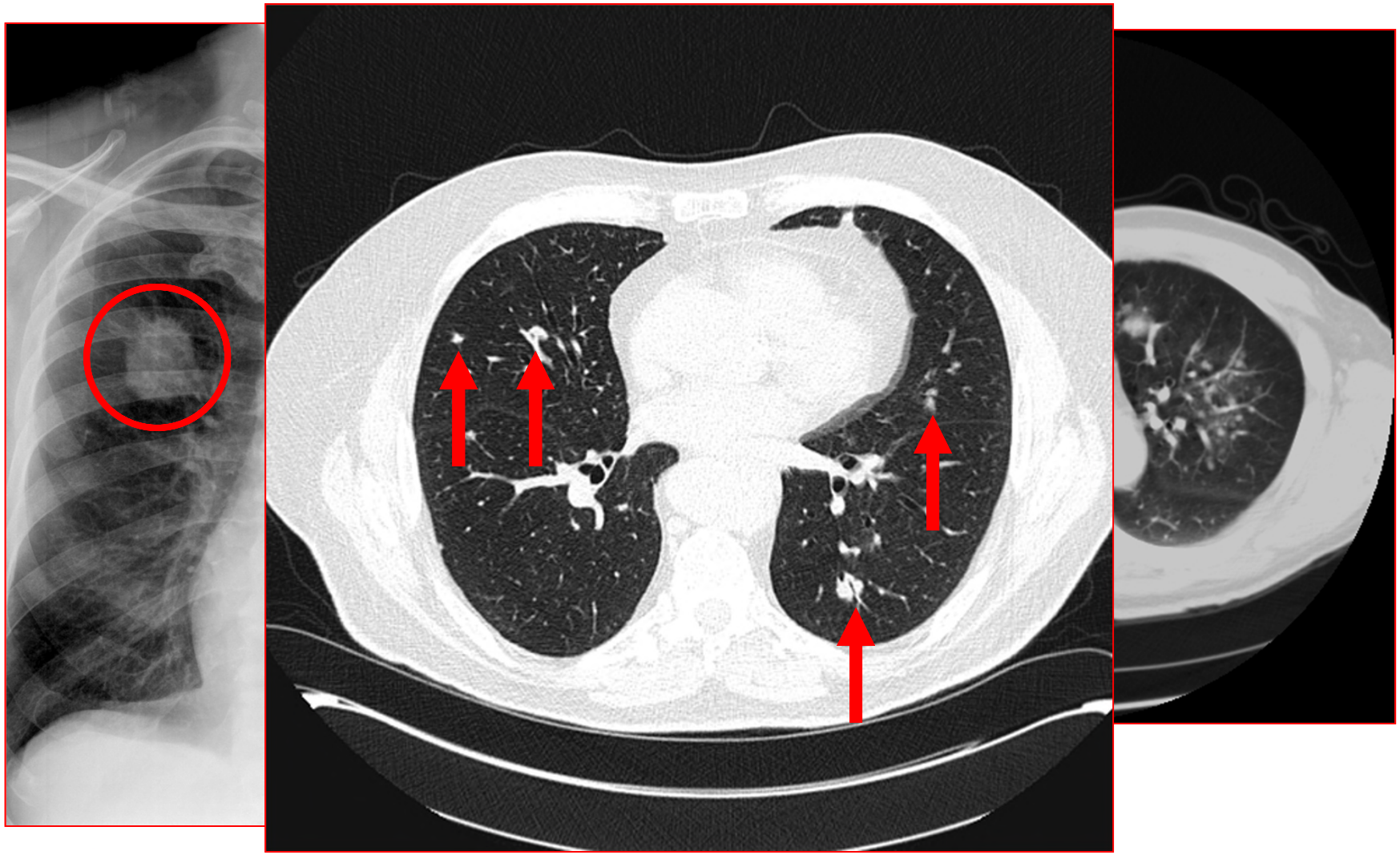
DIAGNOSTIC PROCEDURES FOR LUNG CANCER

Peripheral nodules

Mediastinal staging

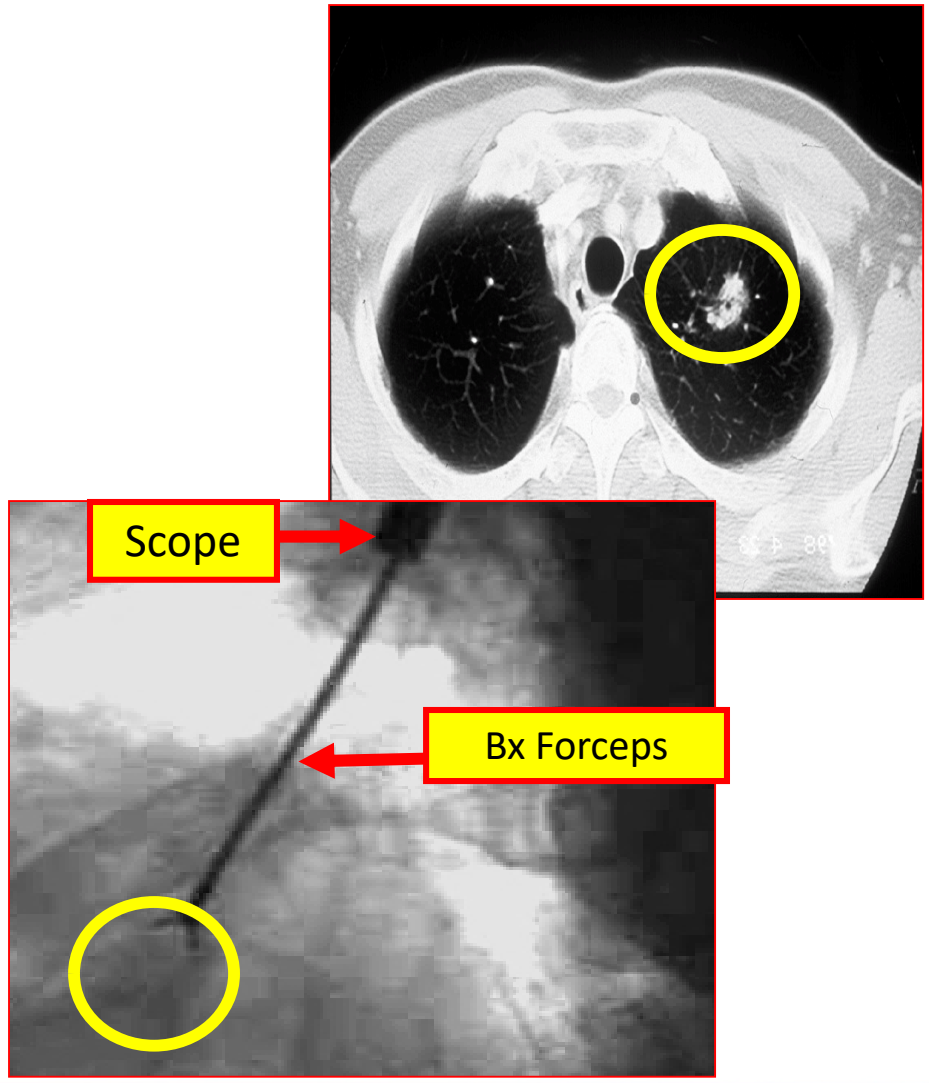


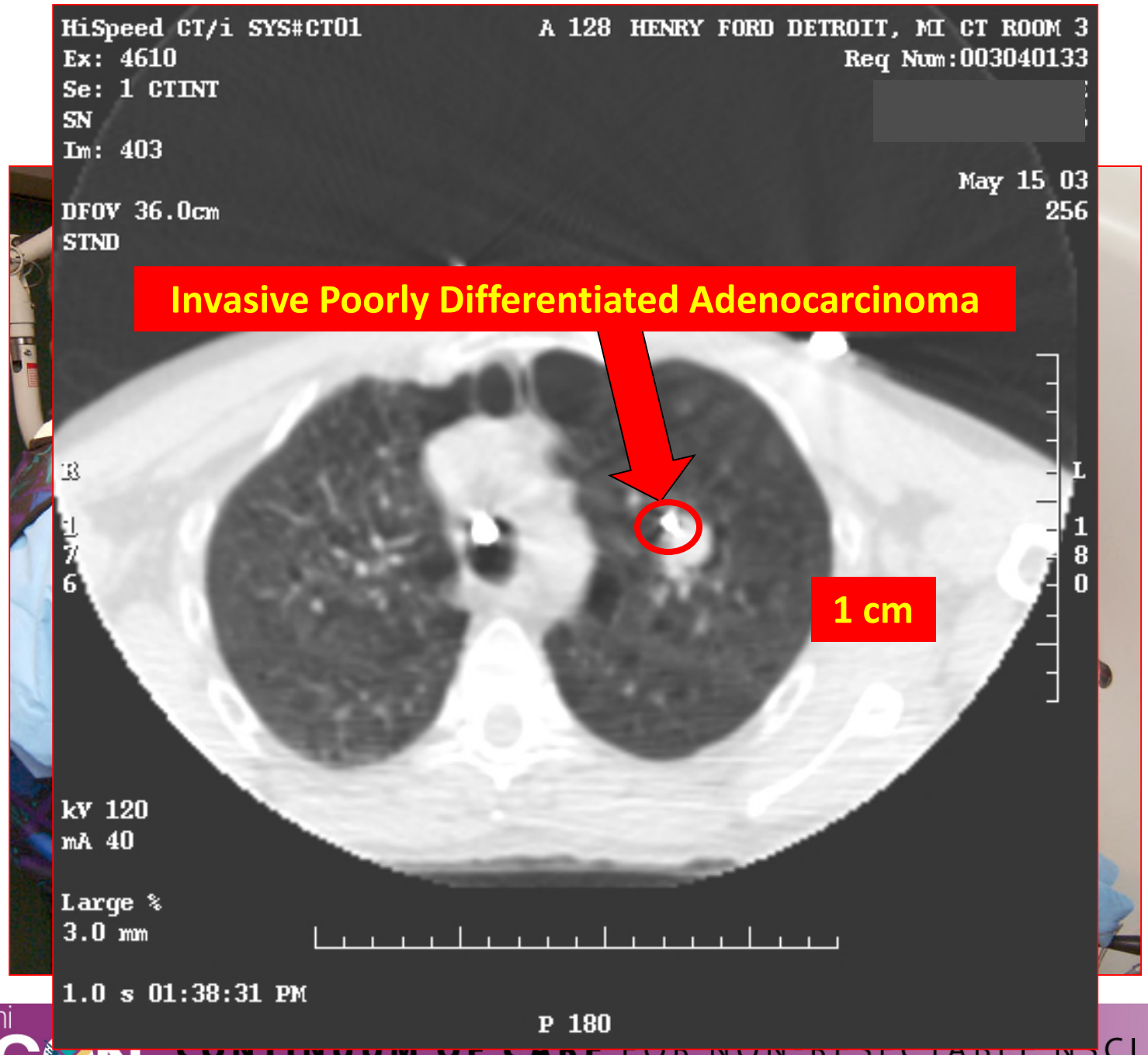
SOLITARY PULMONARY NODULES



TRANSBRONCHIAL BIOPSY OF SPN

- Peripheral lesions are beyond bronchoscopic visualization
- Sampling techniques are guided using fluoroscopy
- Lesions that are $\leq$ 2 cm not visible with fluoroscopy

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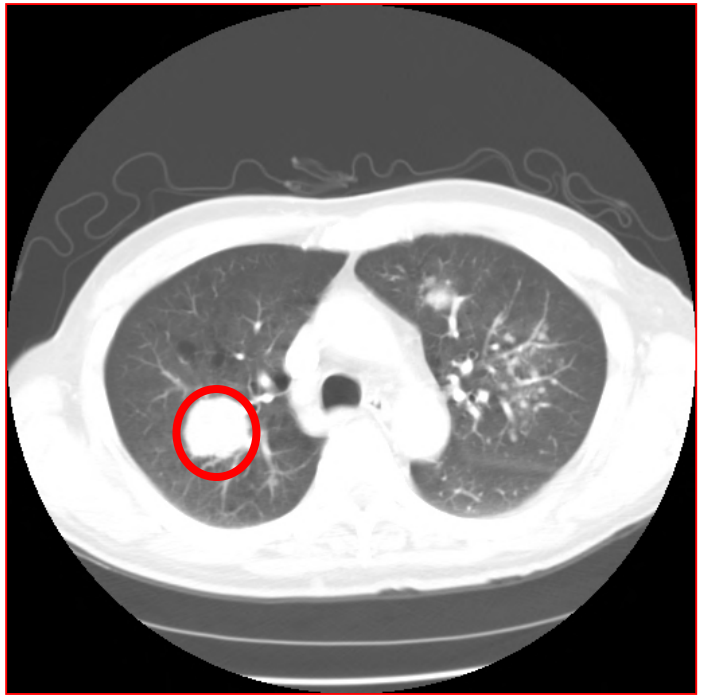
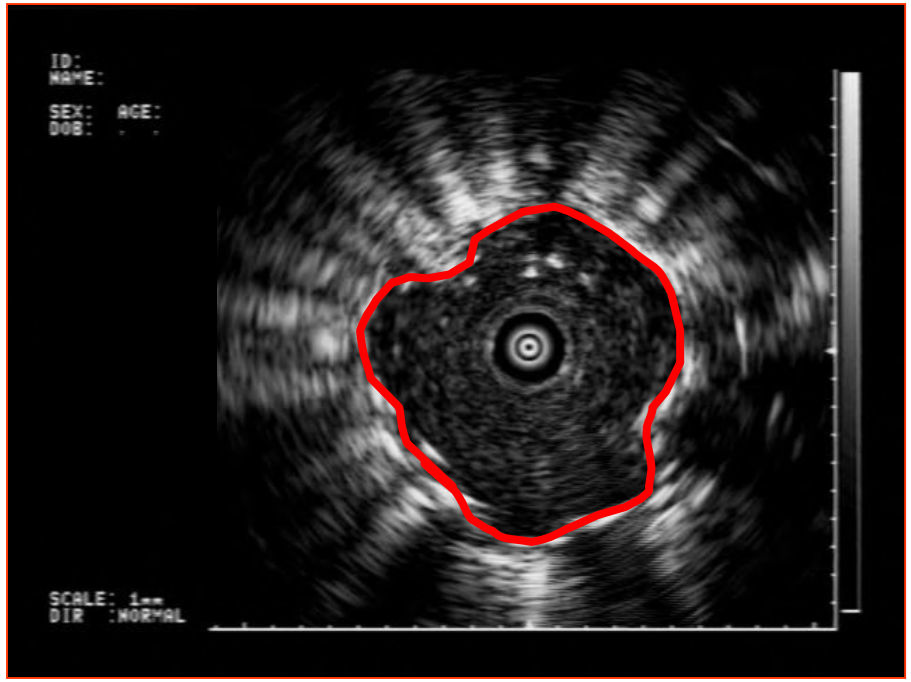
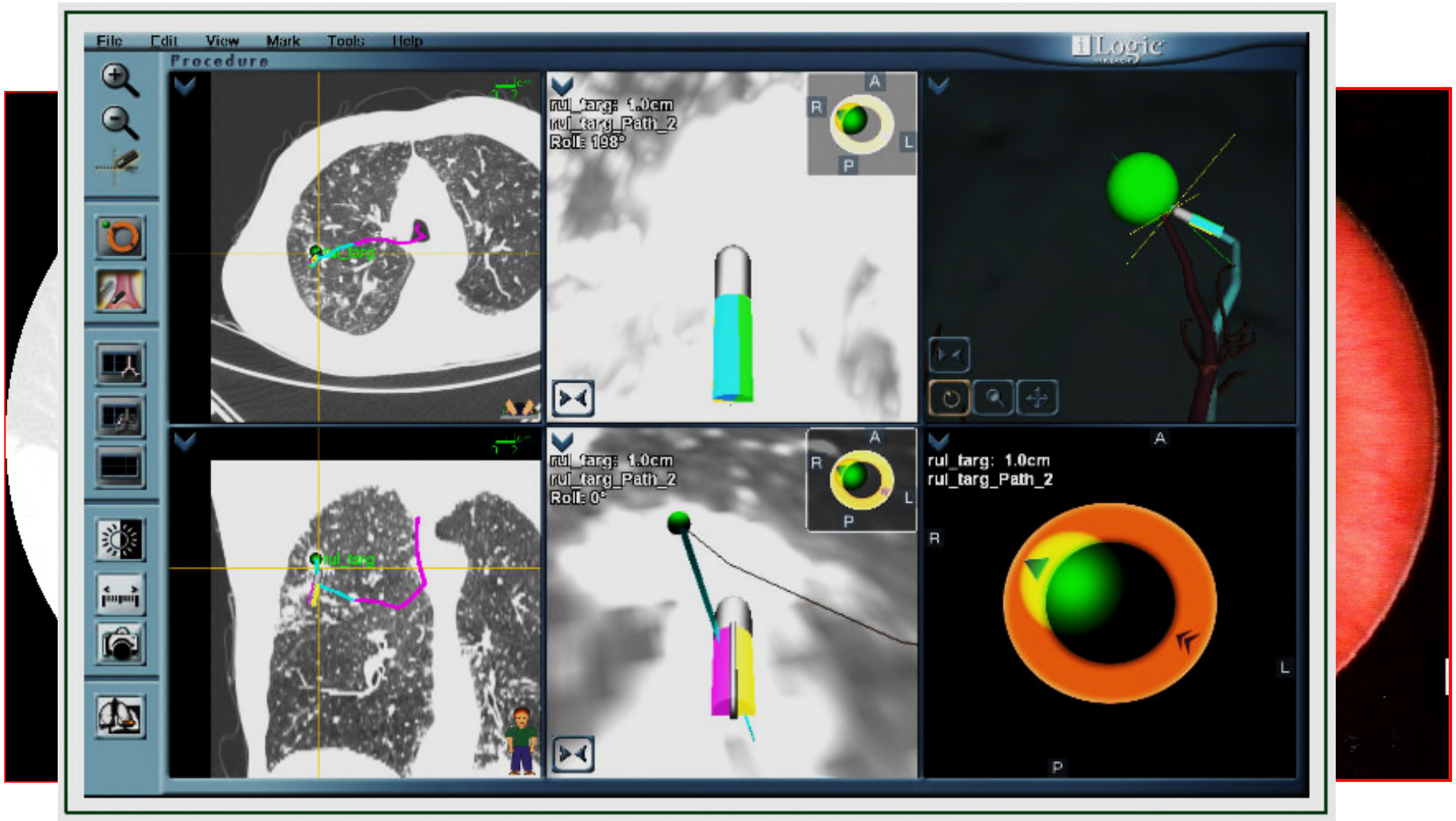
EBUS AND PERIPHERAL LESIONS





- A lung nodule/mass is soft tissue, therefore will transmit ultrasound waves very efficiently
- When the waves run into lung, it causes a very distinct edge, with much of the sound reflected back

ELECTROMAGNETIC NAVIGATION



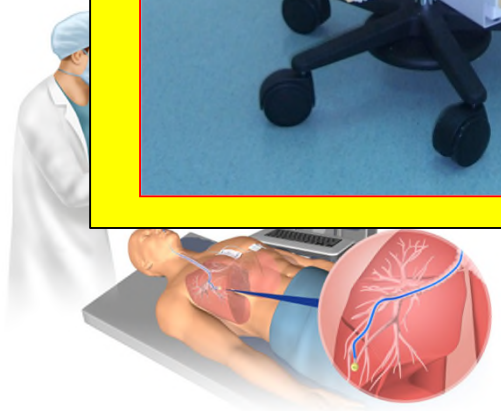
CURRENT DIAGNOSTIC YIELDS FOR ELECTROMAGNETIC NAVIGATION

- Clinical experience trials: Becker 2005, Schwarz 2006, Gildea 2007, Makris 2007, Eberhart 2007, Wilson 2007, Weiser 2008, Bertoletti 2009, Lambrecht 2009, Eberhardt 2009, Zhang 2015
- All authors with yields in the 70-75% range
- 4 meta-analyses report 70% average yield
- These studies were at academic centers
- Studies of all users have demonstrated yields of <50%

ELECTROMAGNETIC NAVIGATION

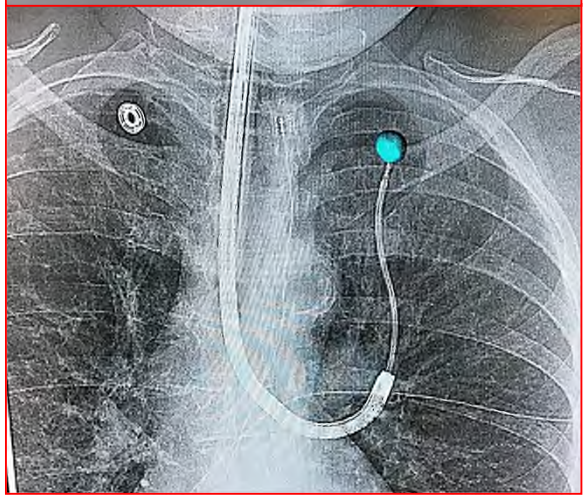
- Olv
- Lu
- Ve
- su

- superDimension LTD
- Five Systems released first year
- HFH
- 2005

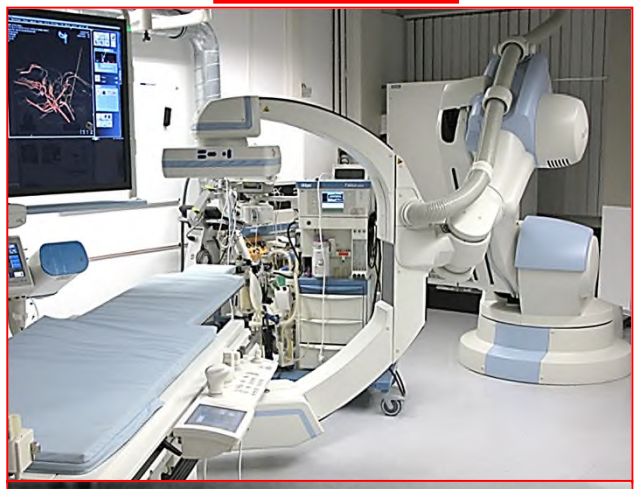


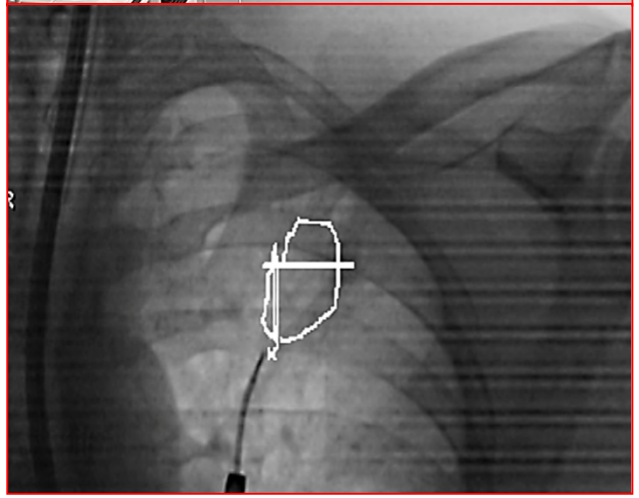
CONE BEAM CT

Philips

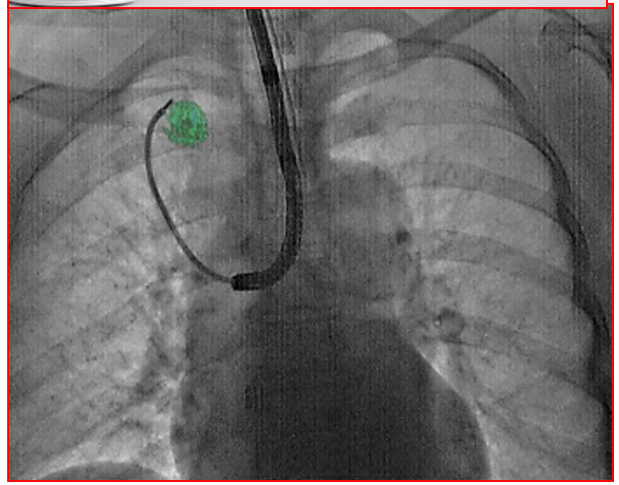


Siemens





GE



CONE-BEAM CT WITH AUGMENTED FLUOROSCOPY AND ENB

- Diagnostic Yield*
  - All lesions 83.7%
  - ≤10mm (n=19) 84.2%
  - ≤20mm (n=65). 83.1%
  - >20mm (n=27). 96.3%
- Sensitivity for Malignancy
  - 91.3% - 95.5%
- Prevalence of Malignancy
  - 71.7% - 75.0%
- Diagnostic Accuracy**
  - All lesions 93.5%
  - ≤10mm (n=19) 89.5%
  - ≤20mm (n=65). 90.8%
  - >20mm (n=27). 100%
- Negative Predictive Value
  - 79.3% - 89.7%
- Average CBCT scans per case: 1.5
  - Average effective dose of 2.0 mSv per CBCT scan

* Diagnostic yield only included definitive malignant or benign diagnoses and excluded all indeterminate results
**Diagnostic accuracy represents the malignant and benign lesions as well as the indeterminate lesions confirmed as benign with clinical and radiographic follow-up divided by the total number of lesions biopsied.

JOBIP 2018; 25:273-281

CURRENTLY AVALIABLE BRONCHOSCOPIC ROBOTS

Auris Monarch

Intuitive Ion

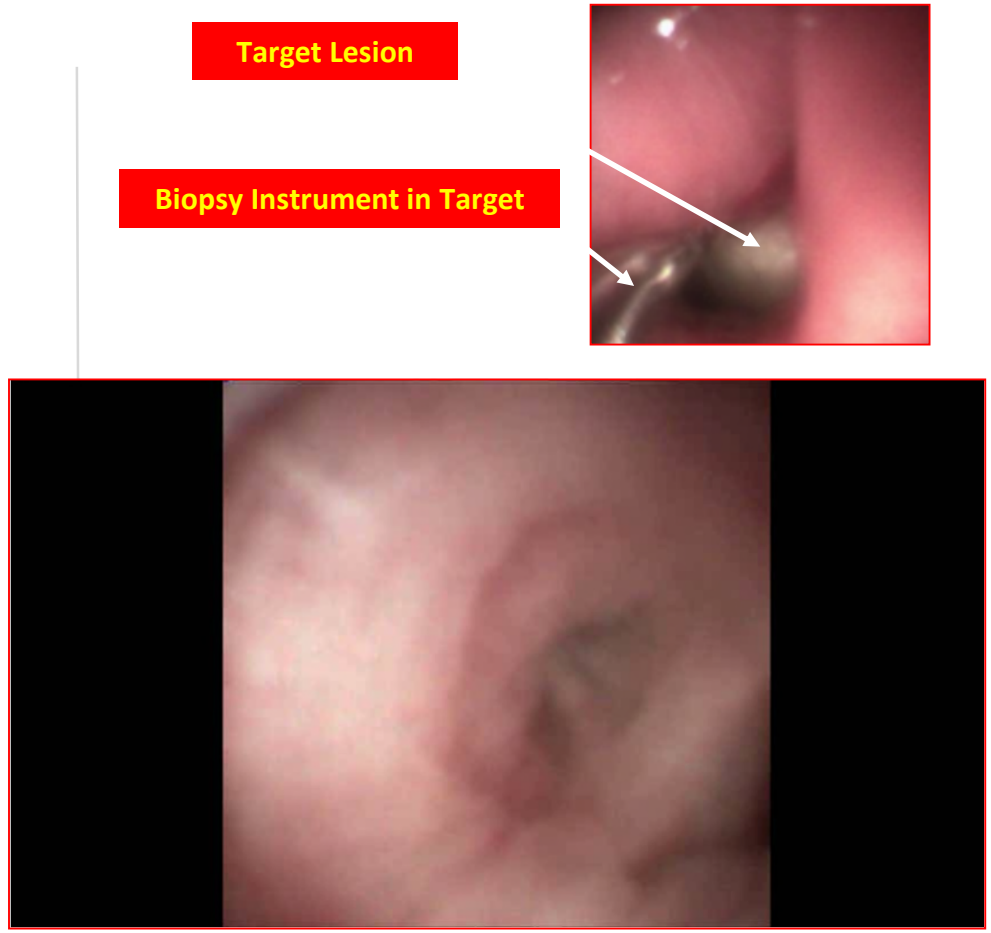
ROBOTIC BRONCHOSCOPY

<u>Requirements for Robotic Bronchoscopy</u>

- Reach
- Access
- Control Stability
- Location feedback
- Ability to perform more complex procedures

FIRST-IN-MAN FEASIBILILITY STUDY: AURIS

- 2014
- Proof of concept
- Robotic endoscopy performed in 15 patients with pulmonary lesions
- Specimens successfully obtained in 14/15 patients using the robotic platform
- No serious adverse events noted



Rojas-Solano J, et al. J Bronchology Interv Pulmonol. 2018

FIRST-IN-MAN INTUITIVE: RESULTS

Nodule Demographics

Nodule Location

- **7th ± 1.5 Generation**
- **66.7% UL's**
- **10% RML**
- **23.3% LL's**

Bronchus sign present

- **60%**

Nodule Size

- **Largest Oblique ⌀:**
- **14.8 mm [10 - 26.4mm]**
- **Largest Cardinal ⌀:**
- **12.3 mm [4.5 – 26.4mm]**

Primary End Points: Feasibility and Safety

97% **Feasibility**

0% **Pneumothorax or Excessive Bleeding**

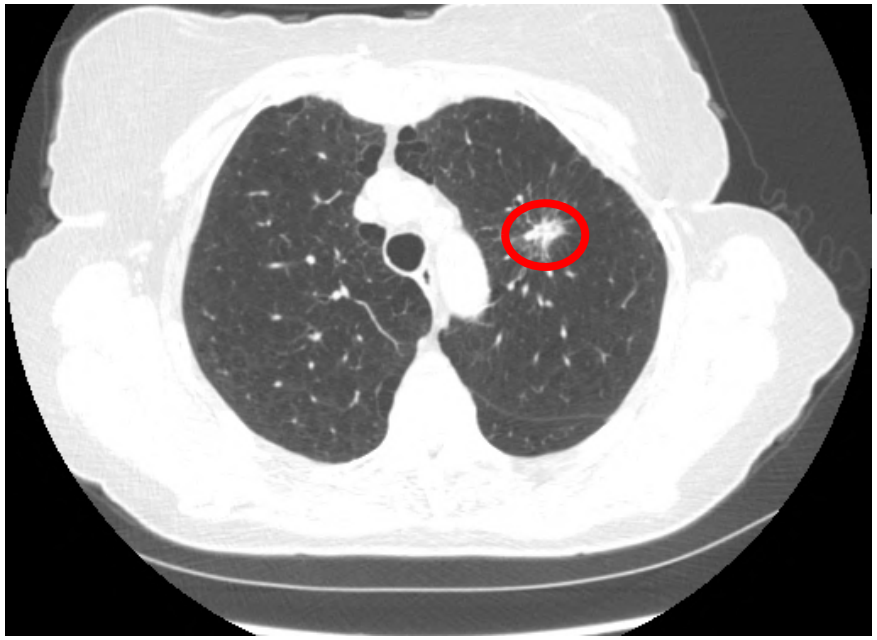
Subject and Sample Results: Clinical Diagnosis through 6 month F/U

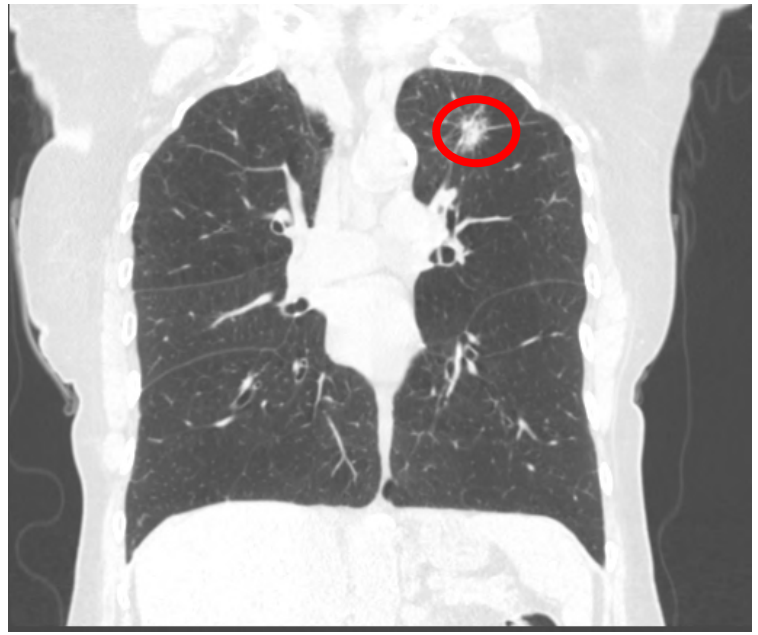
80% **Diagnostic Yield – System Sample**

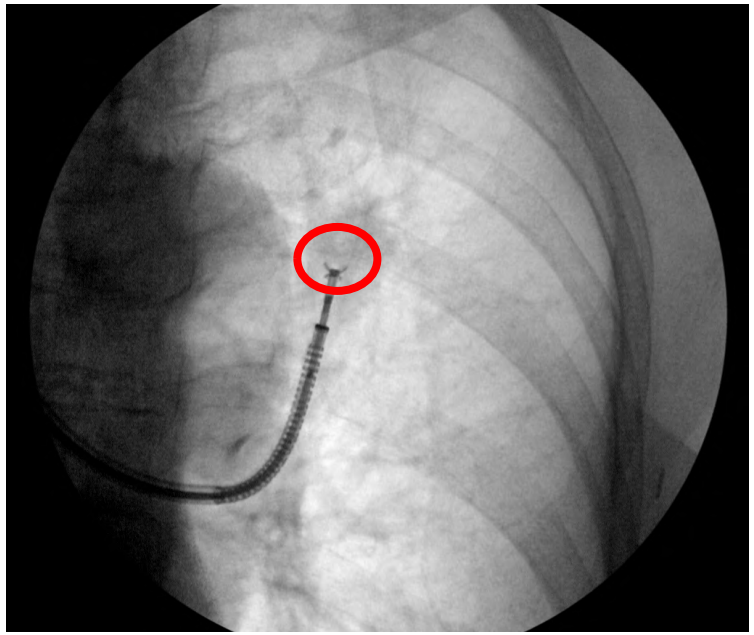
89% **Diagnostic Yield - Malignancy**

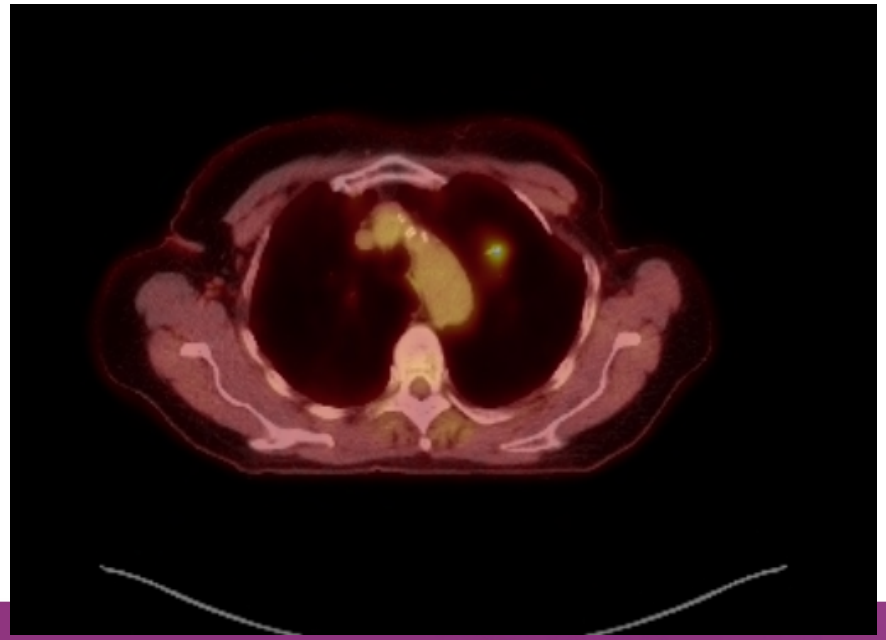
Average size: 14 mm

D. Fielding. First Human Use of a New Robotic-Assisted Navigation System for Small Peripheral Pulmonary Nodules Demonstrates Good Safety Profile and High Diagnostic Yield. CHEST 2017 Conference

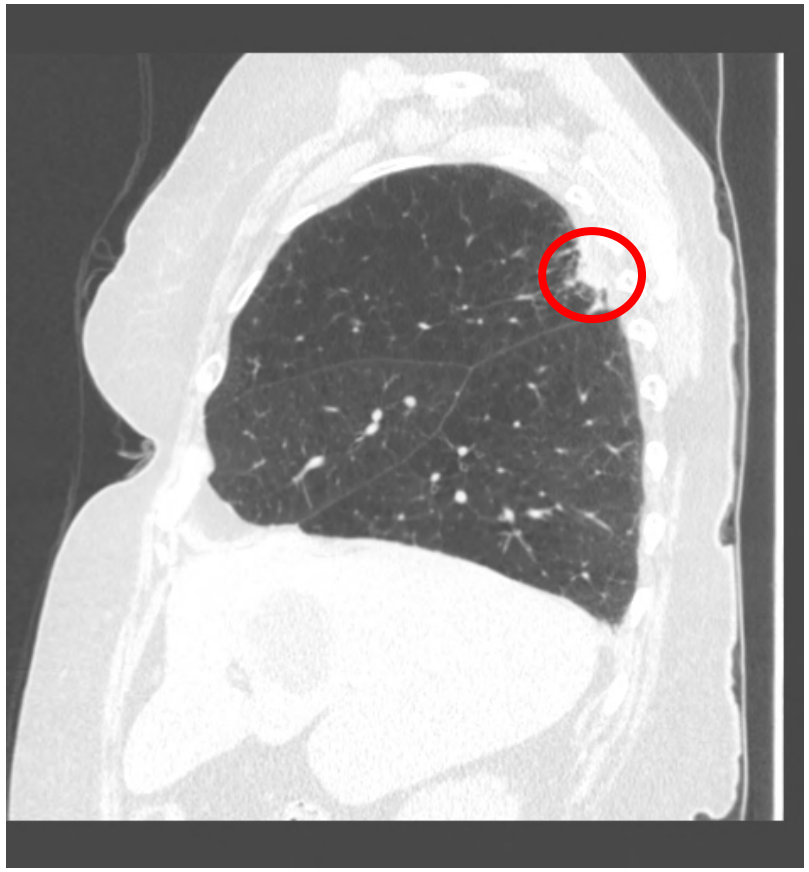


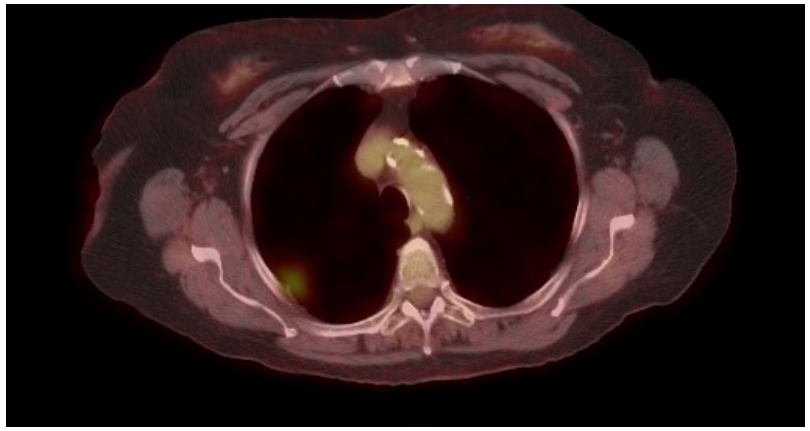


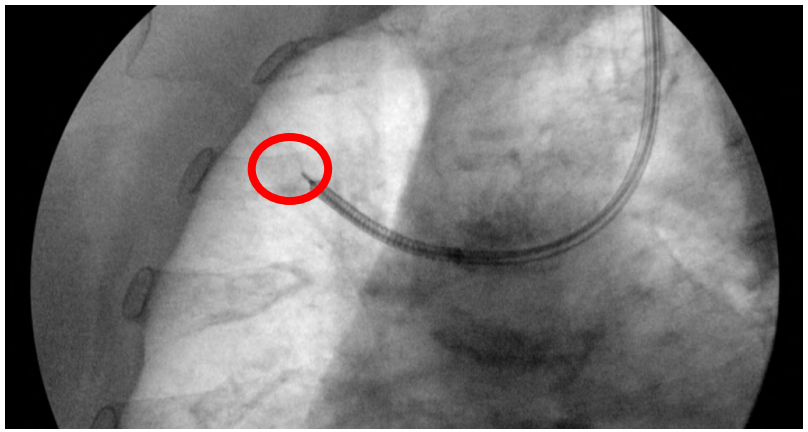


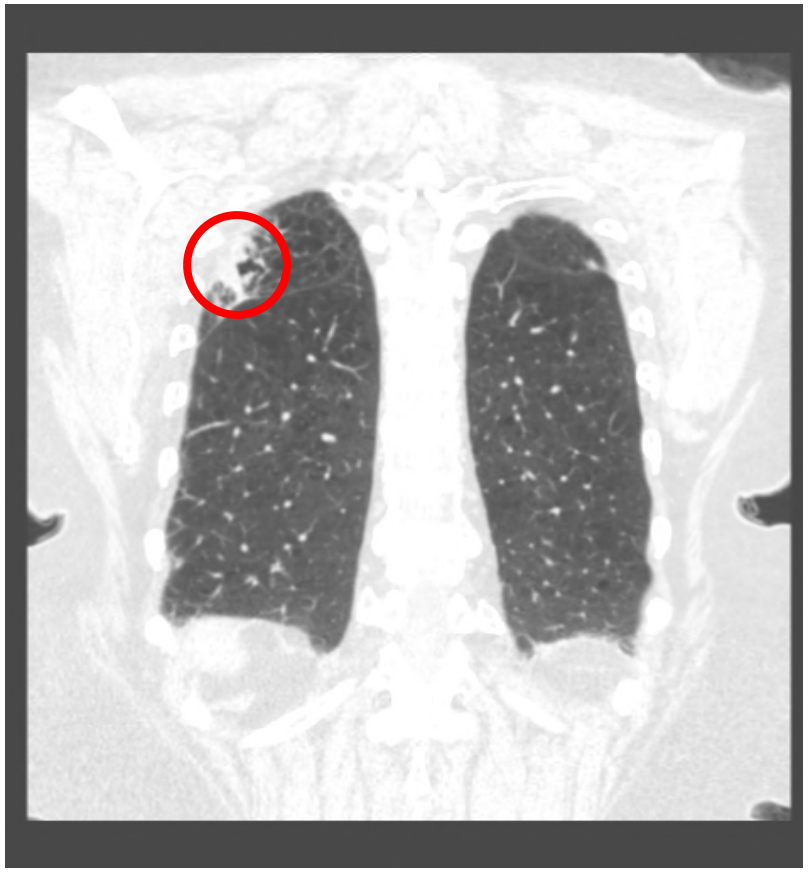


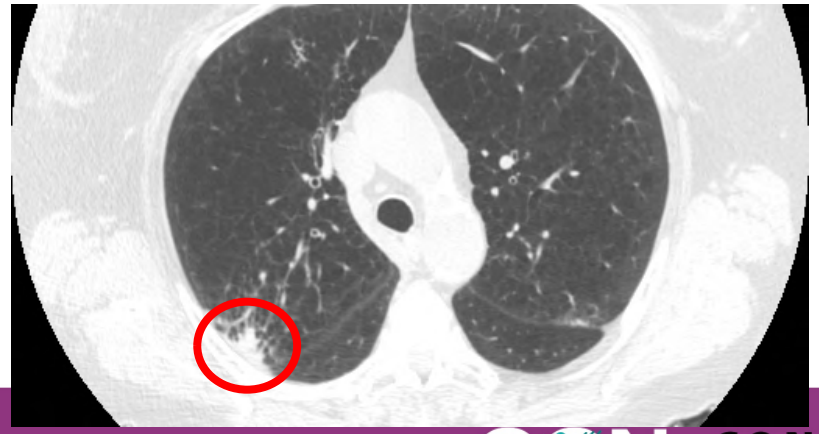
CASE 1: LUL Nodule



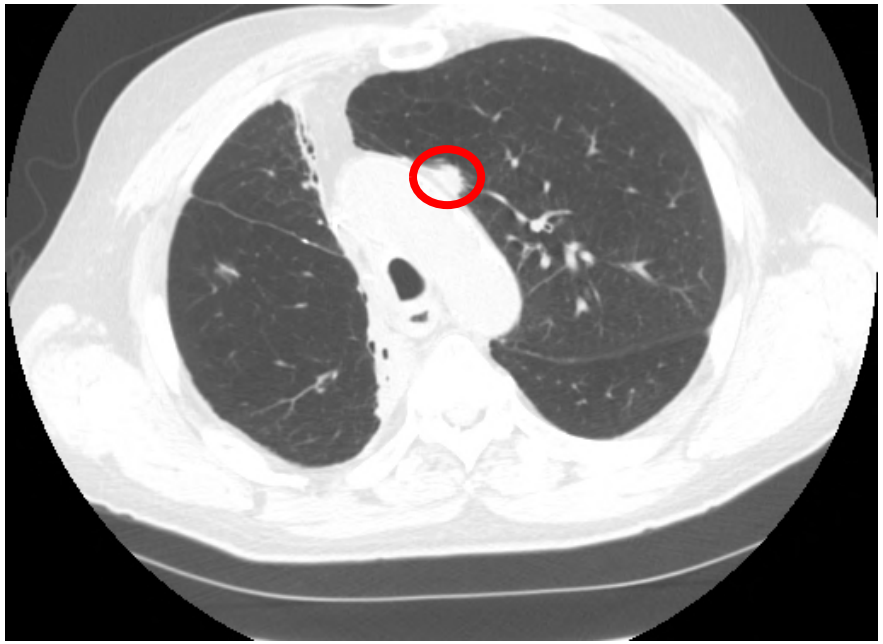


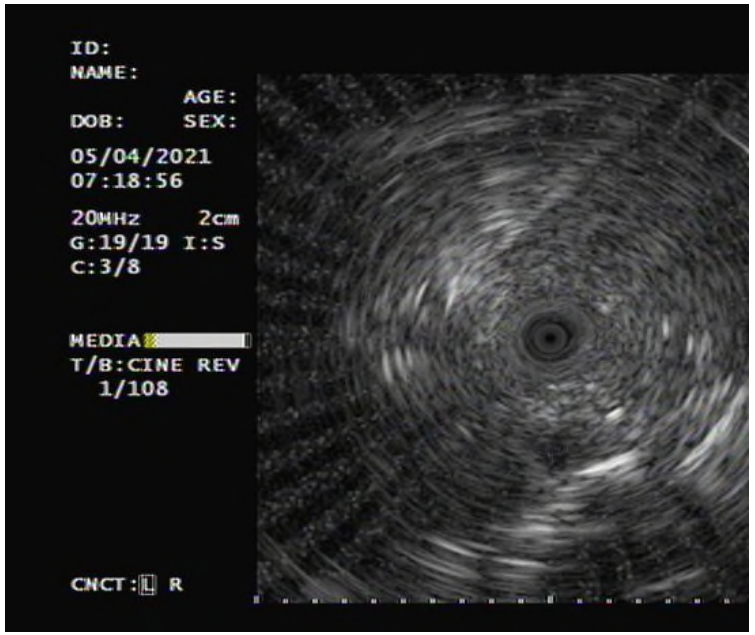


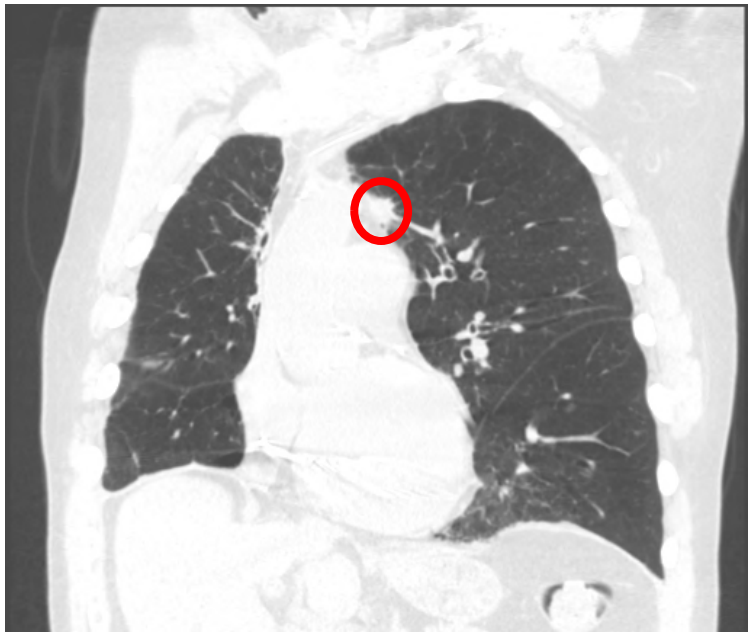


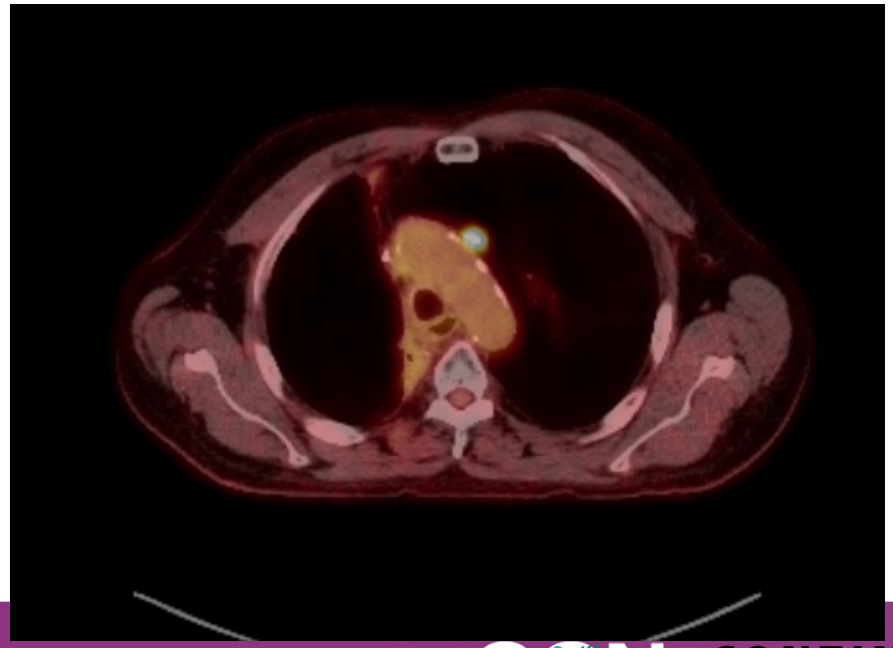


CASE 2: Pleural Based Nodule

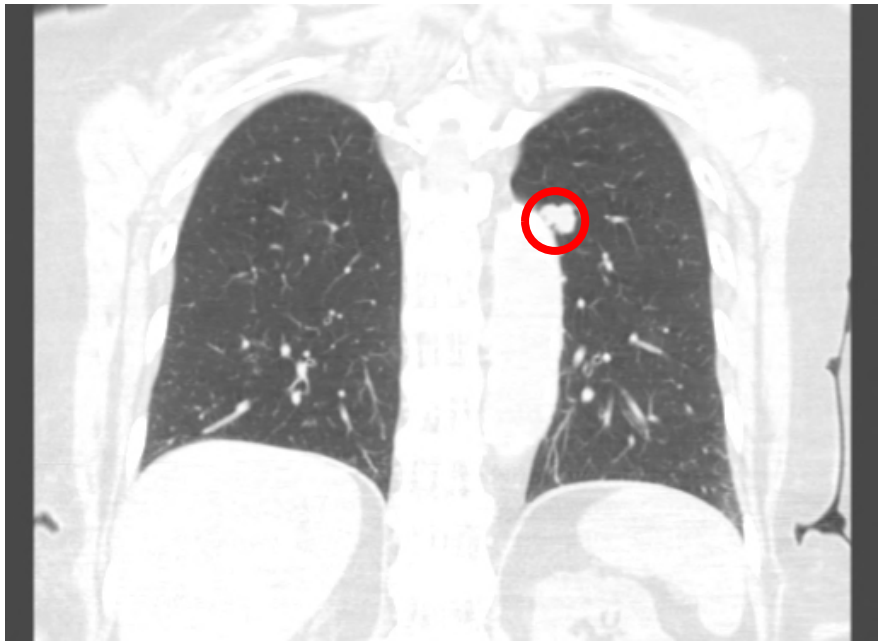


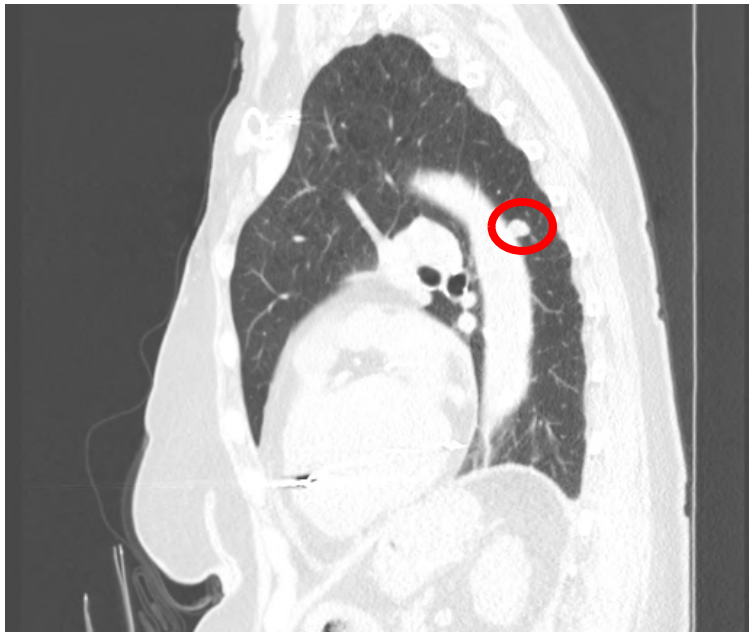


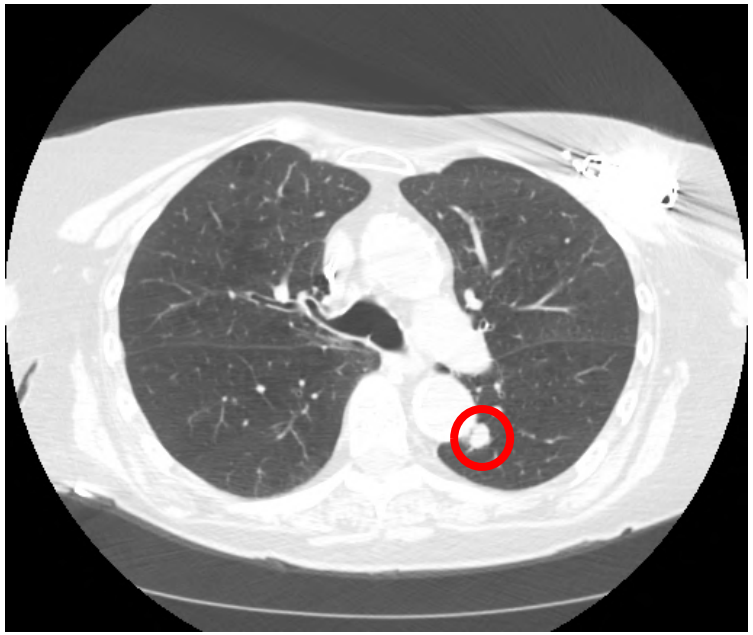


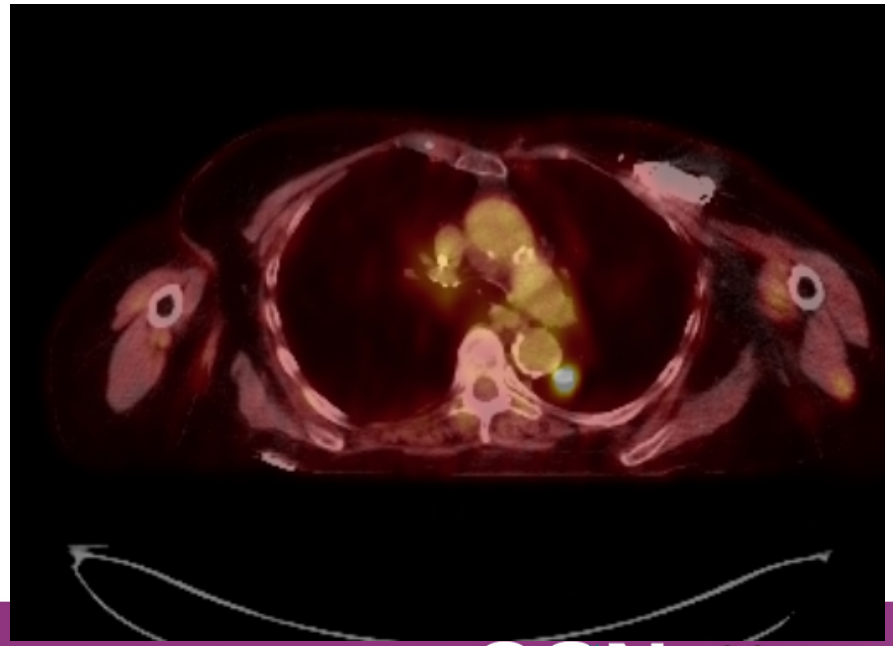


CASE 3: Aortic Arch









CASE 4: Descending Aorta

CLOSING COMMENTS

- Appropriate accurate mediastinal staging is paramount to optimal clinical outcomes
- We are seeing a greater number of nodules than ever before
- Robotic bronchoscopy provides a stable platform for performing biopsies and appear to improve clinical diagnostic yield
- Robotics potentially creates a platform to move into endobronchial therapy that was not available before

Molecular Markers in Non-Small Cell Lung Cancer

Greg Kalemkerian, MD
Medical Oncology
University of Michigan

NSCLC Biomarkers: What to Test

- Immunohistochemistry (IHC):
  - FDA-approved therapy associated with:
    - PD-L1 tumor proportional score [TPS]
  - Requires tissue/cells – histology, cytology, cell block
  - Cannot be done on blood (ctDNA, “liquid biopsy”)

NSCLC Biomarkers: What to Test

- Next Generation Sequencing (NGS):
  - FDA-approved therapies associated with:
    - Mutations: *EGFR*, *BRAF* V600E, *MET* exon 14 splice, *KRAS* G12C
    - Rearrangements: *ALK, ROS1, RET, NTRK*
    - Microsatellite instability (MSI)
    - Tumor Mutational Burden (TMB)
  - Other markers may suggest investigational therapy (e.g. *HER2*)
  - Can be done on histology, cytology or ctDNA ("liquid biopsy")

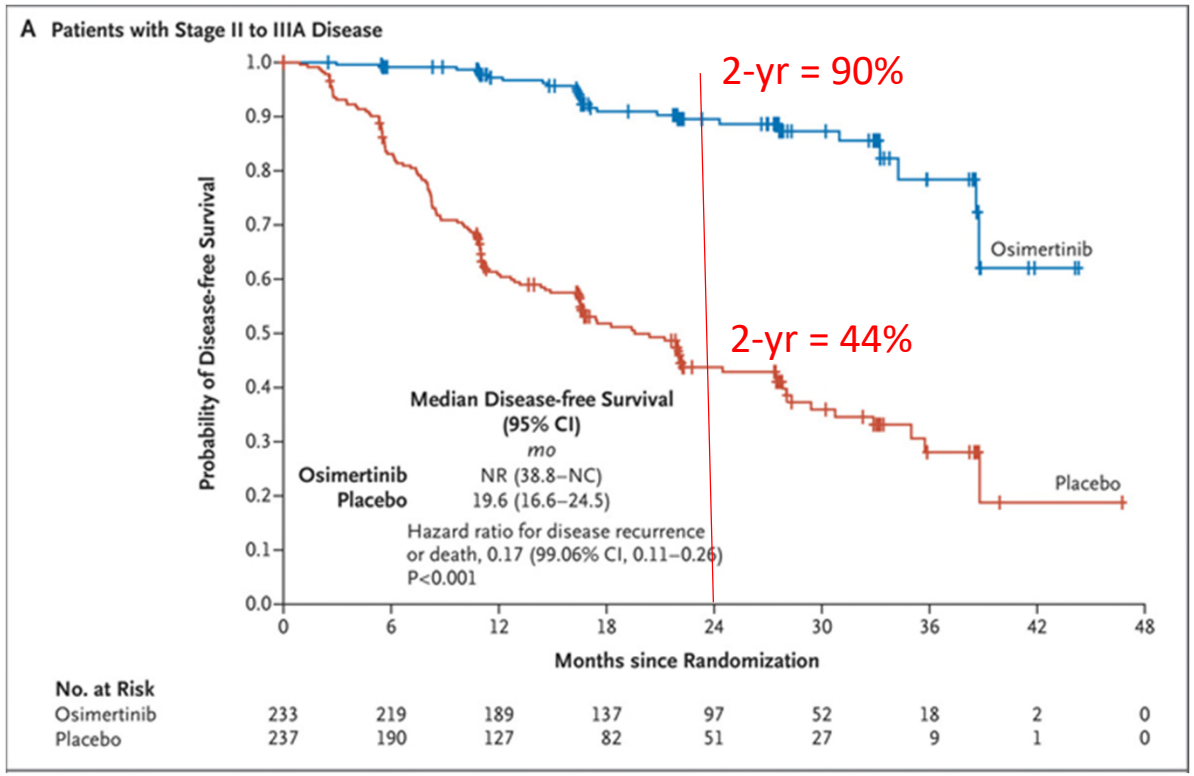
NSCLC Biomarkers: When to Test

- Stage II-III resected adenocarcinoma:
  - *EGFR* mutations - to guide adjuvant therapy with osimertinib
- Stage III any histology:
  - NGS - may identify lack of utility of immunotherapy (e.g. *EGFR*-mut)
- Stage IV:
  - NGS – to guide targeted therapy (adenoca and non-smoking SqCCa)
  - PDL1 TPS – to guide immunotherapy (all histologies)

ADAURA: Adjuvant Osimertinib in EGFR+

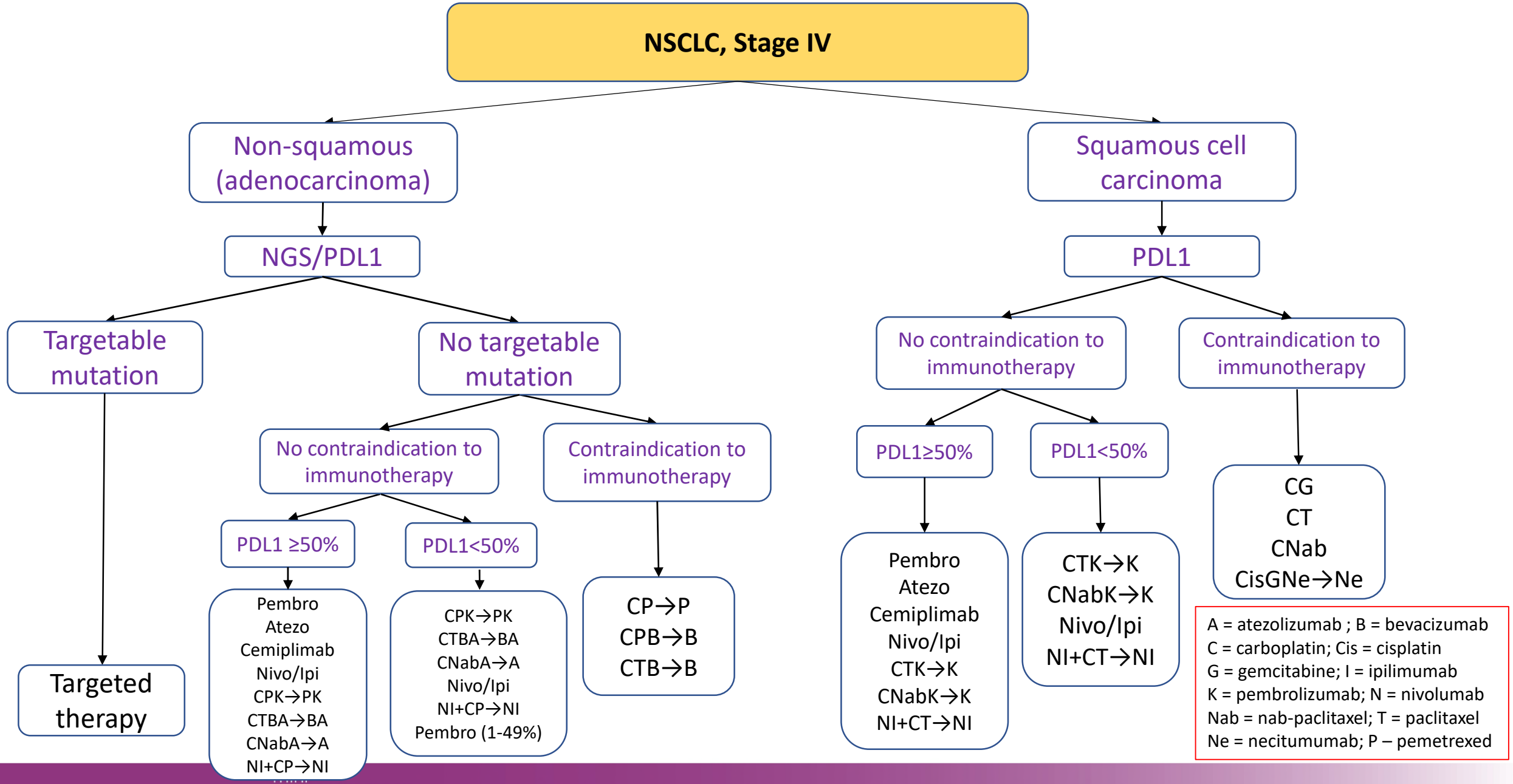
- Stage IB-IIIA, completely resected
- EGFR deletion 19 or L858R
- Osimertinib vs. Placebo × 3 years
- 60% received adjuvant chemo
- 1° endpoint = DFS in stage II & IIIA
- Unplanned IDMC (2 years early)
- Enrollment complete – all pts out > 1 year (29% mature)
- N – Osimertinib = 339, Placebo = 343

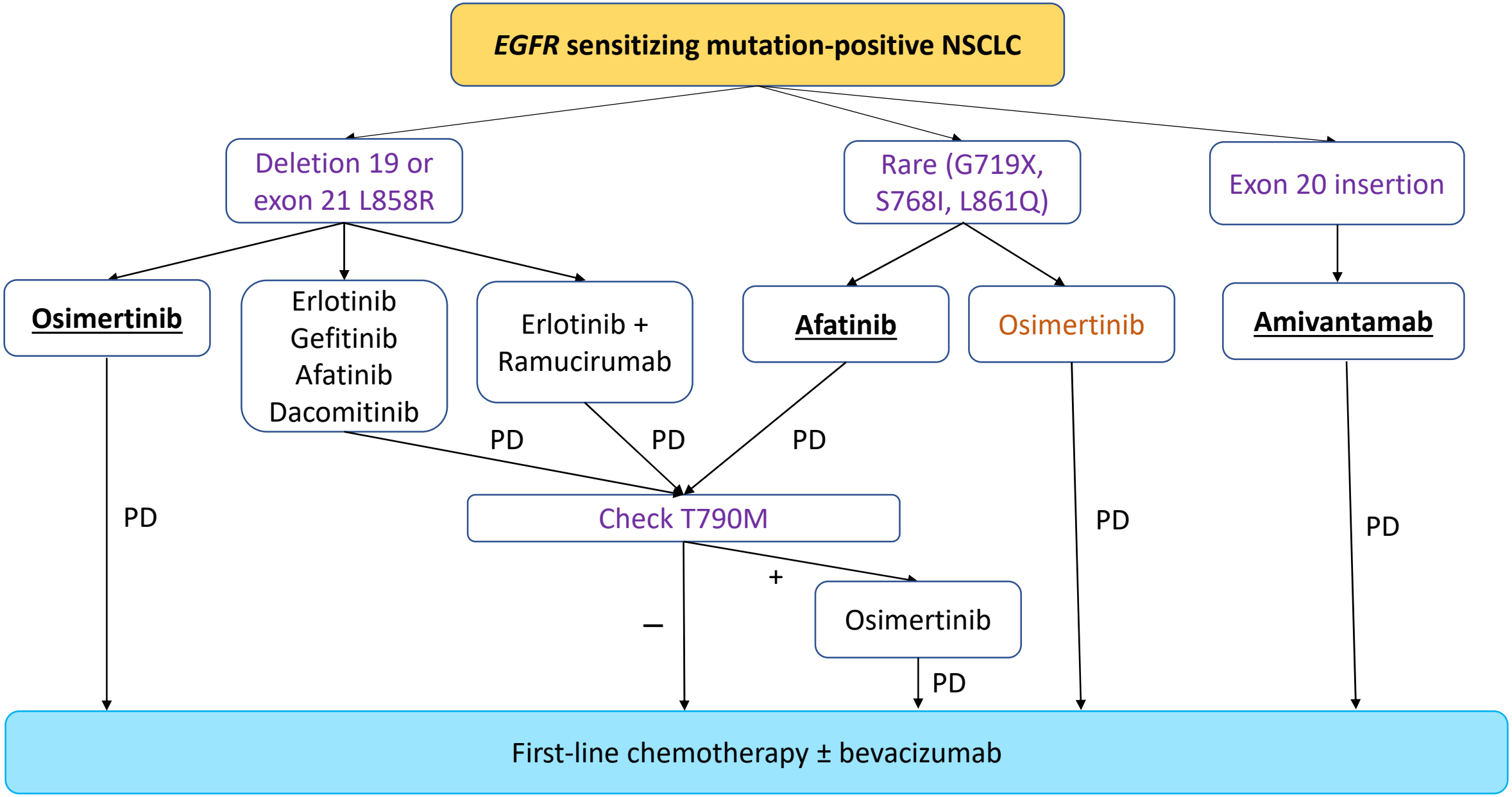
Disease-free Survival



- Overall survival data is immature

Wu, et al. NEJM 383:1711, 2020


NSCLC, Stage IV
Non-squamous (adenocarcinoma)
Squamous cell carcinoma
NGS/PDL1
PDL1
Targetable mutation
No targetable mutation
No contraindication to immunotherapy
Contraindication to immunotherapy
Targeted therapy
No contraindication to immunotherapy
Contraindication to immunotherapy
PDL1 ≥50%
PDL1<50%
PDL1≥50%
PDL1<50%
Pembro
Atezo
Cemiplimab
Nivo/Ipi
CPK→PK
CTBA→BA
CNabA→A
NI+CP→NI
CPK→PK
CTBA→BA
CNabA→A
Nivo/Ipi
NI+CP→NI
Pembro (1-49%)
CP→P
CPB→B
CTB→B
Pembro
Atezo
Cemiplimab
Nivo/Ipi
CTK→K
CNabK→K
NI+CT→NI
CTK→K
CNabK→K
Nivo/Ipi
NI+CT→NI
CG
CT
CNab
CisGNe→Ne
A = atezolizumab ; B = bevacizumab
C = carboplatin; Cis = cisplatin
G = gemcitabine; I = ipilimumab
K = pembrolizumab; N = nivolumab
Nab = nab-paclitaxel; T = paclitaxel
Ne = necitumumab; P – pemetrexed


EGFR sensitizing mutation-positive NSCLC
Deletion 19 or exon 21 L858R
Rare (G719X, S768I, L861Q)
Exon 20 insertion
Osimertinib
Erlotinib
Gefitinib
Afatinib
Dacomitinib
Erlotinib + Ramucirumab
Afatinib
Osimertinib
Amivantamab
PD
PD
PD
PD
PD
PD
Check T790M
+
–
Osimertinib
PD
First-line chemotherapy ± bevacizumab

Multidisciplinary Team Care

Greg Kalemkerian, MD
Medical Oncology
University of Michigan

Lung Cancer Multidisciplinary Team

- Medical Oncology
- Radiation Oncology
- Thoracic Surgery
- Pulmonary Medicine
- Interventional Pulmonary
- Palliative Care
- Diagnostic Radiology
- Interventional Radiology
- Nuclear Medicine
- Anatomic Pathology
- Molecular Pathology

- Physicians, Advanced Practice Providers, Housestaff, Nursing Staff, Research Coordinators, Clinical Coordinators, Patient Navigators, Social Workers

Lung Cancer MD Tumor Board

- Systematic Review (Coory, et al. Lung Cancer 60:14-21, 2008)
  - 16 studies (1 randomized, 7 before-after cohorts)
  - 2 of 5 studies showed improved survival with Tumor Board
  - Tumor Board → increased formal staging, decreased time to treatment, more curative treatment (surgery, RT)

- Deviations from TB recommendations (Osarogiagbon, et al. JTO 6:510-516, 2011)
  - N=376 patients; 37% with care discordant from TB recommendations
  - Discordance → delay in therapy (p=0.002), decreased PFS (p=0.02, HR 1.4), decreased OS (p=0.004, HR 1.7)

LUNG CANCER: SURGICAL EVALUATION

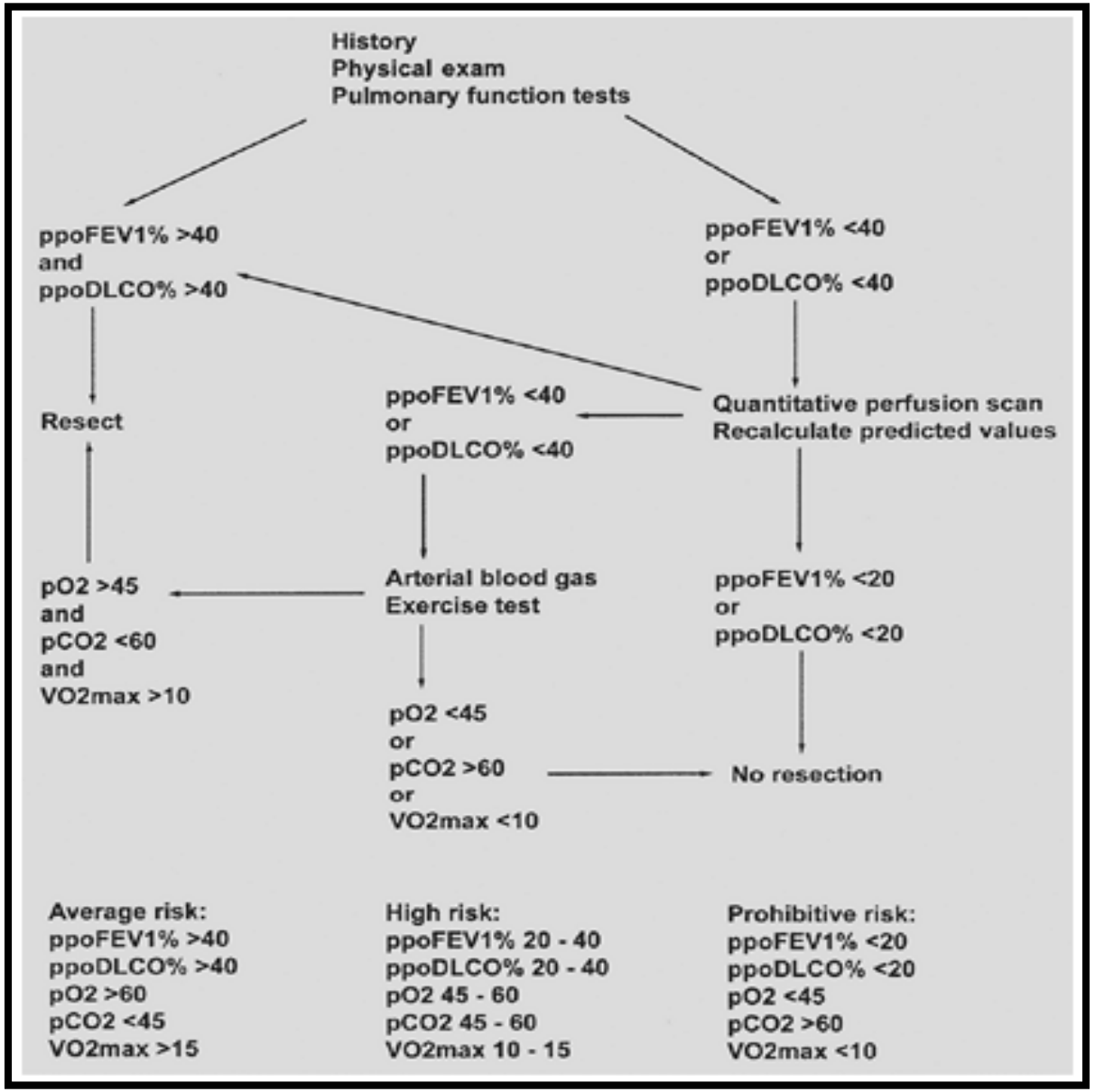
Janani Reisenauer, MD

Lung Cancer Surgery

- Surgical Treatment
  - Remove the affected part of the lung
    - Wedge resection – removes a wedge of lung
    - Segmentectomy – removes an anatomic segment of lung
    - Lobectomy – remove a lobe of the lung
    - Bilobectomy – remove 2 lobes
    - Pneumonectomy – remove an entire lung
  - Mediastinal lymphadenectomy
    - Removes lymph nodes from the mediastinum
  - Can be done OPEN, VATS OR RATS
    - No difference in literature between VATS and RATS
    - MIS should be considered for all stage I lung cancer, and many stage II and III
    - Neoadjuvant treatment, prior surgery, or central tumor are not absolute contraindications for MIS

Functional status

- Pulmonary Function testing
- V/Q
- Arterial Blood Gas
- Cardio Pulmonary Exercise Test



Candidacy

- PPO FEV_1 = preoperative $FEV_1 \times (1 - y/z)$
- PPO DLCO = preoperative DLCO × (1 – y/z)
  - y = Number of functional or unobstructed lung segments removed.
  - z = Total number of functional segments
- % PPO FEV_1 = computed PPO FEV_1 × 100/predicted normal FEV_1
- % PPO DLCO = computed PPO DLCO × 100/predicted normal DLCO
- Criteria strongly suggesting inoperability include PO_2 of <45 mm Hg, PCO_2 of >60 mm Hg, predicted postoperative DL_{CO} of <40%, predicted postoperative FEV_1 <40%, or a VO_2max of <10 mL/kg per minute.

PULMONARY FUNCTION TESTING

SPIROMETRY

	NORMAL	LLN	FOUND	%PRED.	FOUND	%CHNG	%PRED.
VC MAX	3.16	2.32	2.71	86 %	2.80	3 %	89 %
FVC	3.16	2.32	2.71	86 %	2.80	3 %	89 %
FEV 1	2.45	1.79	0.97	40 %	0.99	1 %	40 %
FEV1/FVC	78.0	65.0	35.9	46 %	35.2	-2 %	45 %
FEF25-75%	2.03	0.96	0.27	13 %	0.30	12 %	15 %
PEF	5.8	3.2	2.8	48 %	3.0	7 %	51 %
FET			14.72		19.69	34 %	

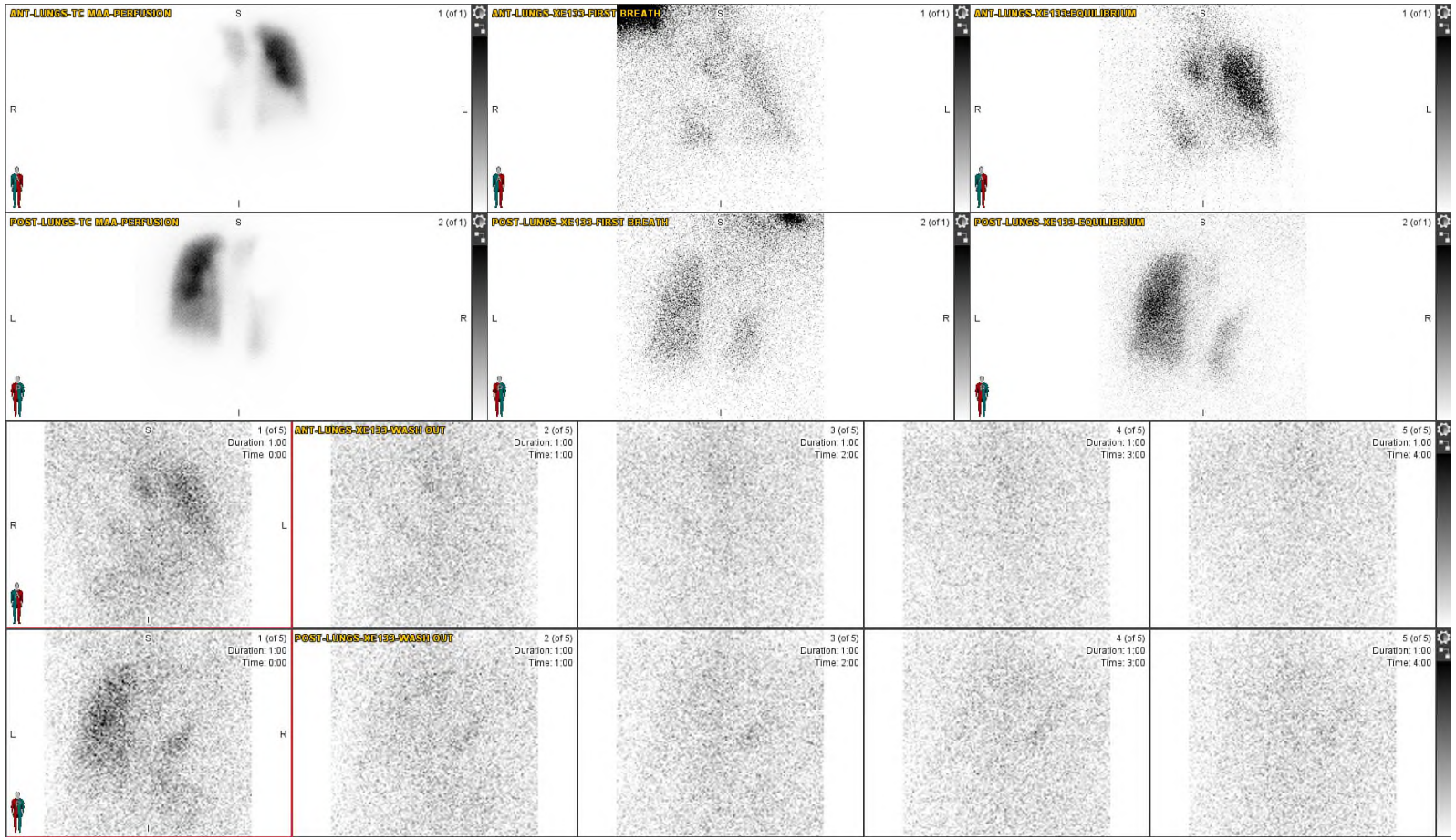
DIFFUSION CAPACITY

	NORMAL	LLN	FOUND	%PRED.	FOUND	%PRED
DLCO_SB	21.3	16.1			9.7	45 %
DLCOcSB	21.3	16.1			9.5	45 %
Hb					14.00	
VA_SB	5.23	4.18			5.02	96 %

CARDIOPULMONARY EXERCISE TESTING

- VO2 (oxygen consumption) test
- stress test that measures your exercise ability
- Information about the heart and lungs is collected to understand if the body's response to exercise is normal or abnormal.
- Values measured in ml/kg/min; anything less than 10 is prohibitive for surgery

VENTILATION PERFUSION SCAN



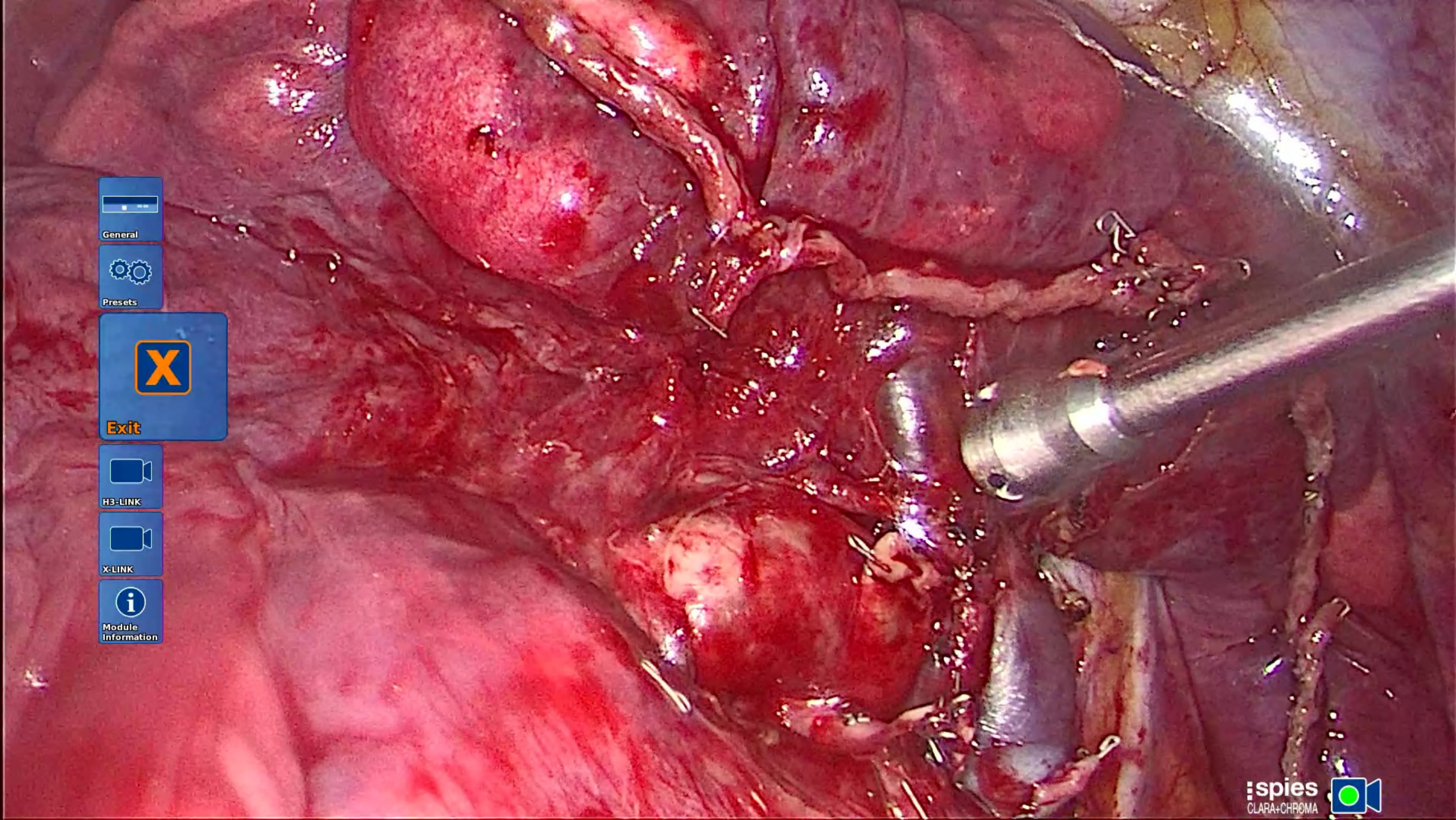
PERFUSION:

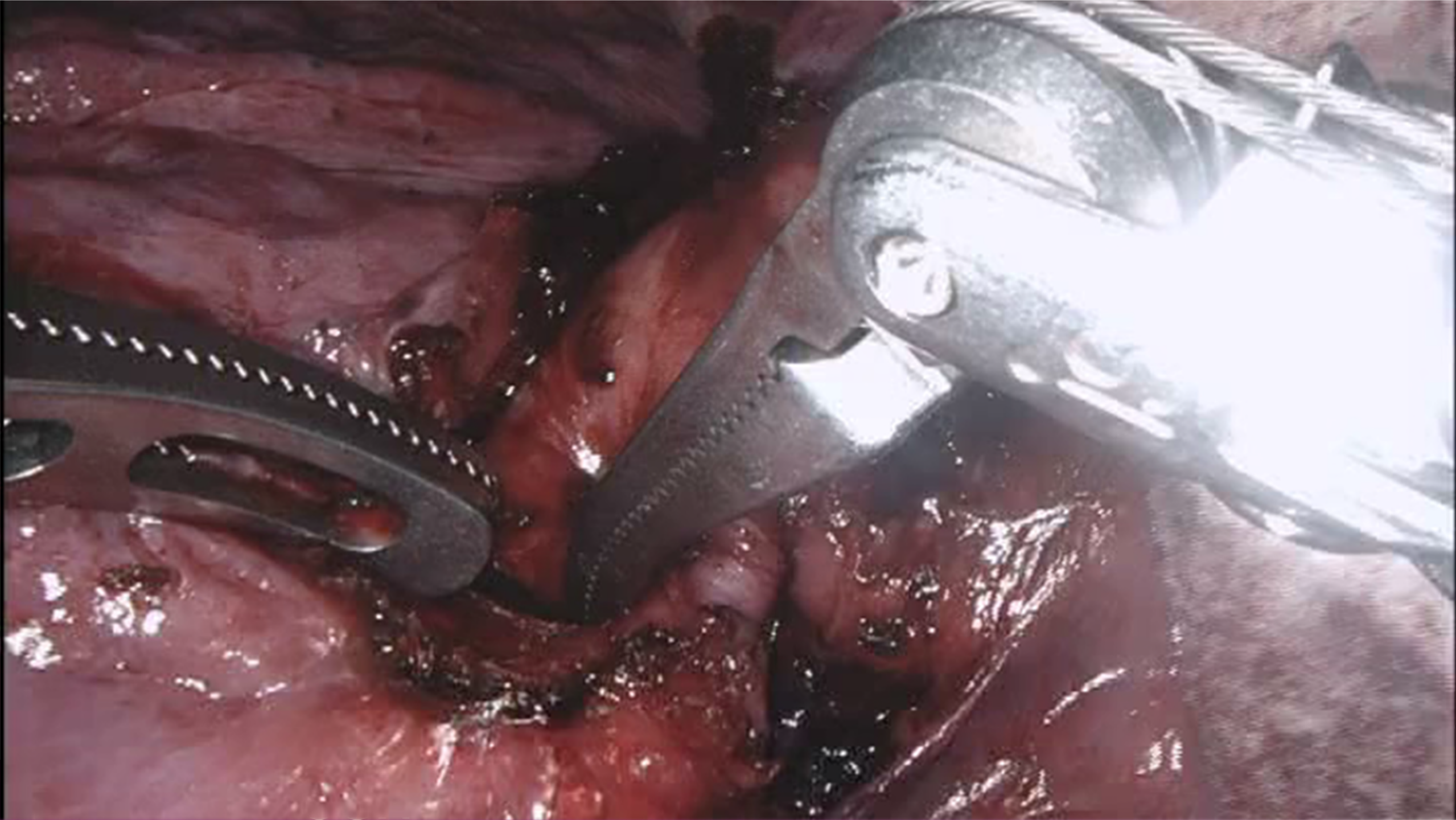
RIGHT: Upper = 5%; Mid = 4%; Lower = 4%; Total = 13%

LEFT: Upper = 37%; Mid = 42%; Lower = 9%; Total = 87%

MINIMALLY INVASIVE SURGERY

- Avoids breaking rib or cutting muscles
- Shorter LOS
- Less pain
- Faster recovery
- Less scar tissue formation


General
Presets
Exit
H3-LINK
X-LINK
Module Information
spies
CLARA+CHROMA

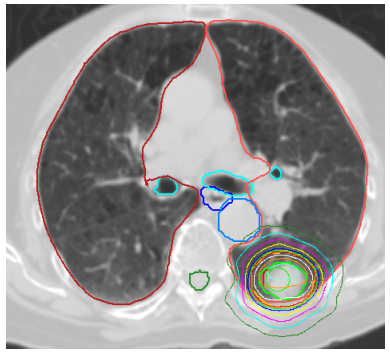
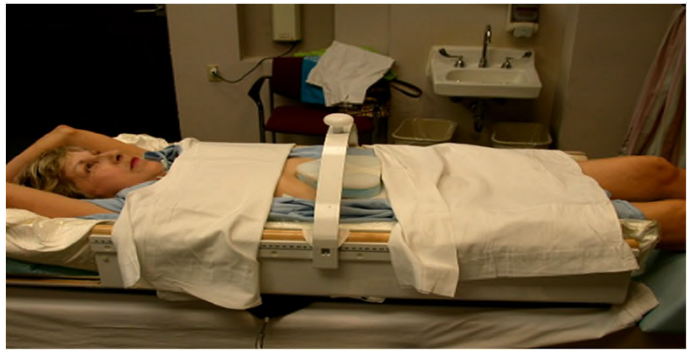
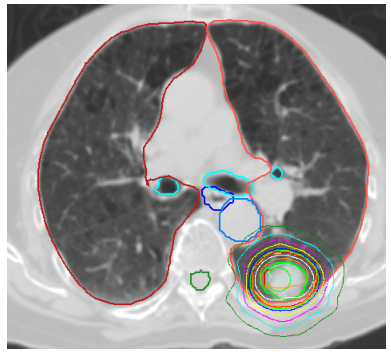
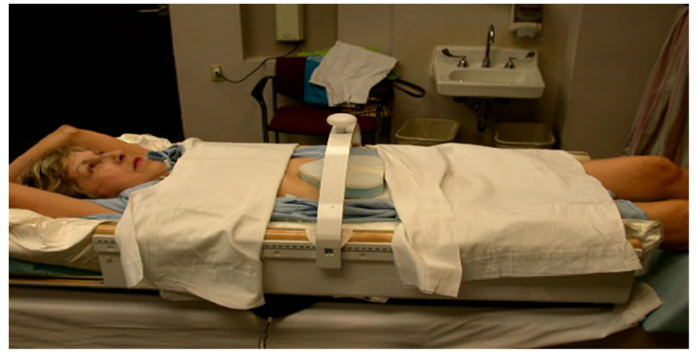


SBRT for Early-Stage Lung Cancer

Megan E. Daly MD
Professor of Clinical Radiation Oncology
University of California Davis Comprehensive Cancer Center

Overview: SBRT for Early-Stage NSCLC

- Standard of care for node negative, medically inoperable, early-stage NSCLC
- Delivery of 1-5 (+) fractions using highly conformal techniques with steep dose gradients, precise immobilization, and motion management
- Goal of ablating tumor

RTOG 0236 Outcomes

Failure Patterns	3-year[1]	5-year[2]
Primary tumor control	97.6%	93%
Local (primary + involved lobe)	90.6%	80%
Locoregional control	87%	62%
Distant Control	77.9%	69%
Disease-Free Survival	48.3%	26%
Overall Survival	55.8%	40%
Grade 4+ Adverse Events	3.6%	3.6%

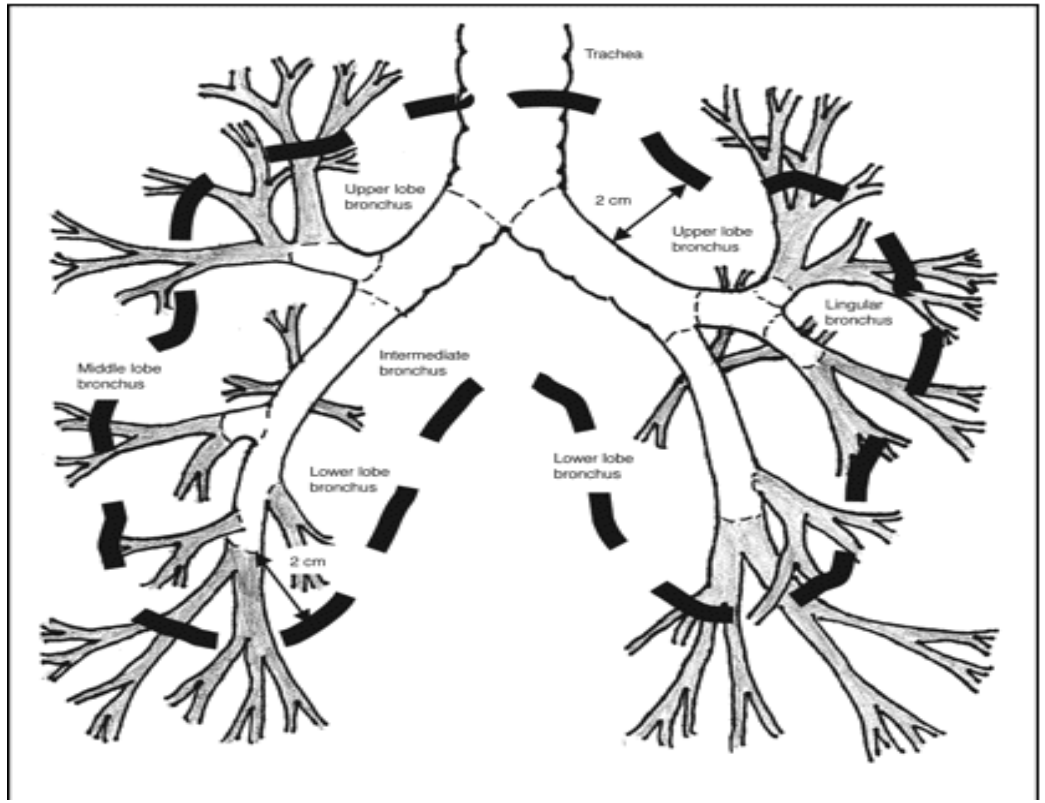
[1]Timmerman R et al, Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA March 2010

[2]Timmerman RD et al, Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. JAMA Oncology

Patient Selection for SBRT

- Tumor location (central versus peripheral)
- Tumor size
- Patient performance status and lung function
- High risk clinic features such as interstitial lung disease

SBRT for Central Tumors



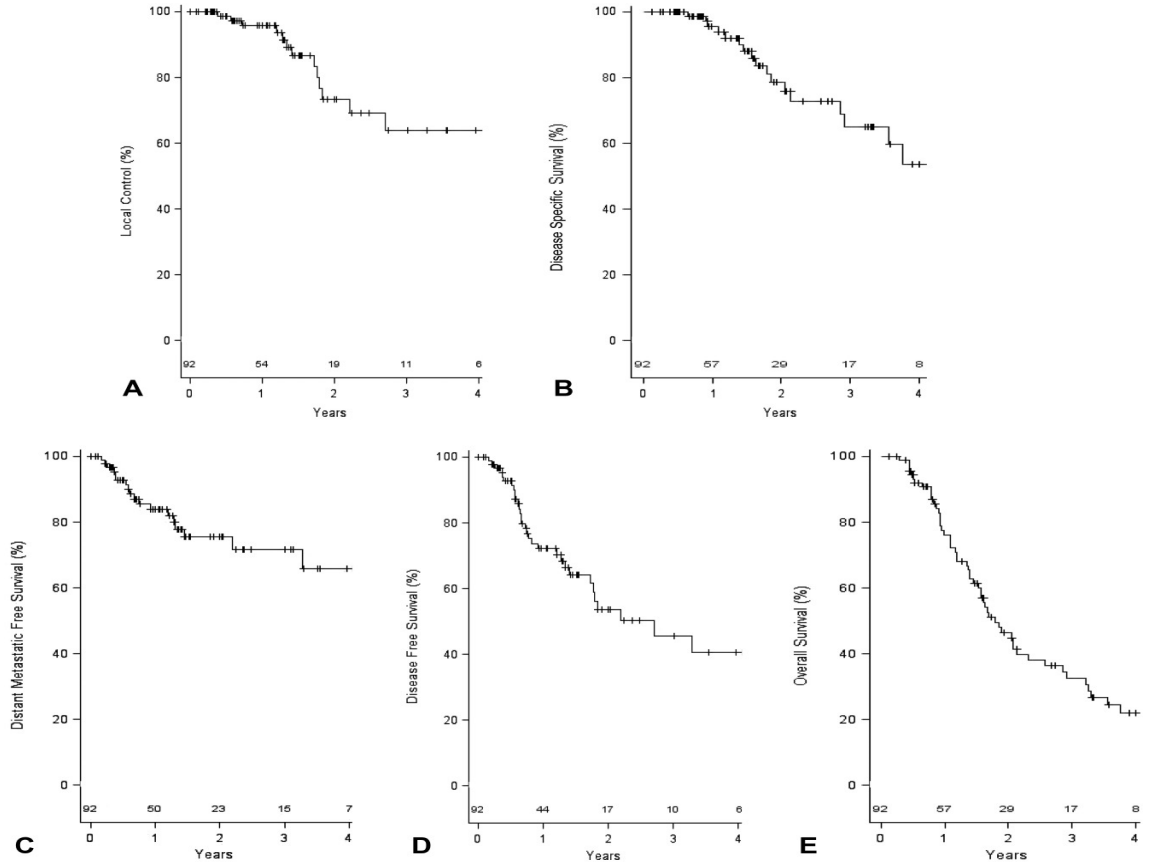
- Frequently defined by the guidelines established in the early IU SBRT trials: within 2 cm of the proximal bronchial tree, defined as the distal 2 cm of the trachea, the mainstem and lobar bronchi
- RTOG 0813 also included tumors with PTV touching/ overlapping mediastinal pleural
- Term “ultracentral” not standardized, but typically refers to tumors with PTV touching or overlapping PBT, trachea, esophagus, +/- great vessels. Tumors abutting the esophagus are often included as they are particularly high risk for esophageal injury.

Prospective Outcomes using SBRT for Central and Ultracentral tumors

	RTOG 0813 (JCO 2019)	HILUS Trial (JTO 2021)
Eligibility	Within 2 cm of PBT or PTV touching mediastinal pleura	Within 1 cm of mainstem or lobar bronchus
Prescription Dose	50-60 Gy in 5 fractions	56 Gy in 8 fractions
Isodose Line	60-90%	65-70%
Dose constraint(s) to Proximal Bronchial Tree	Max <105% of prescription dose <4cc of non-adjacent wall to 18 Gy	Max to contralateral mainstem bronchus/ trachea<48.8 Gy Guideline max< 56 Gy to ipsilateral mainstem bronchus
Dose constraints to great vessels	Max < 105% of Rx dose <10 cc non-adjacent wall to 47 Gy	None
Observed Toxicity	15 grade 3+ AE (15%) 4 grade 5 AE (4%) – All hemoptysis	22 grade 3+ AE (33.8%) 10 grade 5 AE (15.4%), 6 hemoptysis

SBRT for Large Tumors

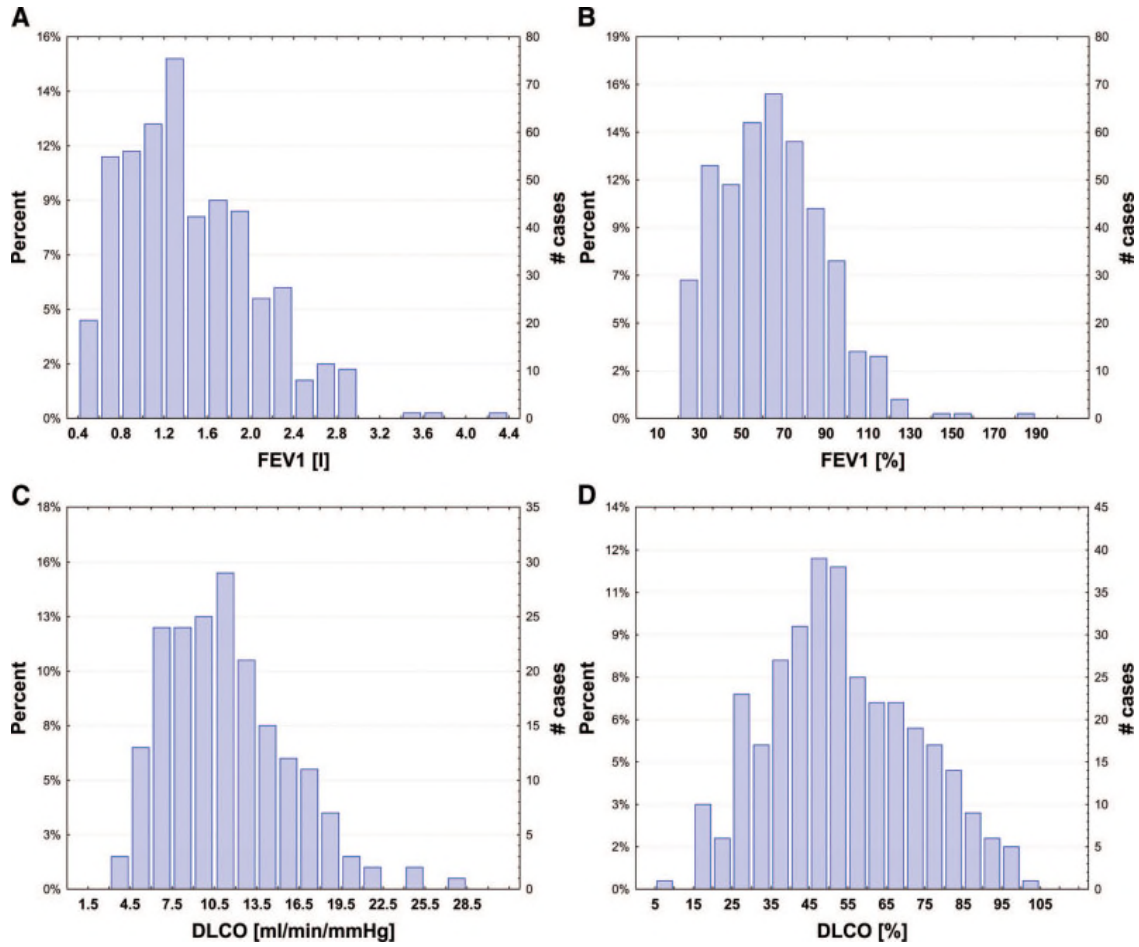
- Multi-institution analysis of 92 patients with NSCLC 5-7.5 cm
- 2-year disease-specific survival of 78.6%
- 2-year OS 46.4%
- Most recurrences were distant
- 1 grade 5 pneumonitis (7.5 cm tumor); otherwise limited toxicity



Verma V et al. Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors. Cancer 2017.

Role of Pulmonary Function

- No clear lower threshold for safe SBRT
- Pre-treatment DLCO associated with OS



Guckenberger M et al. Is There a Lower Limit of Pretreatment Pulmonary Function for Safe and Effective Stereotactic Body Radiotherapy for Early-Stage Non-small Cell Lung Cancer? JTO 2012

SBRT with Interstitial Lung Disease

Study	N	Radiation Pneumonitis Rates
Bahig et al (Montreal). PRO 2016	28	32% grade 3+ 21% grade 5
Ueki et al (Kyoto), JTO 2015	20	55% grade 2+ 10% grade 3+
Glick et al (Princess Margaret), CLC 2018	39	20.5 grade 2+ 10.3% grade 3+ 5.1% grade 5
Yamaguchi et al (Kitakyushu), Lung Cancer 2013	16 (subclinical)	19% grade 2+ 12.5% grade 4+
Onishi et al (Japanese multi-institution), Cancers 2018	242	6.9% grade 5
Finazzi T et al (Amsterdam), WCLC 2019	24	20.8% grade 3+ 12.5% grade 5

Summary

- SBRT is an excellent and low toxicity treatment option for medically inoperable, early stage NSCLC
- Patient selection factors include tumor size, location, comorbidities, and pulmonary function
- Even quite frail patients with relatively poor pulmonary function may be candidates for SBRT

Locally Advanced NSCLC: Standard Treatment and Clinical Trials

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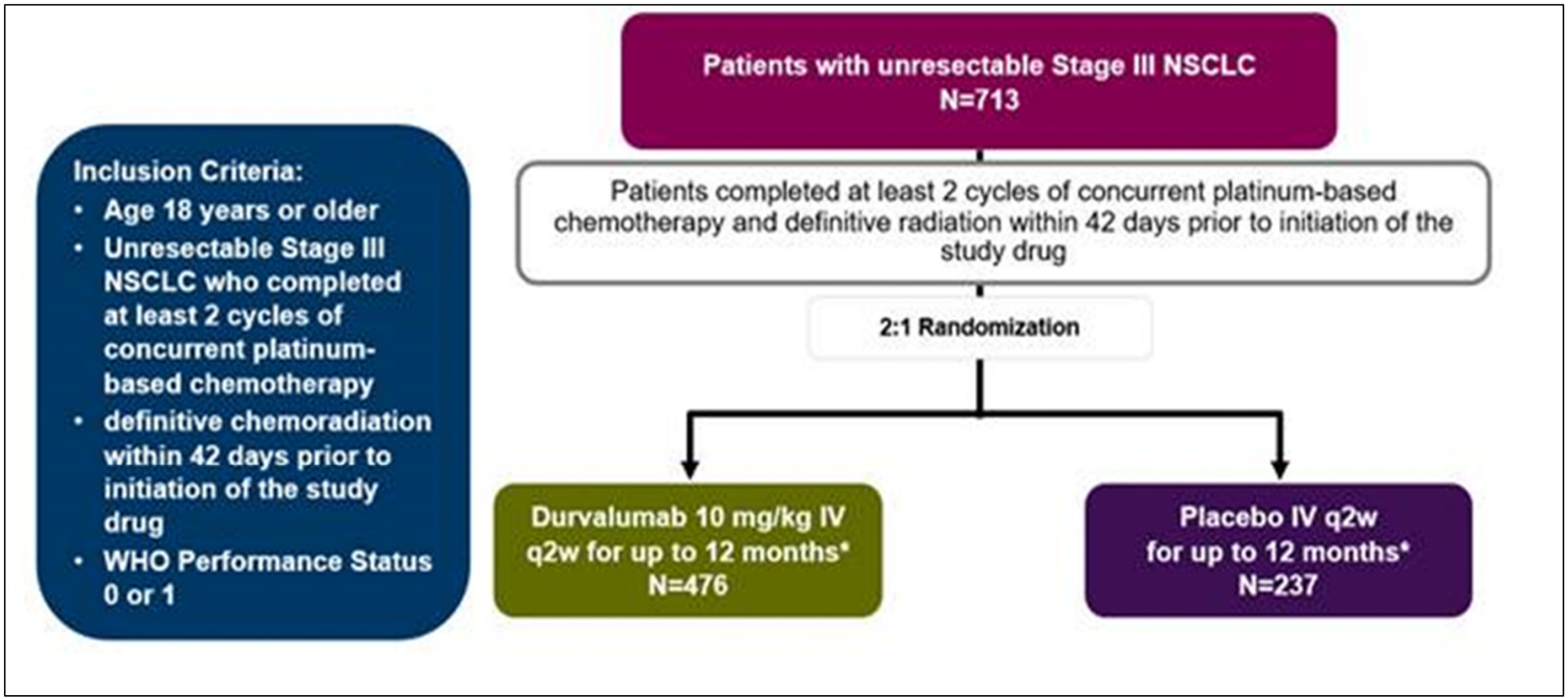
NSCLC: Stage III, Multimodality treatment options

- Sequential Chemotherapy → Radiotherapy
  - Better than RT alone
- Concurrent Chemotherapy + Radiotherapy
  - Better than sequential chemo/RT
- Chemotherapy +/- Radiotherapy → Surgery
  - Better than surgery alone; Equal to chemo/RT alone ?
- Chemotherapy + Radiotherapy → Chemotherapy
- Chemotherapy + Radiotherapy → Immunotherapy
  - Better than chemo/RT alone
- Immunotherapy +/- Chemotherapy → Surgery (investigational)

Stage IIIA/B/C (T1-4 N2-3), PS 0-2, < 10% wt. loss

- Concurrent Chemo + Definitive RT → Durvalumab
  - *Chemotherapy:*
    - Carboplatin + Paclitaxel weekly × 6 weeks or
    - Cisplatin/Carboplatin + Etoposide × 2 cycles or
    - Cisplatin/Carboplatin + Pemetrexed × 3-4 cycles (non-squamous)
  - *Definitive RT:*
    - 60-70 Gy in 2-2.3 Gy fractions
  - *Immunotherapy (consolidation):*
    - Durvalumab 10 mg/kg q 2 weeks or 1500 mg q 4 weeks × 1 year

PACIFIC: CT/RT + Consolidation Durvalumab

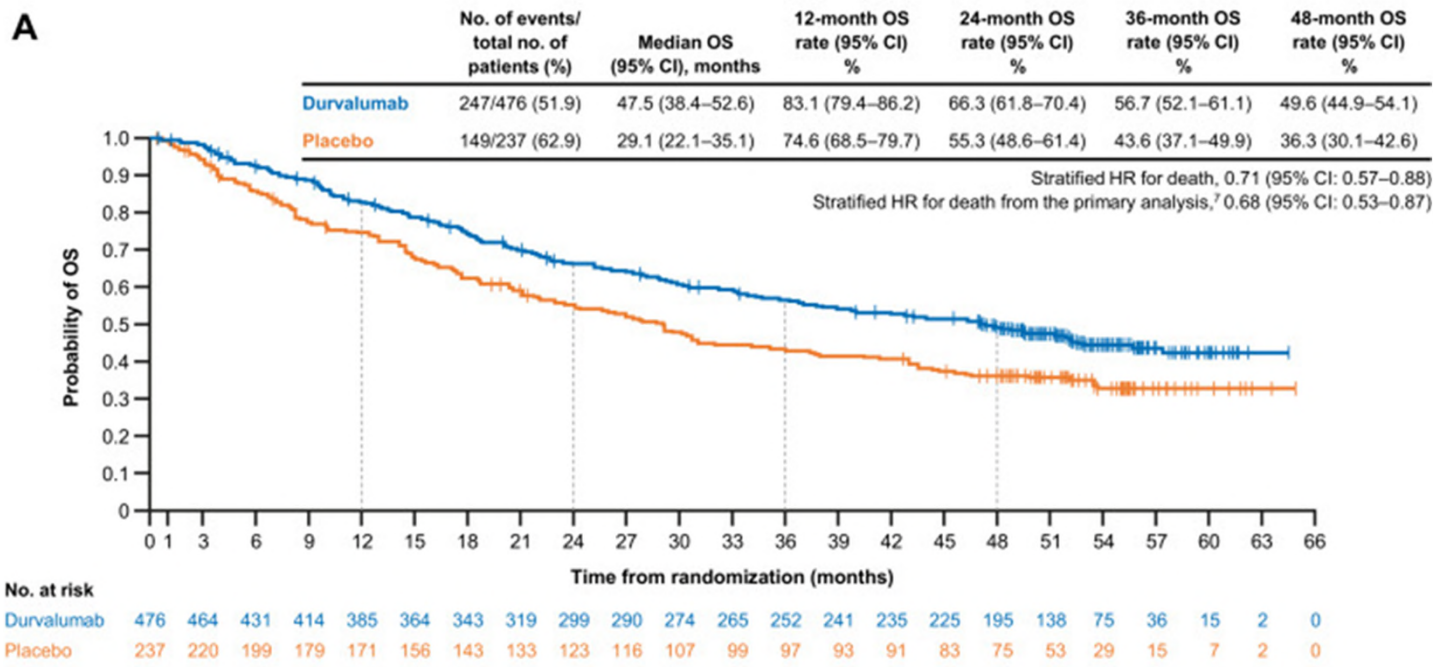


- Primary end-points: PFS and overall survival

Antonia SJ, et al. NEJM 377:1919, 2017

PACIFIC: CT/RT + Consolidation Durvalumab

	CT/RT + DURV	CT/RT	HR
N	473	236	
Median OS	47.5 mo.	29.1 mo.	0.72 (0.59-0.89)
5-year OS	**42.9%**	**33.4%**	



Overall Survival

Antonia, et al. NEJM 379:2342, 2018
Faivre-Finn, et al. J Thorac Oncol 16, 860, 2021
Spigel, et al. J Clin Oncol 39(15S); abstr 8511, 2021

PACIFIC-2: Ph III CT/RT + Durvalumab or Placebo

- Eligibility: N=300 pts; unresectable stage III NSCLC, PS 0-1
- Randomization (2:1):
  - Durvalumab 1500 mg q4w + concurrent CT/RT → durvalumab
  - Placebo q4w + concurrent CT/RT → durvalumab
- Primary endpoints: PFS and ORR
- Secondary endpoints: OS, CR rate, DOR, DCR, time to death/distant metastases, time to second progression, safety, quality of life
- Enrollment: On-going, began 3/2018

Antonia SJ, et al. NEJM 377:1919, 2017

Stage IIIA, non-bulky N2/T3-4 N1/T4 N0, PS 0-1

- *Option 1:* concurrent chemo/RT → durvalumab
- *Option 2* (if no pneumonectomy): neo-adjuvant chemo ± RT (45 Gy) → resection ± durvalumab consolidation
- *Option 3:* neo-adjuvant immunotherapy ± chemo → resection ± immunotherapy consolidation (investigational)

Stage IIIA Intergroup 0139: Neoadjuvant CT/RT

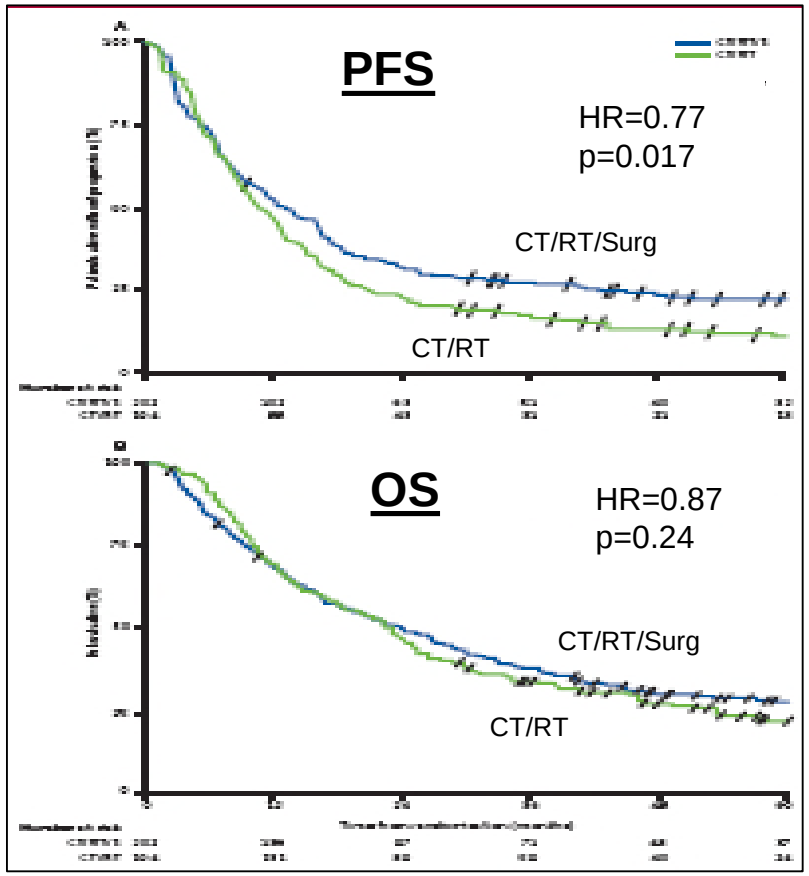
- Biopsy-proven stage IIIA (T1-3 N2) NSCLC
- *Arm 1* - PE + RT (45 Gy) → surgery → PE
  Arm 2 - PE + RT (61 Gy) → PE

	N	PFS		OS	
		Median	5-year	Median	5-year
CT/RT→Surgery	202	13 mo.	22%	23.6 mo.	27%
CT/RT	194	11 mo.	11%	22.2 mo.	20%
HR		0.77 (0.62-0.96)		0.87 (0.70-1.10)	
P-value		0.017		0.24	

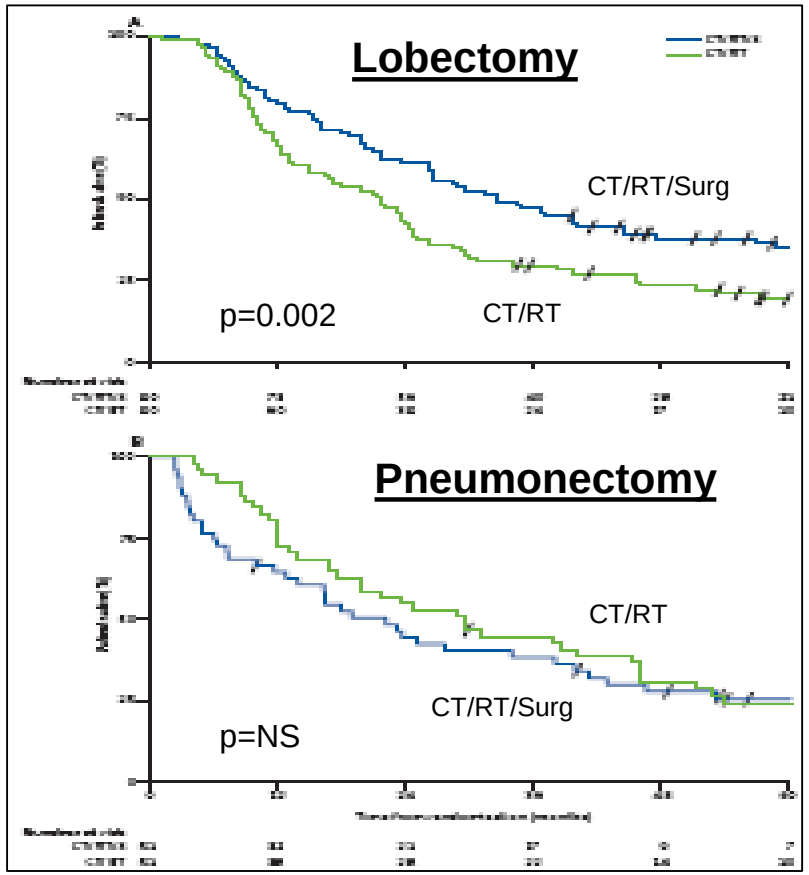
Albain, et al. Lancet 374:379, 2009

Stage IIIA Intergroup 0139: Neoadjuvant CT/RT

Entire Population



OS by Surgery Type



Albain et al. Lancet 374:379, 2009

CM816: Phase III Neo-adjuvant Chemo + Nivo

- Eligibility: stage IB (≥4 cm)-IIIA NSCLC, PS 0-1, no EGFR/ALK
- Randomized: Nivo 360 mg + Chemo q3w × 3 cycles vs.
  Chemo q3w × 3 cycles

	N	Went to Surgery	R0 Resection	Clinical ORR	Path Response		Toxicity		
					pCR	mPR	Gr 3-4 TRAE	Gr 3-4 Surgical	Delay in Surgery
Nivo + Chemo	179	83%	83%	54%	**24%**	**37%**	34%	11%	21%
Chemo	179	75%	78%	37%	**2.2%**	**9%**	37%	15%	18%
OR					**13.9**				
p-value					**<0.0001**				

Spicer, et al. J Clin Oncol 39(15S); abstr 8503, 2021; Forde, et al. AACR 2021, abstr CT003

Questions and Answers