NCCN Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer

The following slide deck is from a series of five live webinars presented between March 2014 and August 2014.

Please see instructions under each section for information on accessing the archived recording for that webinar.

This activity is supported by educational grants from Genentech, USA and Pfizer.

Permissions Information

- The use of these slides should be limited to educational, non-commercial presentations and handouts.
- Content and attributions should not be altered.
- The following slides may not be published or posted online without permission from the Continuing Education Department at the National Comprehensive Cancer Network. (education@nccn.org)

Table of Contents

Faculty Biographies

The following faculty presented during this live webinar series between March 2014 and August 2014.

Richard T. Cheney, MD, is Chairman of the Department of Pathology and Laboratory Medicine at Roswell Park Cancer Institute and Director of Dermatopathology in the Department of Dermatology at State University of New York at Buffalo.

Lucian R. Chirieac, MD, is Associate Professor, Department of Pathology, Harvard Medical School and Associate Pathologist, Pathology, Brigham And Women's Hospital (BWH) in Boston, Massachusetts.

Todd Demmy, MD, is Clinical Chair, Department of Thoracic Surgery and Professor of Oncology at Roswell Park Cancer Institute; and Professor of Surgery in the School of Medicine and Biomedical Sciences at State University of New York at Buffalo.

Teresa Knoop, MSN, RN, AOCN, is an Assistant Director at the Vanderbilt-Ingram Cancer Center in Nashville, TN, where she supervises the Clinical Trials Information Program. The program serves as the referral center for Phase I, II, and III trials at the center and provides healthcare professionals and consumers with services, specialists, and second opinions. Ms. Knoop also directs special projects related to clinical research integration and Phase I program growth and development.

Faculty Biographies (continued)

The following faculty presented during this live webinar series between March 2014 and August 2014.

Billy W. Loo, Jr., MD, PhD, is Assistant Professor of Radiation Oncology and the Thoracic Radiation Oncology Program Leader at Stanford University in Stanford, California.

Peter Loud, MD, is Vice Chair, Diagnostic Radiology and Director of Body Imaging, Department of Diagnostic Radiology at Roswell Park Cancer Institute; and Clinical Associate Professor of Radiology in the School of Medicine and Biomedical Sciences at State University of New York at Buffalo.

Gregory A. Otterson, MD, is a Professor of Medicine, Attending Physician in Solid Tumor Oncology, and Co-Director of the Thoracic Oncology Program, at Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University.

Douglas E. Wood, MD, is the Professor and Endowed Chair in Lung Cancer Research in the Department of Surgery at the University of Washington in Seattle, Washington, where he is the Chief of the Division of Cardiothoracic Surgery.

Disclosure Information

The ACCME/ANCC/ACPE defines “conflict of interest” as when an individual has an opportunity to affect CE content about products or services of a commercial interest with which he/she has a financial relationship.

ACCME, ACPE, and ANCC focuses on financial relationships with commercial interests in the 12-month period preceding the time that the individual is being asked to assume a role controlling content of the CE activity. ACCME, ACPE, and ANCC have not set a minimal dollar amount for relationships to be significant. Inherent in any amount is the incentive to maintain or increase the value of the relationship. The ACCME, ACPE, and ANCC defines “’relevant’ financial relationships” as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.

All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.

Nurse Planner: Kristina M. Gregory, RN, MSN, OCN is the nurse planner for all NCCN educational activities.

Faculty Disclosures

All faculty and activity planners participating in NCCN continuing education activities are expected to disclose any relevant financial relationships with a commercial interest as defined by the ACCME's, ANCC's, and ACPE's Standards for Commercial Support. All faculty presentations have been reviewed for adherence to the ACCME's Criterion 7: The provider develops activities/educational interventions independent of commercial interests (SCS 1, 2, and 6) by experts on the topics. Full disclosure of faculty relationships will be made prior to the activity.

The faculty listed below have no relevant financial relationships to disclose:

Richard T. Cheney, MD
Todd Demmy, MD
Teresa Knoop, MSN, RN, AOCN
Peter Loud, MD

Faculty Disclosures

The faculty listed below have disclosed the following relevant financial relationships:

Lucian R. Chirieac, MD
Medical Science Affiliates: Consultant Fees/ Honoraria
Shook, Hardy & Bacon: Consultant Fees/ Honoraria
Wilcox and Savage: Consultant Fees/ Honoraria

Billy W. Loo, Jr., MD, PhD
Varian Medical Systems: Grant/Research support:
RaySearch Laboratories: Grant/Research support

Gregory A. Otterson, MD
Boehringer Ingelheim GmbH: Scientific Advisor, Grant/Research Support
Bristol-Myers Squibb Company: Grant/Research Support
Celgene Corporation: Scientific Advisor, Grant/Research Support
Genentech, Inc. Scientific Advisor: Grant/Research Support,
GlaxoSmithKline: Grant/Research Support
Pfizer Inc.: Grant/Research Support
Synta Pharmaceuticals: Grant/Research Support

Dr. Wood
Lung Cancer Alliance: Scientific Advisor
Spiration: Consulting Fees, Honoraria, Grant/Research Support

Planning Staff Disclosures

NCCN DISCLOSURES

The activity planning staff listed below has no relevant financial relationships to disclose:

Robert W. Carlson, MD; Ann Gianola, MA; Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Joan S. McClure, MS; Diane McPherson; Melanie Moletzsky; Deborah Moonan, RN, BSN; Liz Rieder; Shannon K. Ryan; Shannon Scarinci; Jennifer McCann Weckesser

The activity planning staff listed below has disclosed the following relevant financial relationships:

Valesta Tejan-Kamara
AstraZeneca Pharmaceuticals: Stock/Shareholder

The NCCN clinical information team listed below, who have reviewed content, have no relevant financial relationships to disclose:

Kristina M. Gregory, RN, MSN, OCN
Miranda Hughes, PhD

NCCN Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer
Interdisciplinary Cooperation: A Model Tumor Board in Non-Small Cell Lung Cancer

Presented live on March 7, 2014

By

Richard T. Cheney, MD
Roswell Park Cancer Institute

Billy W. Loo, MD, PhD
Stanford Cancer Institute

Gregory A. Otterson, MD (Program Chair)
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research

Douglas E. Wood, MD
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

A recording of this live webinar is available at http://education.nccn.org/node/49240 until June 17, 2015.

Intended Audience and Learning Objectives

Intended Audience:

This slide deck is designed to meet the educational needs of medical oncologists, radiation oncologists, surgical oncologists, pathologists, nurses, pharmacists, and other healthcare professionals who manage patients with non-small cell lung cancer.

Learning Objectives:

Following this section, participants should be able to:

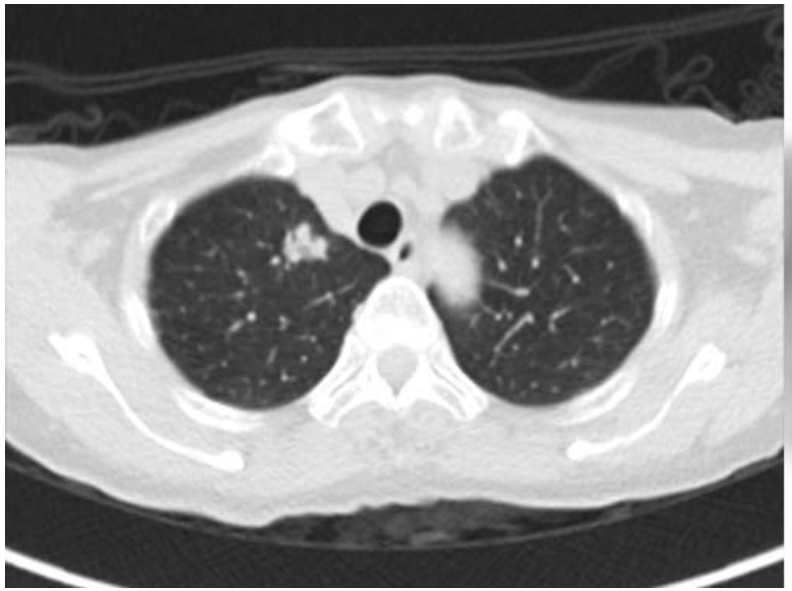
- Describe the respective contributions made by various multidisciplinary teams to the management of NSCLC

National Comprehensive Cancer Network®

Case #1

Case

- 70 yo Asian non-smoking woman, CT follow up of incidental CXR finding shows 1.6 cm RUL solid nodule
- CT guided biopsy: adenocarcinoma
- PET-CT: hypermetabolic RUL primary; equivocal/borderline uptake in non-enlarged subcarinal node



Question 1

There is insufficient material for molecular testing. Which of the following is most appropriate:

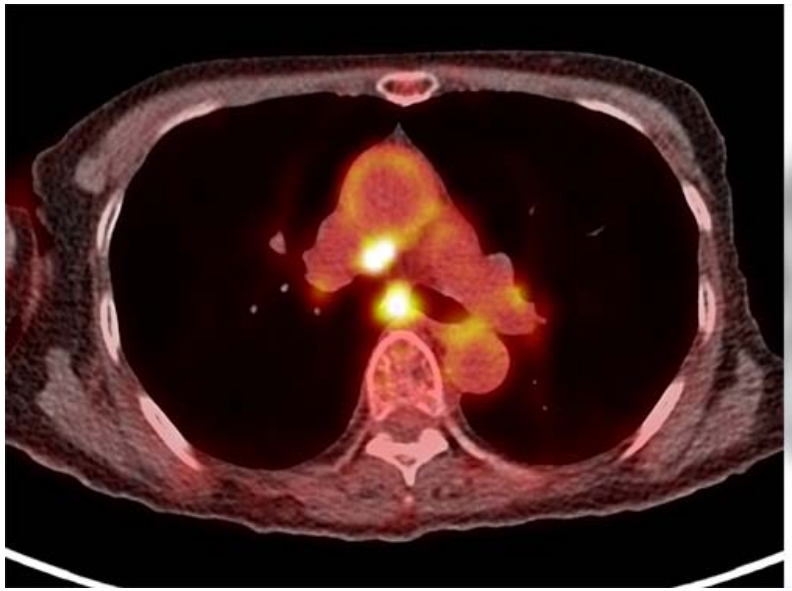
a. Repeat biopsy of primary site to obtain material for molecular testing

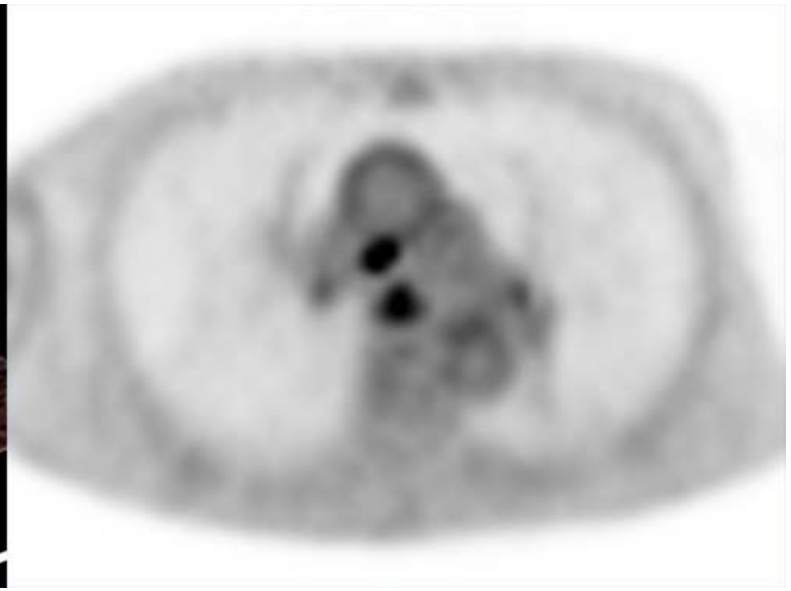
b. Biopsy mediastinum (EBUS/TBNA vs. mediastinoscopy)

c. No additional biopsy is needed

Case

- Patient refused surgery and additional biopsies
- Repeat PET-CT: New/progressive hypermetabolism in station 4R & 7 nodes, not enlarged by CT criteria; stable mild uptake in bilateral hilar nodes
- Brain MRI negative for metastases





Question 2

Stanford MEDICINE

The patient was felt to be physiologically frail and high risk for surgery. Which of the following is most correct:

a. Mediastinal biopsy is needed for staging

b. Mediastinal biopsy is not needed for staging, but is needed for molecular studies

c. Mediastinal biopsy is needed for both staging and molecular studies

d. Mediastinal biopsy is not needed

Question 3

EBUS TBNA shows metastatic adenocarcinoma in station 4R. FISH is positive for EML4-ALK fusion. Performance status is ECOG 1. Which of the following is the most appropriate management:

a. Crizotinib

b. Concurrent chemotherapy with RT

c. Induction crizotinib followed by chemoRT

d. Concurrent chemoRT and crizotinib

e. ChemoRT followed by adjuvant crizotinib

RTOG 1306-Alliance 31101 Schema

Patient Population: (See Section 3.0 for Eligibility)
Histologically or cytologically confirmed non-squamous NSCLC; unresectable stage IIIA or IIIB disease; patients must be surgically staged to confirm N2 or N3 disease.

Required Sample Size: **156 for the EGFR mutation cohort and 78 for the ALK translocation cohort**

Stratification

Weight Loss (in prior 6 mos.)	Stage	Chemotherapy
1. ≤ 5%	1. IIIA	1. cisplatin & etoposide
2. > 5%	2. IIIB	2. paclitaxel & carboplatin

EGFR TK Mutation Cohort

RANDOMIZE

Arm 1: Induction Therapy: Erlotinib, 150 mg/day for 12 weeks* → Concurrent †chemotherapy and IMRT or 3D-CRT 60 Gy in 30 fxs

Arm 2: Concurrent †chemotherapy and radiation, 60 Gy

ALK Tran L Cohort

RANDOMIZE

Arm 3: Induction Therapy: Crizotinib, 250 mg/bid for 12 weeks* → Concurrent †chemotherapy and IMRT or 3D-CRT 60 Gy in 30 fxs

Arm 4: Concurrent †chemotherapy and radiation, 60 Gy

*If CT at 6 weeks into induction therapy does not show at least PR, the patient will proceed directly to concurrent chemotherapy and IMRT or 3D-CRT, provided there is no progression that would preclude definitive chemoradiotherapy, in which case the patient will go off protocol treatment and be treated as appropriate for systemic disease . See Section 11.3 for definitions of responses.

RTOG Radiation Therapy Oncology Group | NRG Oncology

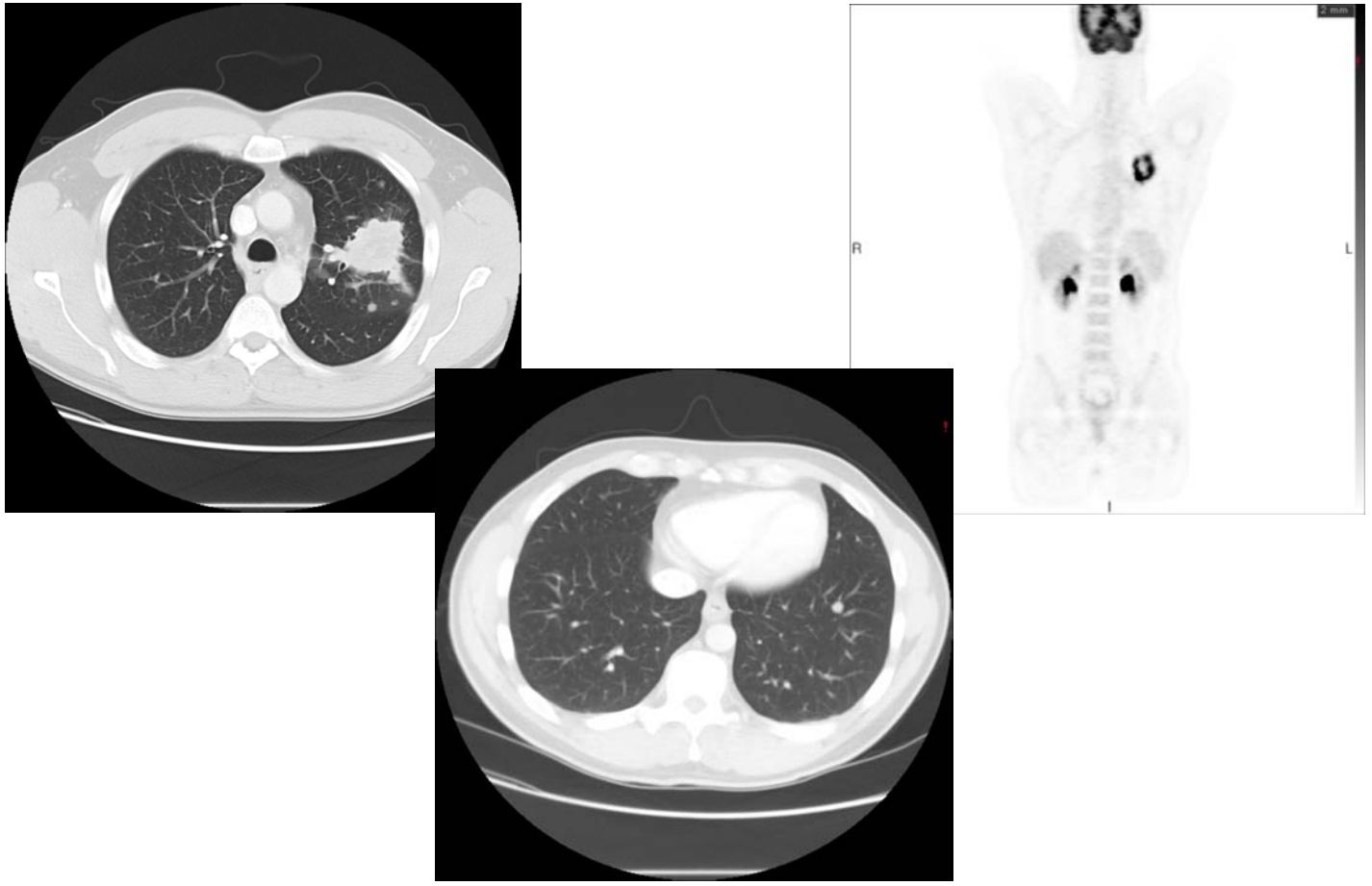
National Comprehensive Cancer Network®

Case #2

Case

- 43 yo never smoking male in his usual state of health until he developed intermittent hemoptysis.
- Physical examination unremarkable
- Radiographic imaging
  - Chest x-ray showed LUL mass
  - CT chest confirmed this, but also demonstrated an additional 1 cm LLL nodule. No mediastinal adenopathy or extra-thoracic disease was identified.
  - PET was confirmatory
  - Brain MRI was negative.

Initial images



Question 1

- Patient is healthy, fit for intervention(s). What next?
  1. Proceed to surgery (pneumonectomy)
  2. Mediastinal evaluation
     1. EBUS
     2. Mediastinoscopy
  3. Definitive chemo-radiation

What happened

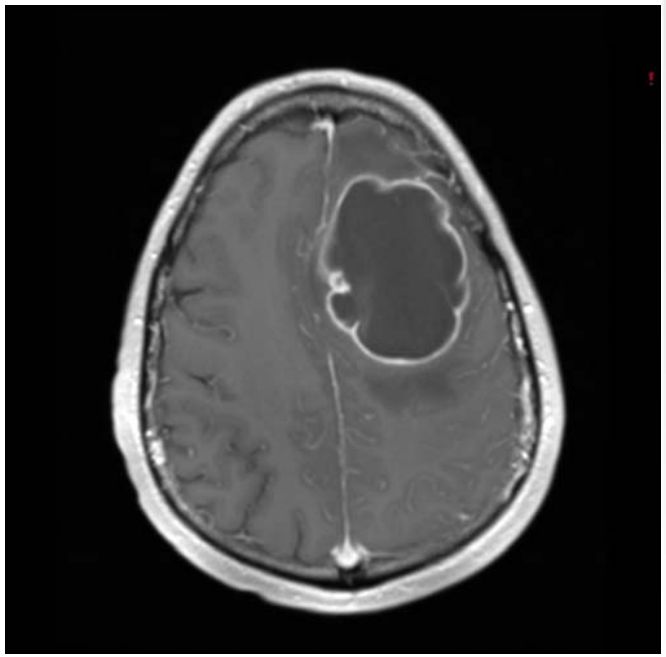
- Mediastinoscopy showed no involvement
- The patient went on to LUL lobectomy and LLL segmental resection
- Pathology revealed a T4N0 adenosquamous carcinoma with 18 bp in-frame deletion of EGFR within exon 19 (T4 by virtue of multiple ipsilateral, both lobes, lung nodules)

Question 2

- What Adjuvant therapy to you recommend?
  1. Cisplatin based chemotherapy x 4 cycles
  2. EGFR TKI for 1-2 years
  3. Cisplatin based chemotherapy x 4 cycles followed by EGFR TKI for 1-2 years
  4. Cisplatin based chemotherapy followed by mediastinal irradiation

What happened

- Patient recovered from surgery, received 4 cycles of cisplatin + docetaxel for pT4N0 disease.
- Six months later had headaches and altered mental status.
  - Brain MRI showed a large frontal lesion
  - Craniotomy with resection revealed metastatic poorly differentiated squamous carcinoma harboring the same EGFR mutation.
  - No extra- CNS disease (on CT or PET).



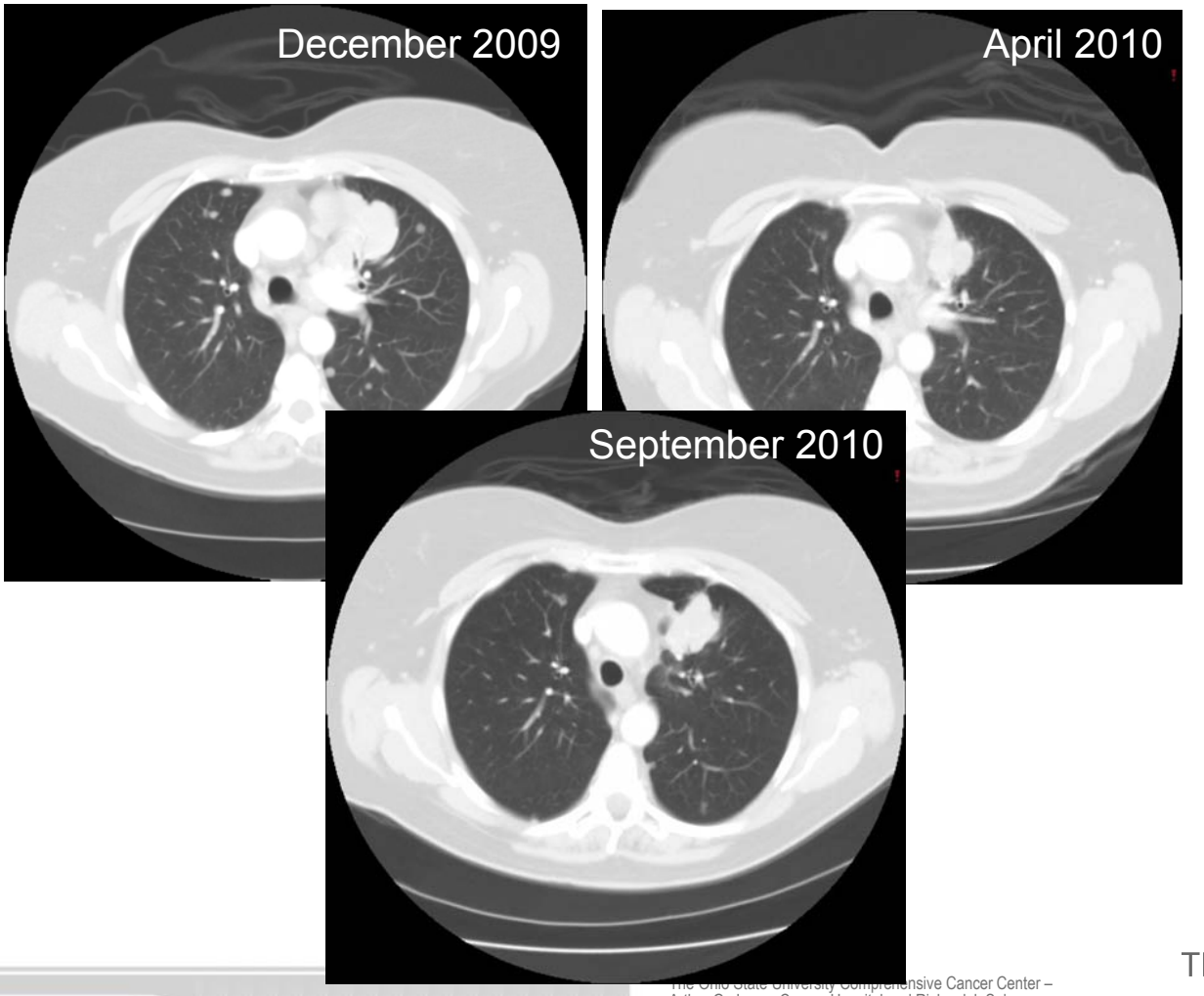
National Comprehensive Cancer Network®

Case #3

Case

- 69 y.o. white female who initially presented with hemoptysis in December 2009
- CXR showed a left hilar mass with multiple bilateral pulmonary nodules.
- Mediastinoscopy showed non-small cell lung cancer (adenocarcinoma).
- She was initially treated with Paclitaxel /Carboplatin /Bevacizumab, but then had progression of disease noted on CT scan in late September, 2010.

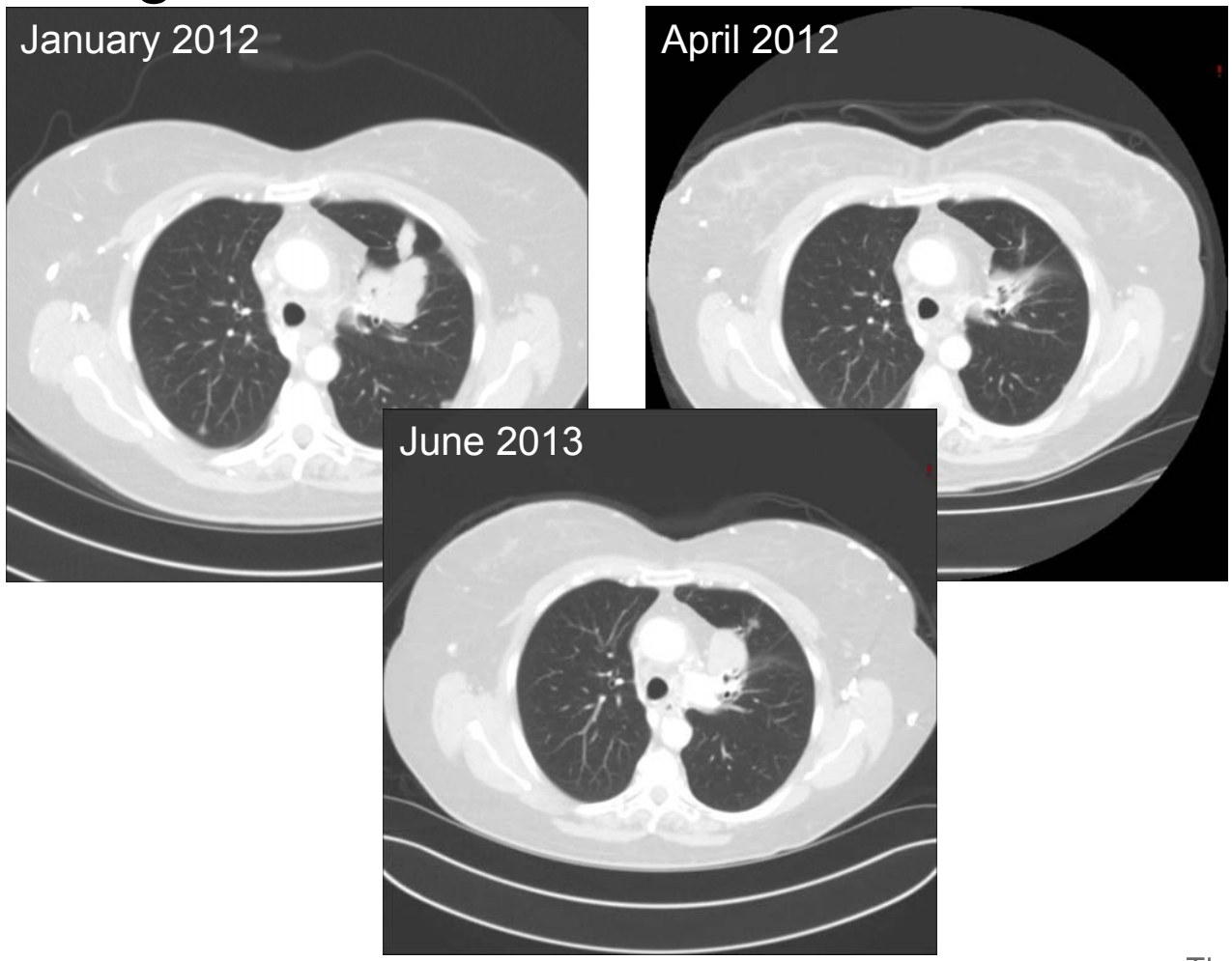
Initial images



Case

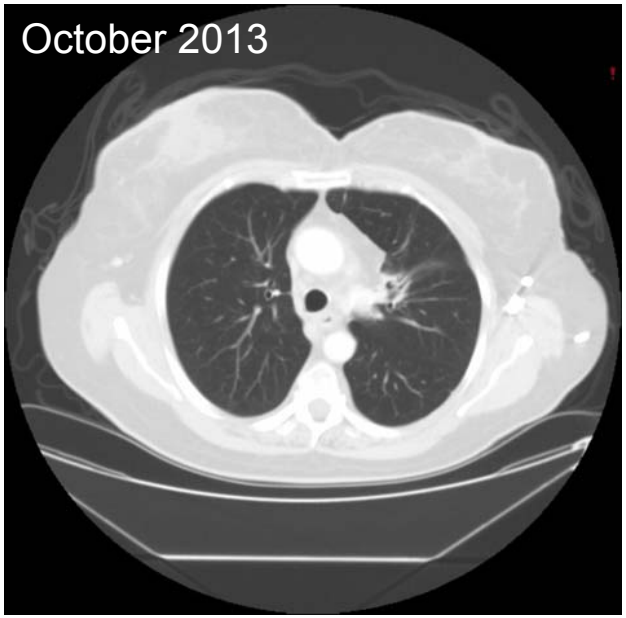
- Testing of archival tissue showed no KRAS or EGFR mutations, but was positive for ALK translocation.
  - Unfortunately, the central laboratory was negative, so ineligible for treatment with crizotinib (only available on trial at that time)
  - She then received treatment on trial with pemetrexed
- January 2012, progression
  - Re-testing (with FDA approved probe) for ALK
  - 45% cells positive
  - Initiated on crizotinib off trial

Images



What happened

- In June 2013, (16 months after crizotinib started), substantial growth of lung lesions
- Initiated therapy on protocol of crizotinib + HSP90 inhibitor



National Comprehensive Cancer Network®

Case #4

Case

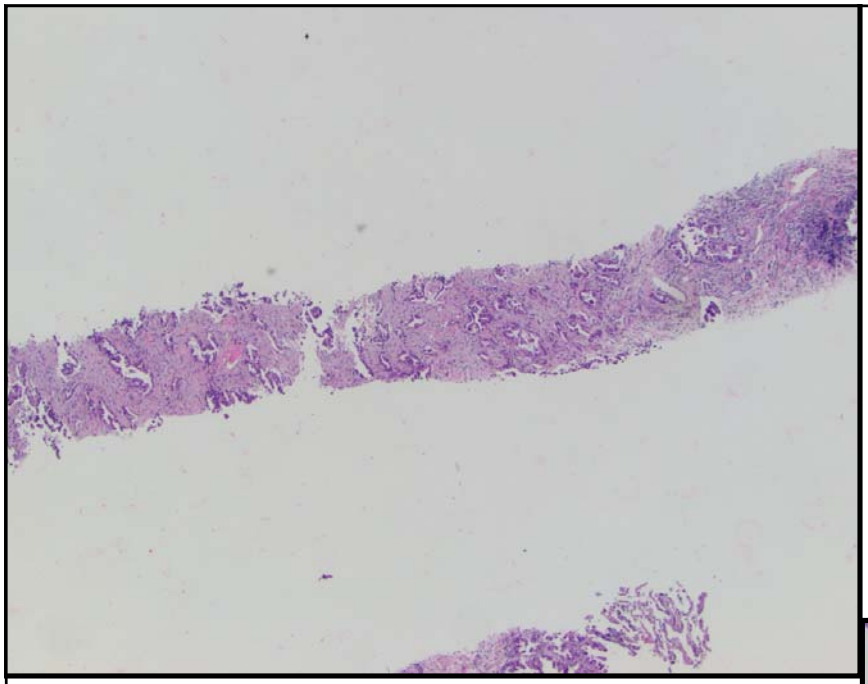
- 53 y.o. non-smoking male who presented with persistent cough
- Patient was evaluated in ED with dyspnea and was found to have a right lower lobe mass and pleural effusion on CXR.
- CT chest revealed a 3.1 cm right lower lobe mass and associated adenopathy.
- Patient underwent CT guided biopsy of the primary lesion and thoracentesis.
- Pathology revealed adenocarcinoma with lung origin. IHC positive for BEREP4, MOC-31, cytokeratin 7, TTF-1. Negative for calretinin, thrombomodulin, gata-3, cytokeratin 20 and CDX-2. Pleural effusion was also positive for adenocarcinoma.

What next?

1. Proceed with platinum based doublet
2. Obtain more tissue for molecular testing
3. VATS pleurodesis

- Patient had VATS, pleurodesis with additional biopsies
- Initiated therapy with paclitaxel + carboplatin + bevacizumab
- During cycle 1, molecular testing showed 49% cells with ROS1 FISH positive results

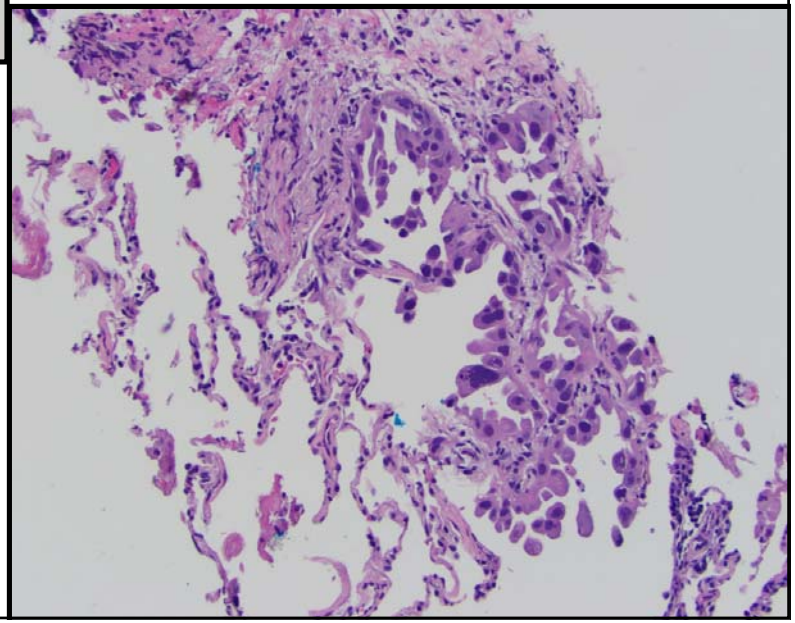
Pathology Support Slides



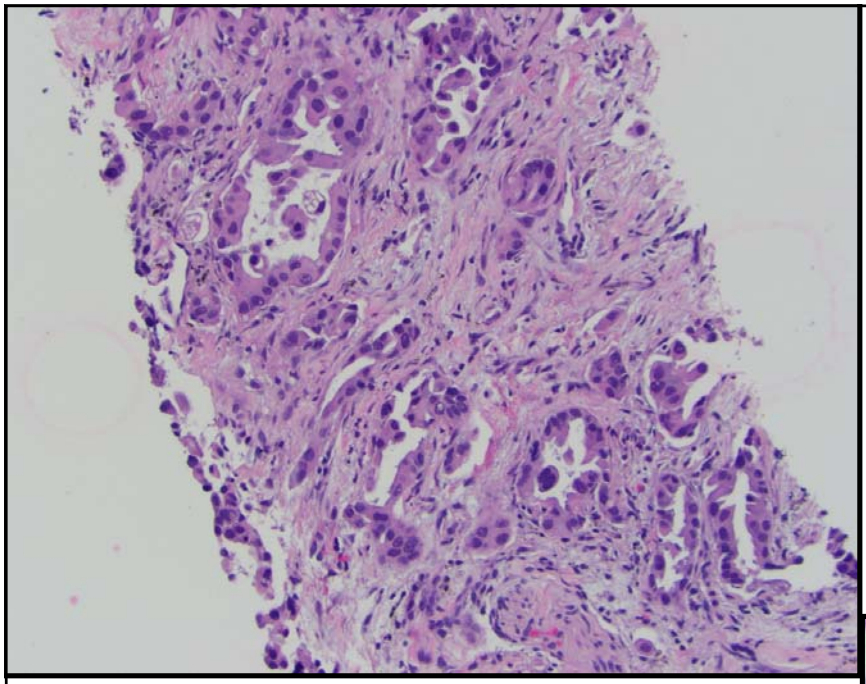
Needle Biopsy RUL

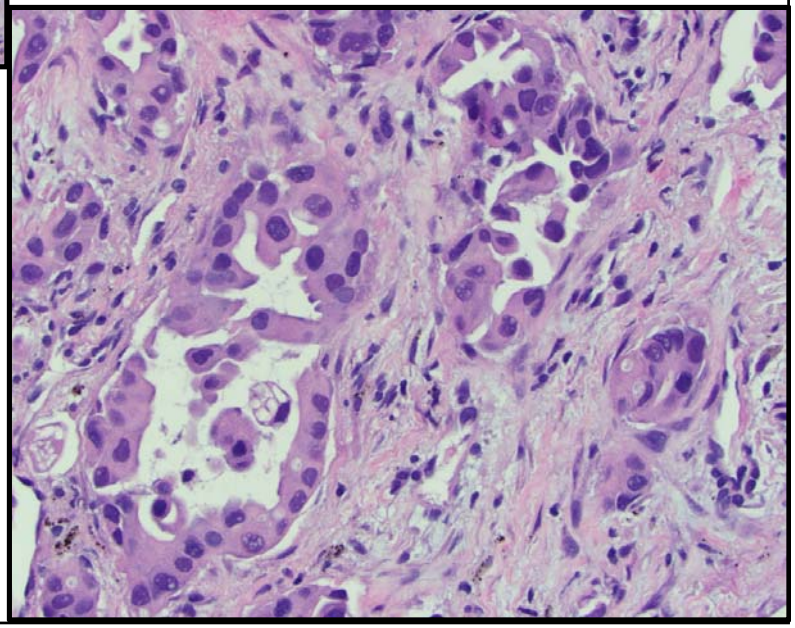
70y/o Asian non-smoking woman

Focal Lepidic pattern



ROSWELL PARK CANCER INSTITUTE





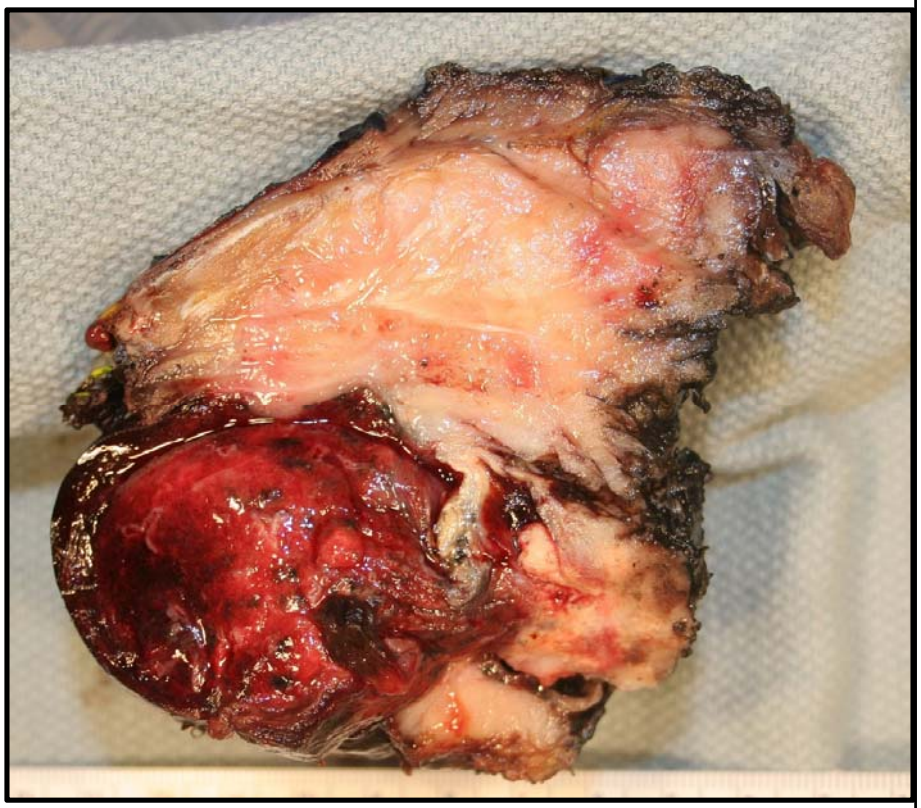
Diagnosis:

Lung, RUL, Needle Bx:
Adenocarcinoma, Invasive, predominant Acinar pattern*

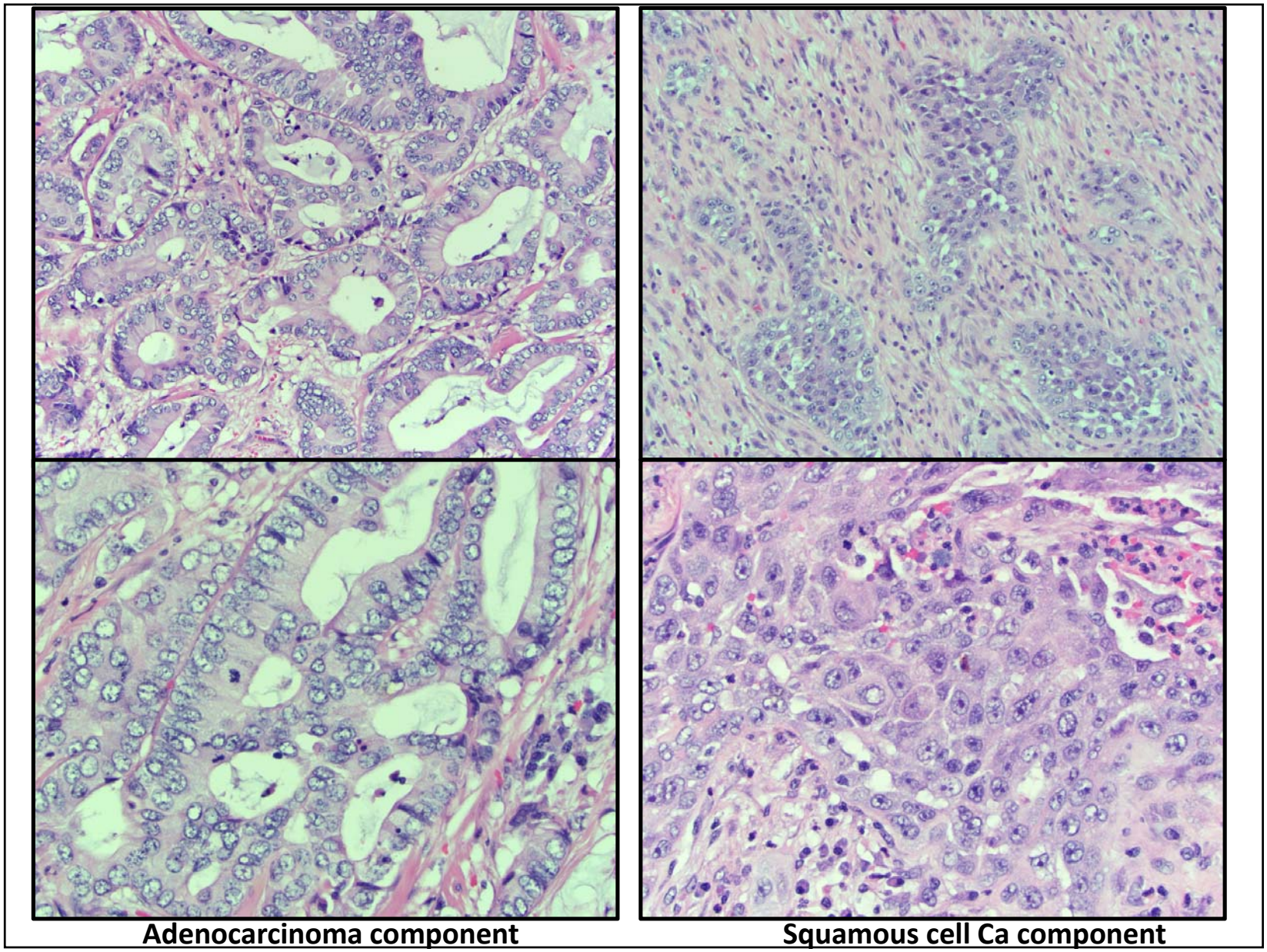
***correlate w/ imaging**

ROSWELL PARK CANCER INSTITUTE

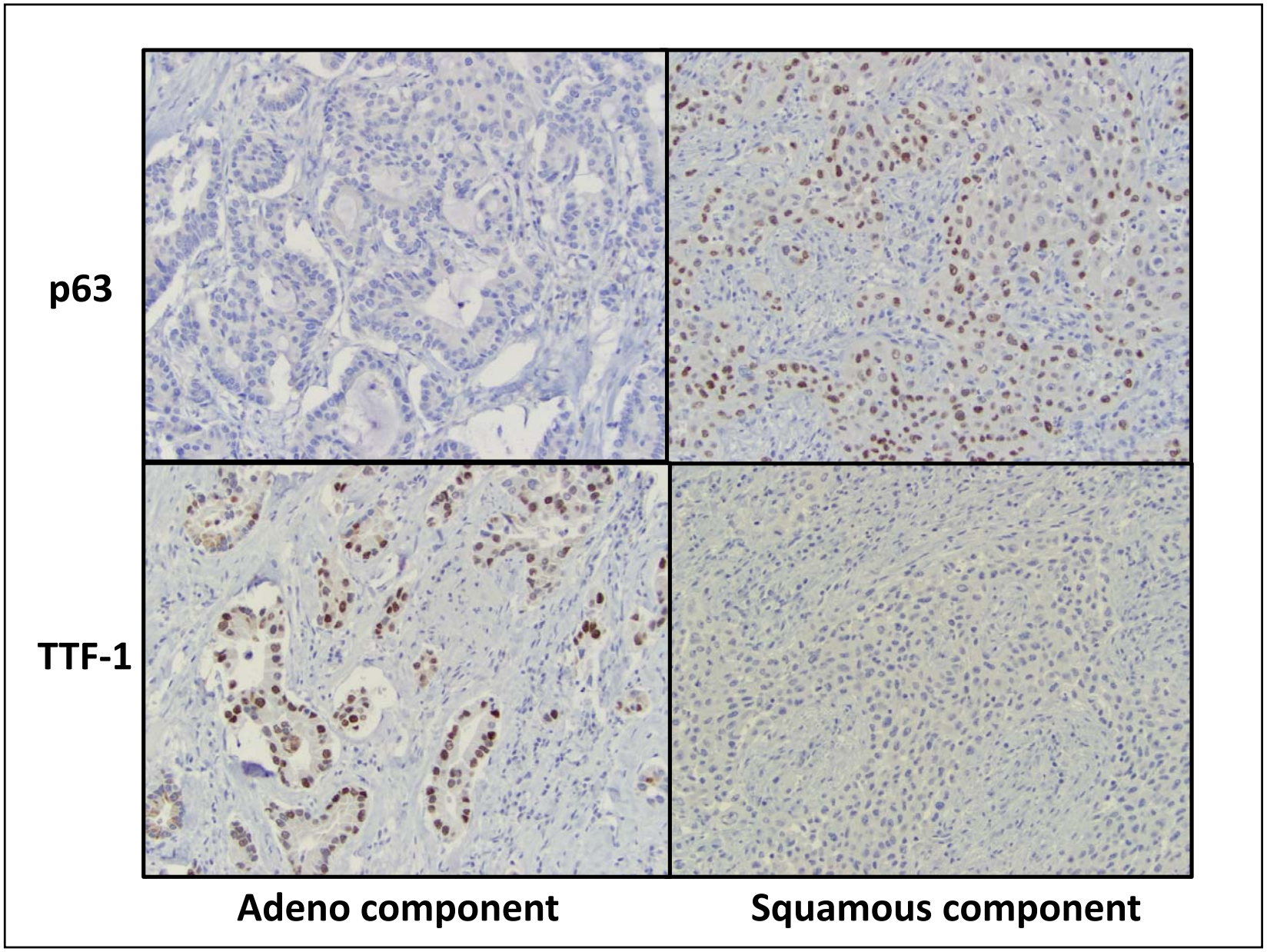
43y/o never smoking male



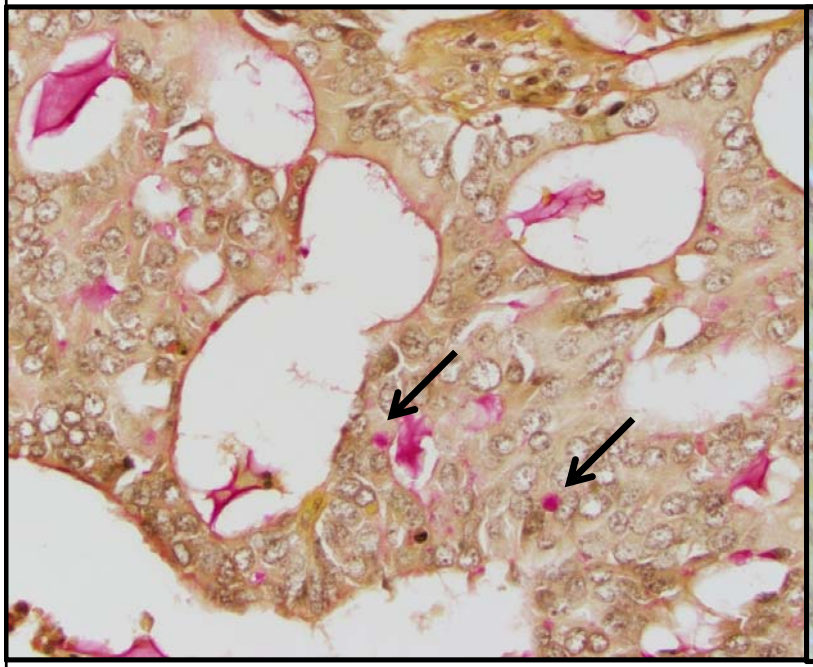
LUL -Lobectomy specimen



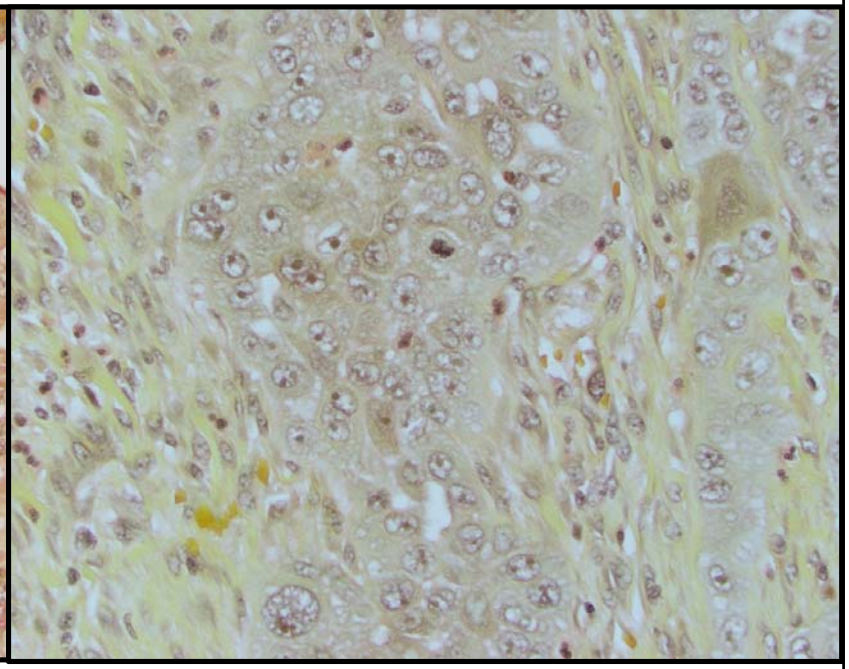
Adenocarcinoma component **Squamous cell Ca component**



Mucin Stain



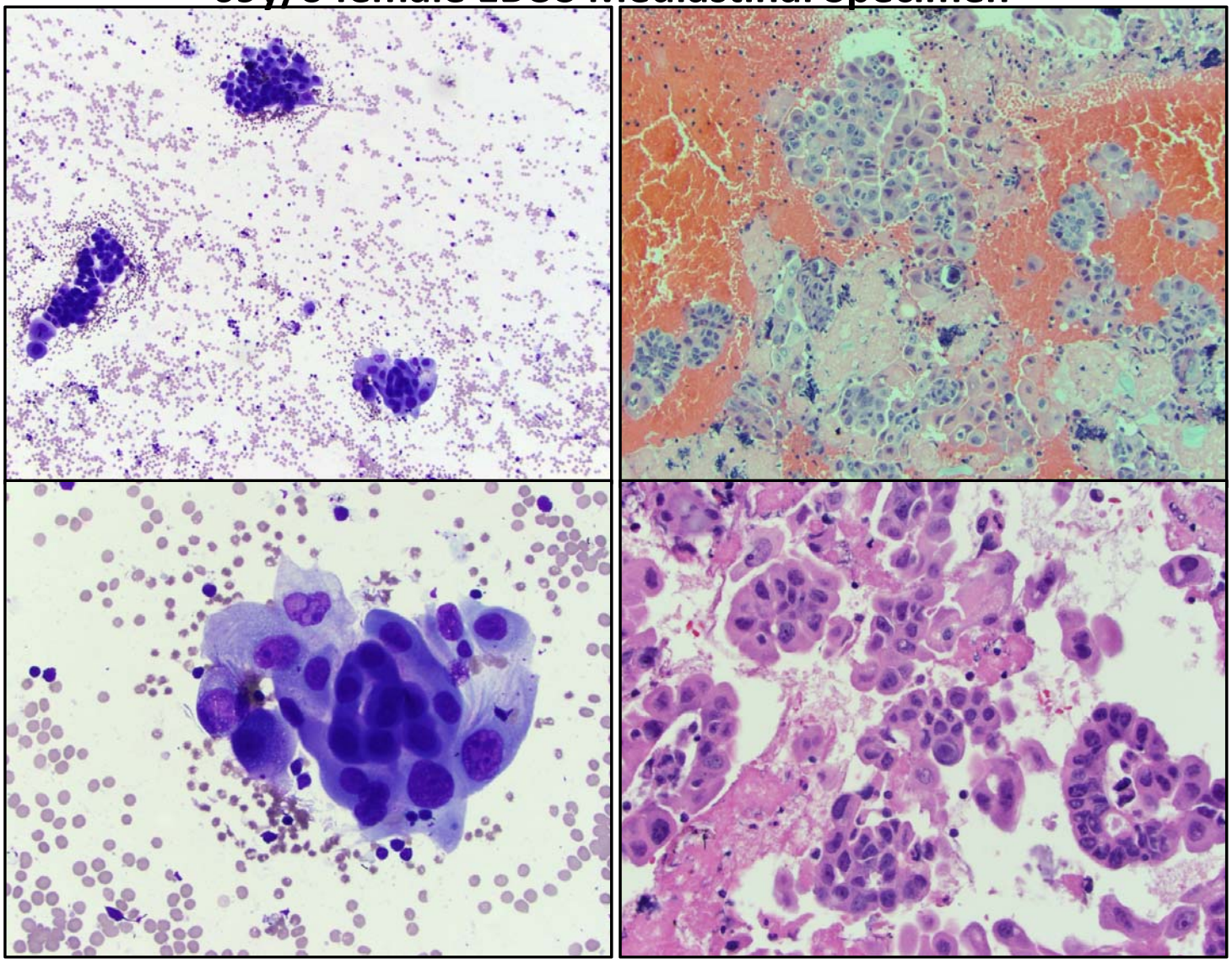
Adeno component- Pos



Squamous component-Neg

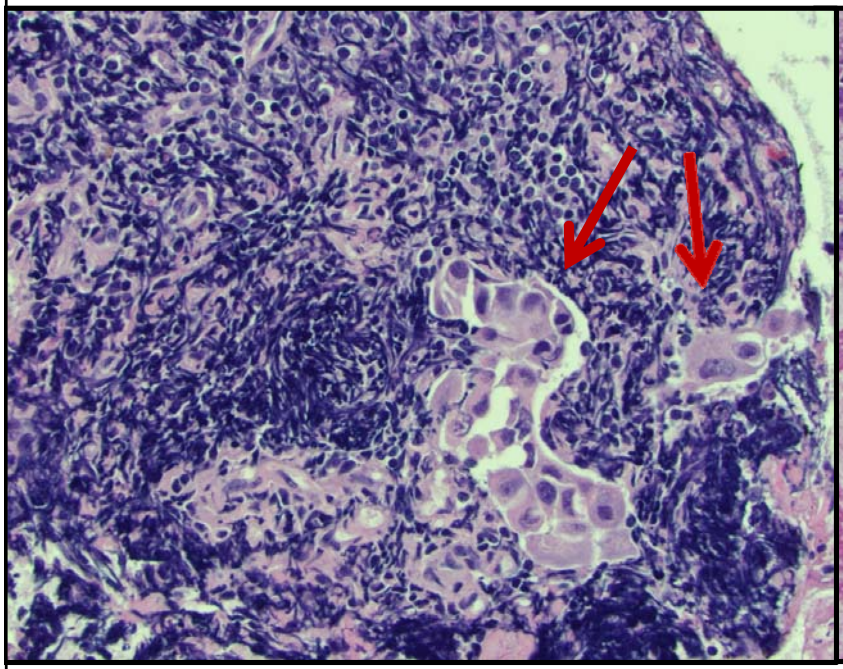
Final Anatomic Diagnosis: Adenosquamous Cell Carcinoma

69y/o female EBUS Mediastinal Specimen

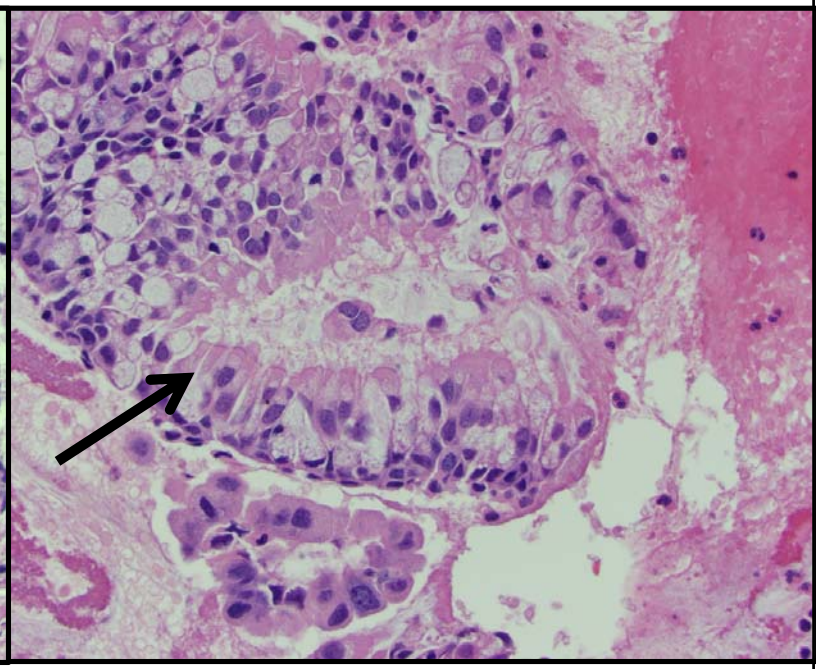


Aspirate Smears **Cell Block- FFPE**

EBUS Mediastinal Specimen

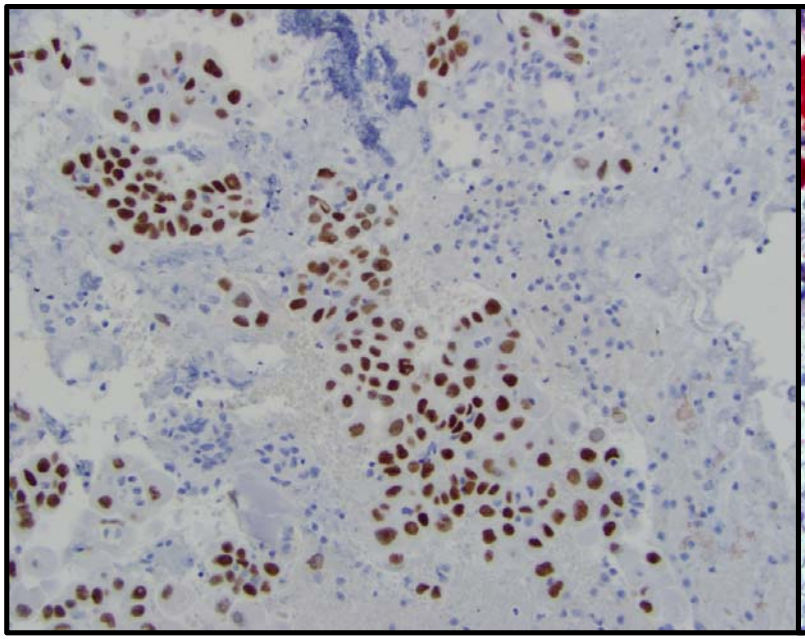


Met in Lymph node Tissue fragment

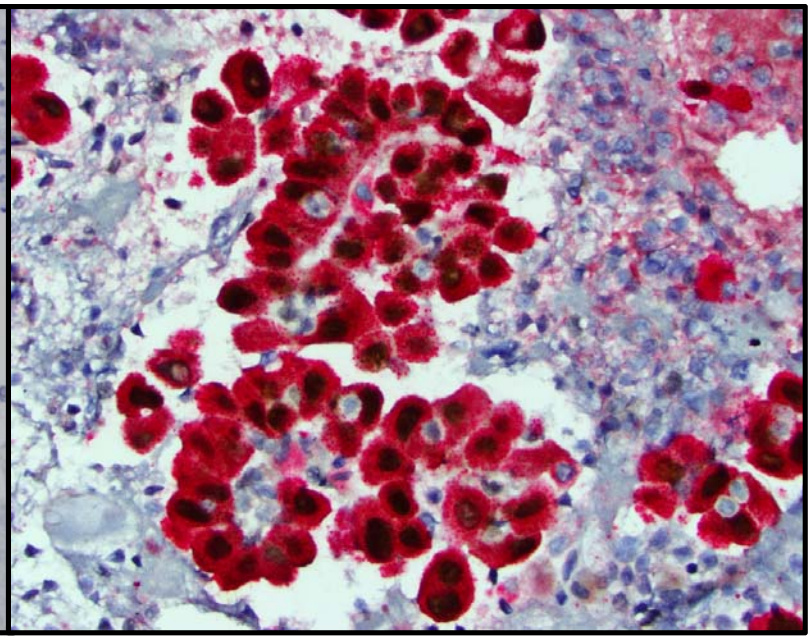


Benign Respiratory Epithelium

EBUS Mediastinal Specimen



Thyroid Transcription Factor-1 (TTF-1)



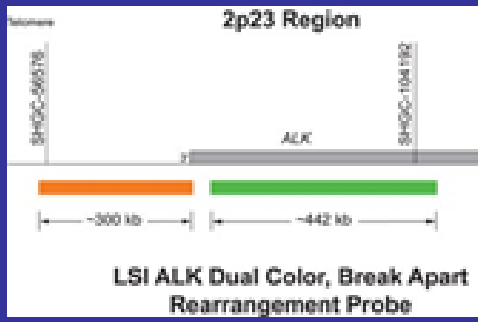
TTF-1 & Napsin-A Double IHC

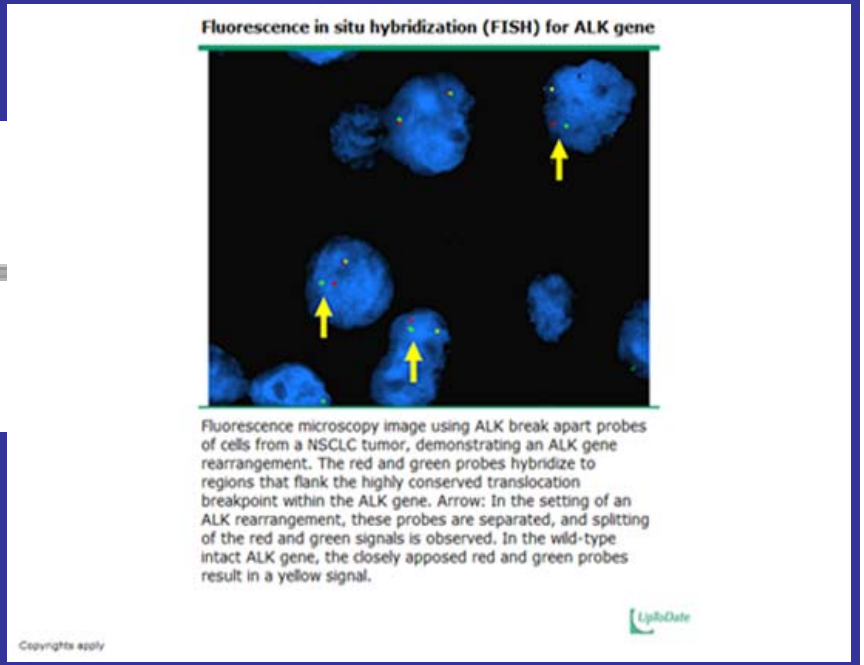
Diagnosis

Lymph Node, Subcarinal, EBUS Fine Needle Aspiration and Cell Block:
-Metastatic Adenocarcinoma, c/w Lung primary

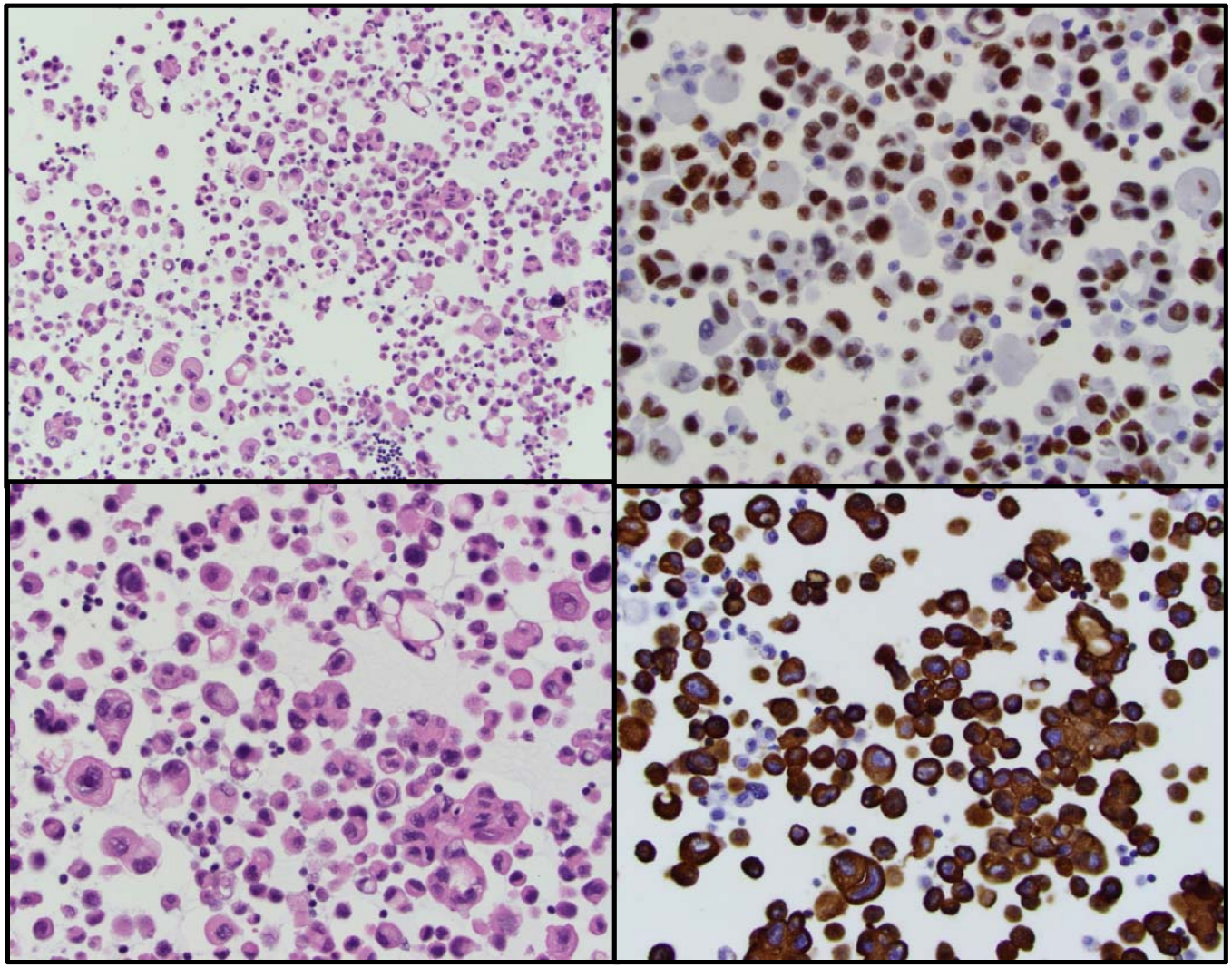
EML4-ALK FISH

An ALK Fish break apart probe is a qualitative test to detect rearrangements in the Alk gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens to aid in identifying those patients eligible for treatment with crizotinib. Ultrasensitive Immunohistochemistry (IHC) may gain more widespread use in the future as newer Antibodies are developed.





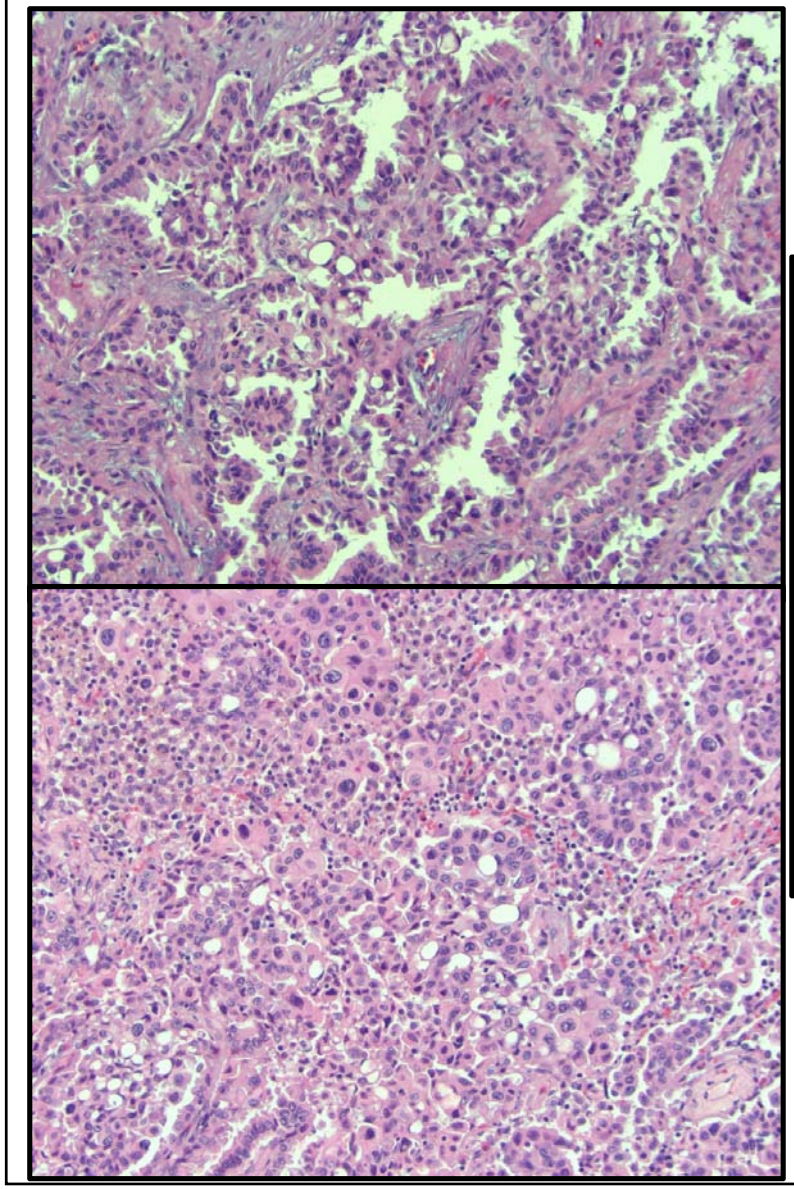
53y/o male, RLL Mass and pleural effusion



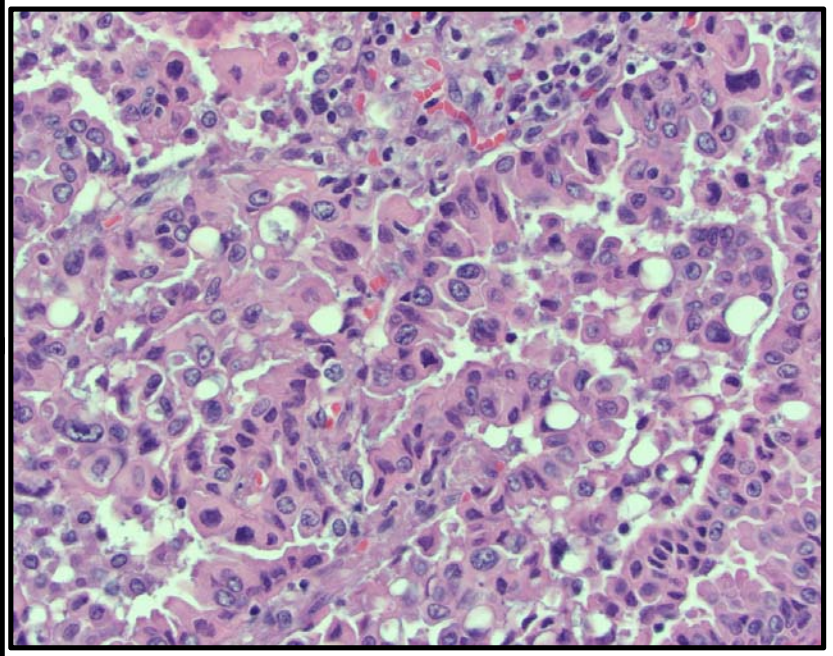
TTF-1

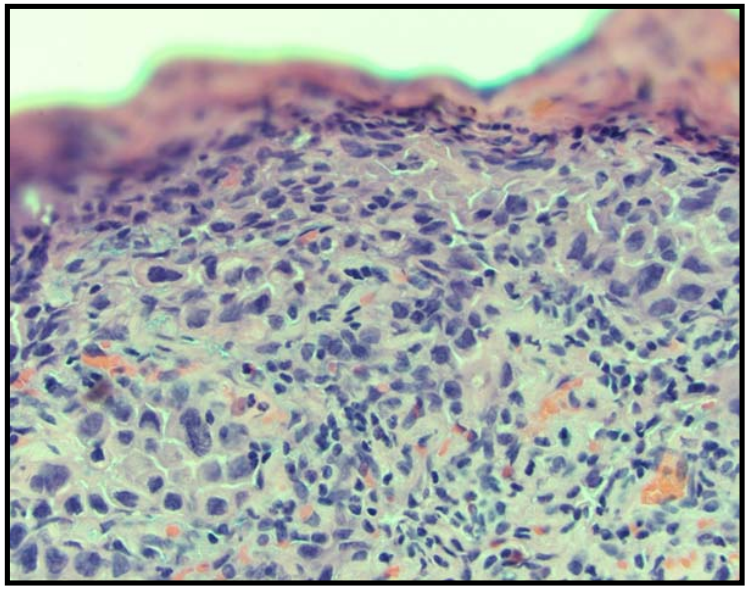
CK7

Pleural Fluid- Adenocarcinoma c/w Lung 1^0

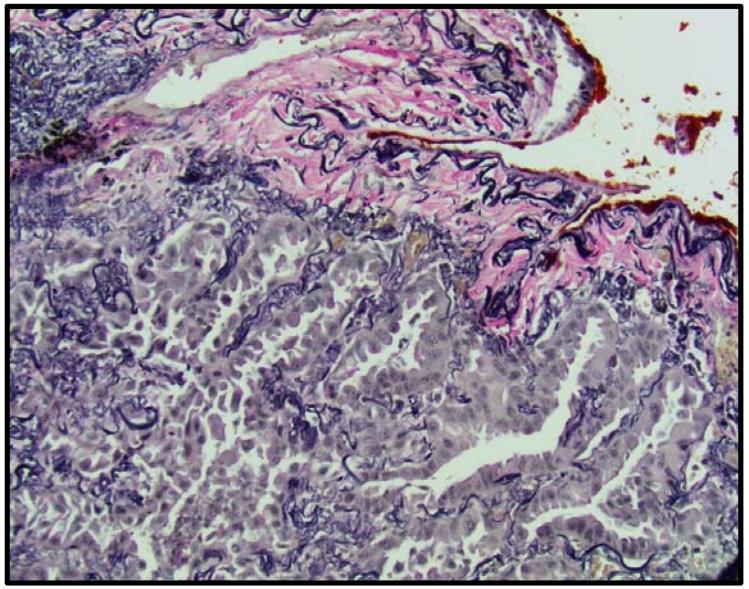


RLL Mass, 3.5 cm





Pleural Surface



Elastic Tissue Stain

Diagnosis

Lung, Right Lower Lobe, VATS resection:

-Moderately Differentiated Adenocarcinoma(G2), mixed pattern with Lepidic (20%), Acinar (35%), Micropapillary (35%) and Solid(10%) components

-See Synoptic Report

Synoptic Report

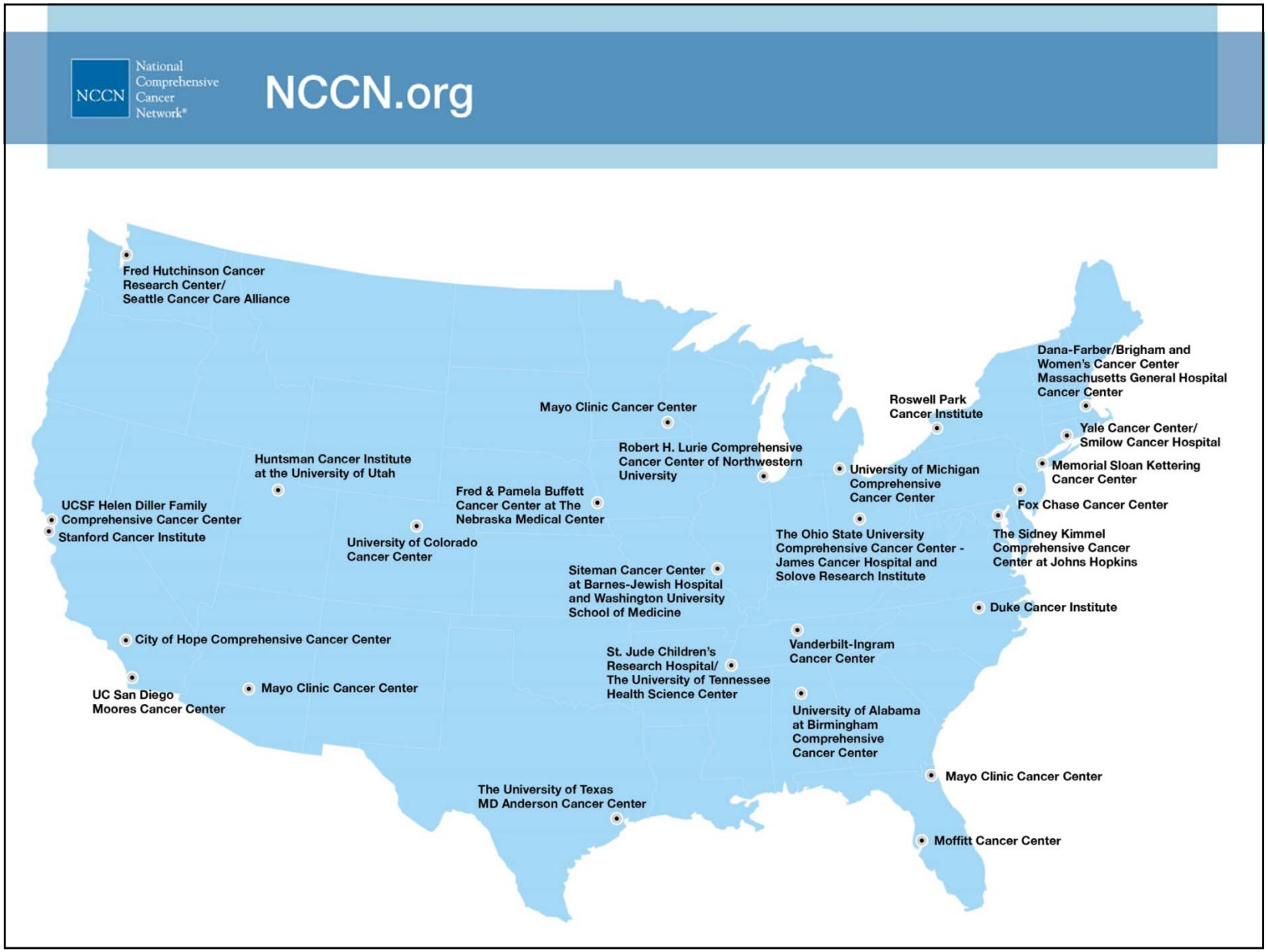
- **Specimens Submitted:**
  - A 4R LN
  - B. Additional 4R LN
  - C. Level 7 LN
  - E. Level 11 LN
  - F. Right lower Lobe
- **Surgical Procedure:** Lobectomy, VATS
- **Laterality:** Right
- **Tumor Site:** Lower Lobe
- **Tumor Location**: Peripheral
- **Tumor Size:** Greatest Dimension: 3.5 cm
  - Additional Dimensions: 2.5cm x 2.0cm
- **WHO Classification:**
  - Adenocarcinoma, mixed subtypes with Lepidic(20%), Acinar (35%), Micropapillary (35%) and Solid(10%)
- **Histologic Grade:** G2, Moderately Differentiated
- **Angiolymphatic invasion:** Present, lymphatic vessel
- **Bronchial Margin**: Uninvolved, 6 cm
- **Visceral Pleural Involvment**: Present (pT2)
- **Satellite Tumor(s):** Absent
- **Lymph Node Involvement:**
  - N1 Ipsilateral Hilar &/or Peribronchial (levels 10-14): Negative (0/12)
  - N2 Ipsilateral Mediastinal &/or Subcarinal (levels 1-9): Negative (0/4)
  - N3: Contralateral Mediastinal, Scalene, or Supraclavicular: Negative (0/1)
- **Non-Neoplastic lung:** Atelectasis
- **Pathologic Staging:** pT2 N0 M1a (AJCC Cancer Staging Manual, 7th Ed)
- **Molecular Results:** See Separate Lung Biomarker Test Report

ROSWELL PARK CANCER INSTITUTE

What is Pathologist Role?

- A-Provide concise, accurate, & timely Dx
- B-Advise clinical team on adequacy of specimen for ancillary molecular testing
- C-Determine most appropriate testing methodology (ie, FISH vs IHC vs NGS) for sample analysis
- D- A only
- E- All of the above

ROSWELL PARK CANCER INSTITUTE



NCCN Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer Evaluation and Workup of Patients with NSCLC

Presented live on March 25, 2014

by:

Gregory A. Otterson, MD
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research

Douglas E. Wood, MD
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

A recording of this live webinar is available at http://education.nccn.org/node/49245 until June 17, 2015.

Intended Audience and Learning Objectives

Intended Audience:

This slide deck is designed to meet the educational needs of medical oncologists, radiation oncologists, surgical oncologists, pathologists, nurses, pharmacists, and other healthcare professionals who manage patients with non-small cell lung cancer.

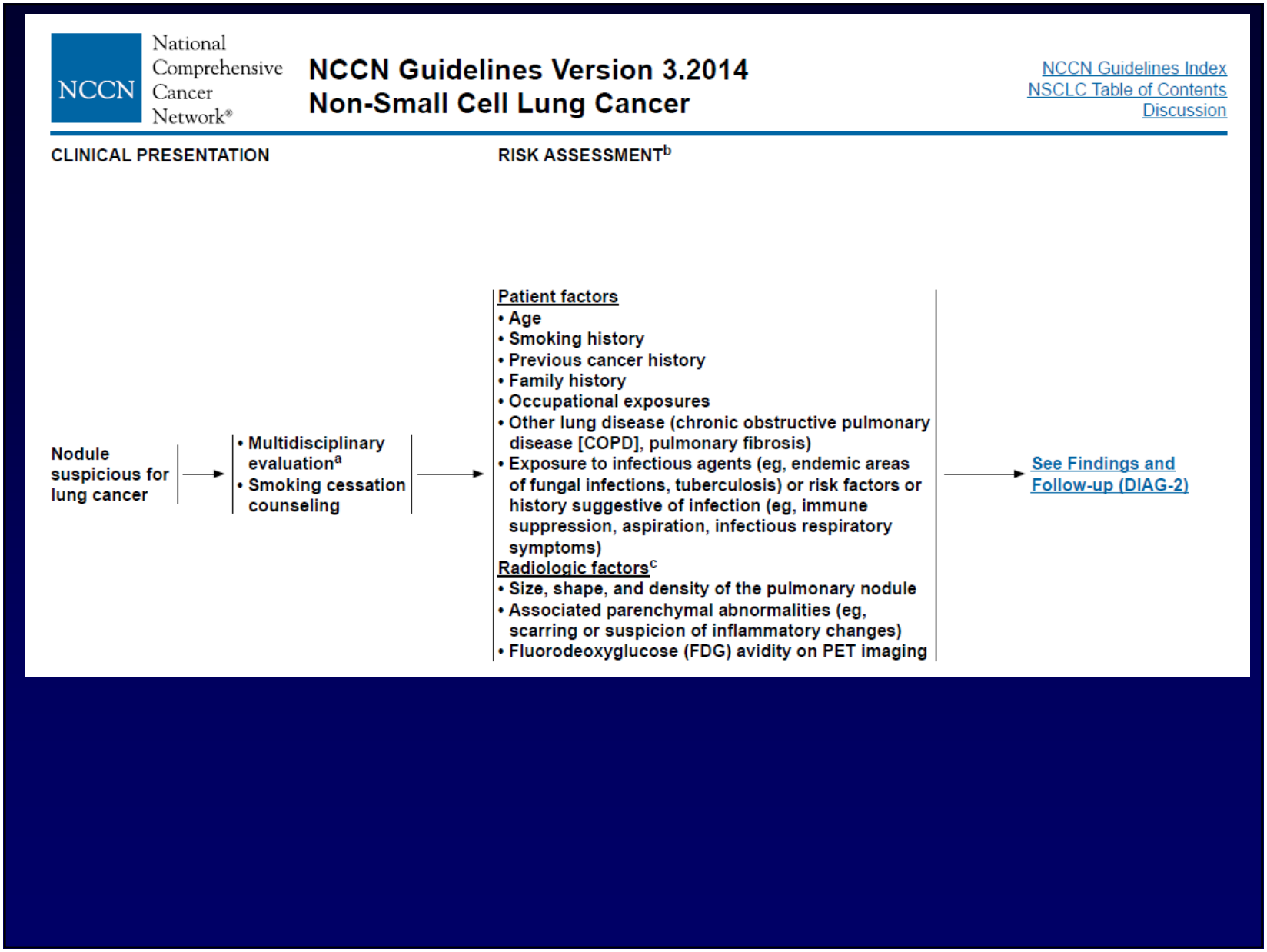
Learning Objectives:

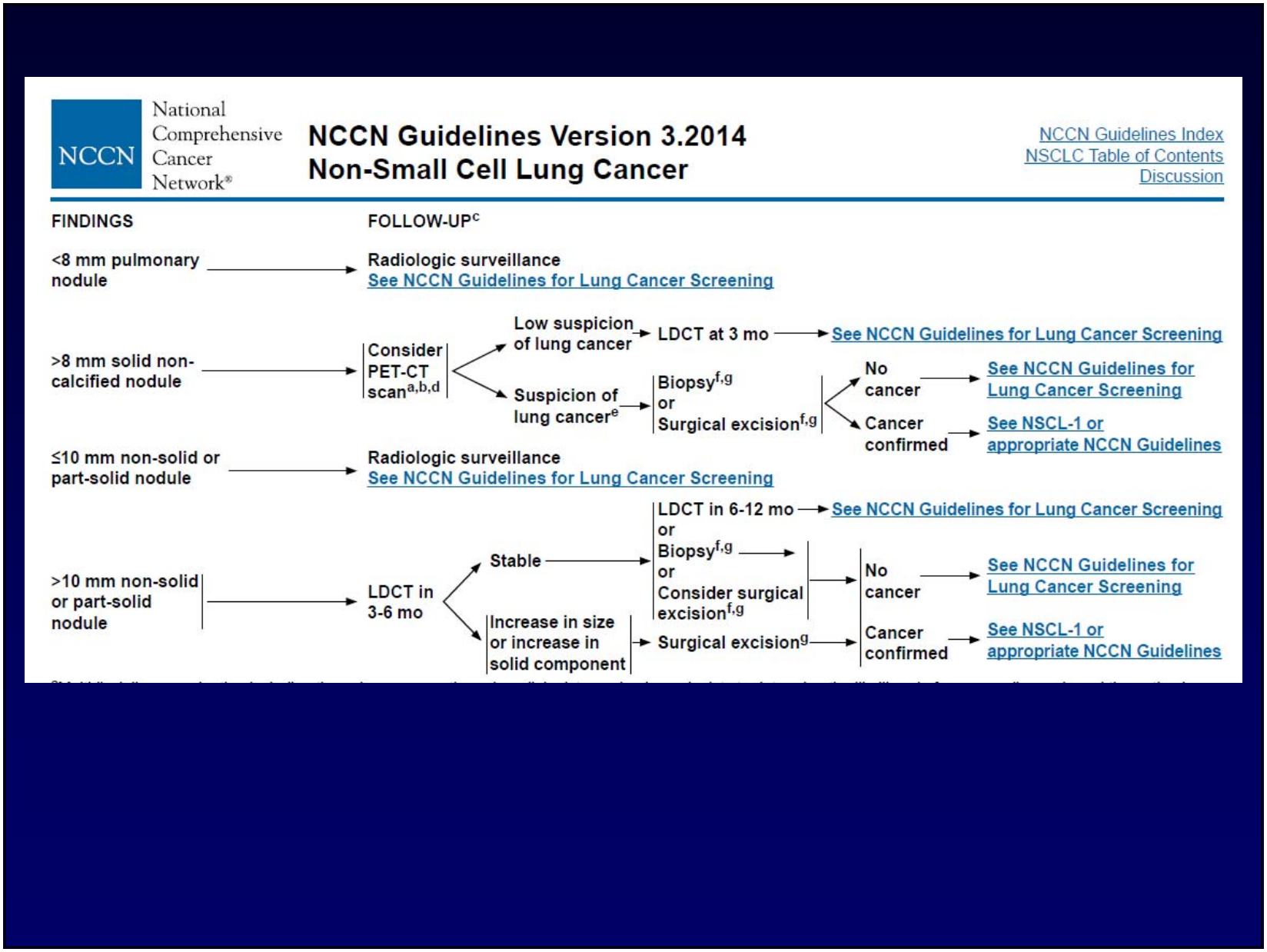
Following this section, participants should be able to:

- Discuss the optimal evaluation and workup of patients with NSCLC

LUNG CANCER STAGING
Why do we do it?

- Stage specific treatment recommendations
- Stage specific prognosis
- Improve patient outcomes



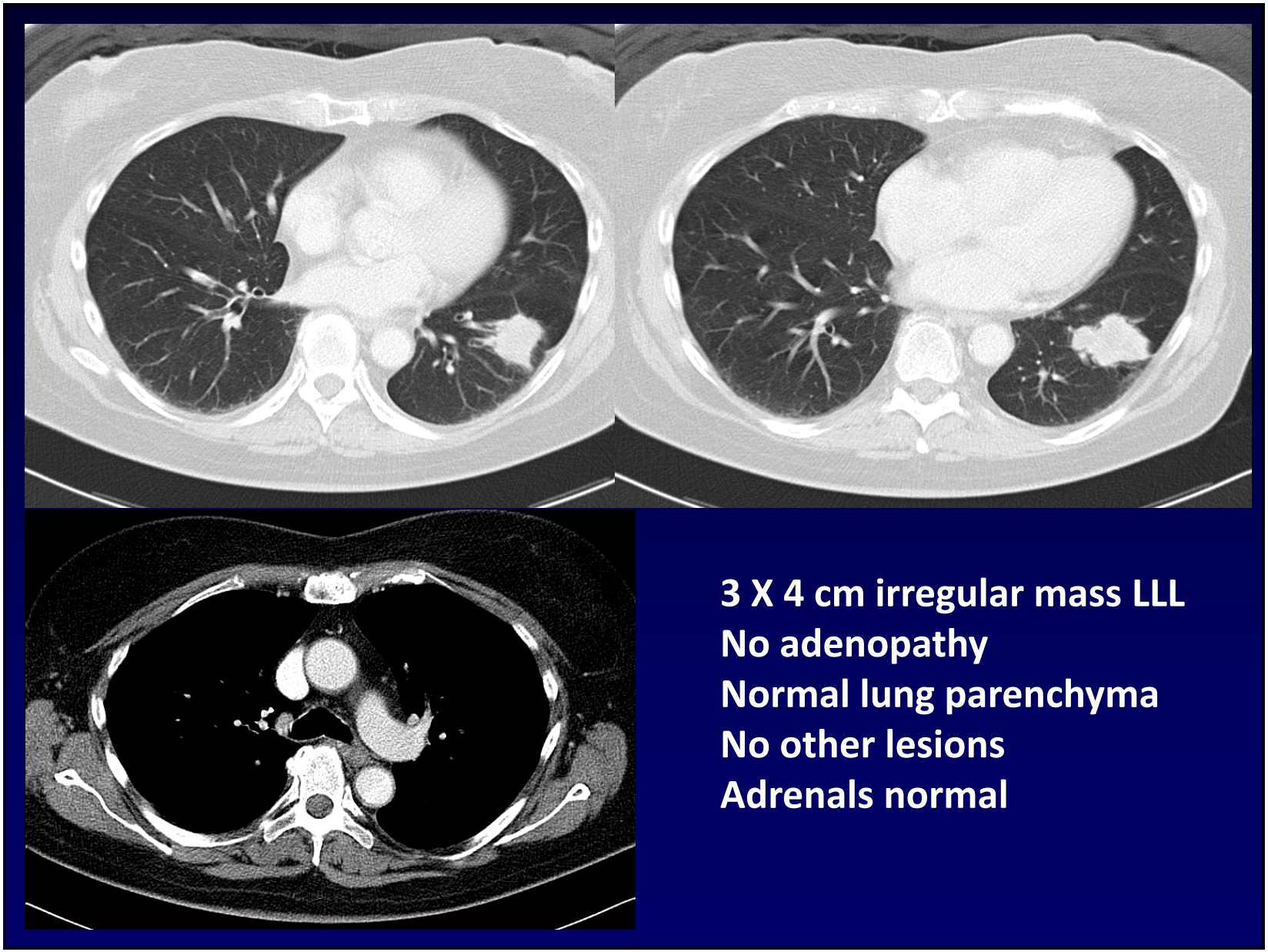


LUNG CANCER STAGING
Assumptions

- Surgery is preferred initial therapy for stage I/II
- Surgery is not the preferred primary therapy for:
  - Unresectable disease (T status)
  - N2 or N3 nodal disease
  - Metastatic disease
- Surgery is the preferred therapy for resectable but locally advanced tumors (T3-4N0-1)
- N2 disease treated with multimodality therapy

Lung Cancer Evaluation

- 68 yo asymptomatic woman
- Abdominal CT for w/u of constipation
  - Abdomen normal
  - Mass at left lung base
- Chest CT with contrast performed
- Asian
- Smoking for 2 years, stopped for 50 years
- No other relevant history
- Physical exam unremarkable



Lung Cancer Evaluation

The patient should be referred to a:

a) **Pulmonologist**
b) **Thoracic Surgeon**
c) **Medical oncologist**
d) **Radiation oncologist**
e) **Interventional radiologist**

LUNG CANCER STAGING
Goals

Accurate

Efficient

Inexpensive

Cost-effective

LUNG CANCER STAGING

Who should do it?

- Pulmonologist
- Medical oncologist
- Radiation oncologist
- Thoracic surgeon
- Radiologist

LUNG CANCER STAGING
Who should do it?

- Non-invasive staging - Lung cancer specialist
  - Timely
  - Efficient
  - Avoid unnecessary tests
  - Avoid multiple follow-up visits
- Non-invasive staging complete in 1-2 weeks
  - Including tissue diagnosis, if necessary

LUNG CANCER STAGING
Who should do it?

- Stage IV → referral to medical oncology
  - Incontrovertible radiologic evidence
  - Biopsy proven
- Stage I-III + suspected but unproven stage IV → mandates evaluation by thoracic surgeon
  - Evaluate resectability
  - Assess N2/3 or M1 disease (+/- biopsy)
  - Evaluate options of multimodality therapy

Lung Cancer Evaluation

The most efficient next step in workup is:

a) **Bronchoscopy with biopsy**
b) **CT guided needle biopsy**
c) **PET scan**
d) **Brain MRI**

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

PRINCIPLES OF DIAGNOSTIC EVALUATION

- Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.
  - A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.
  - A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by FNA.
  - A preoperative biopsy may be appropriate if an intraoperative diagnosis appears difficult or very risky.
  - If a preoperative tissue diagnosis has not been obtained, then an intraoperative diagnosis (ie, wedge resection or needle biopsy) is necessary before lobectomy, bilobectomy, or pneumonectomy.
- Bronchoscopy should preferably be performed during the planned surgical resection, rather than as a separate procedure.
  - Bronchoscopy is required before surgical resection (see NSCL-2).
  - A separate bronchoscopy may not be needed for treatment decisions before the time of surgery and adds time, costs, and procedural risk.
  - A preoperative bronchoscopy may be appropriate if a central tumor requires pre-resection evaluation for biopsy, surgical planning (eg, potential sleeve resection), or preoperative airway preparation (eg, coring out an obstructive lesion).
- Invasive mediastinal staging is recommended before surgical resection for most patients with clinical stage I or II lung cancer (see NSCL-2).
  - Patients should preferably undergo invasive mediastinal staging as the initial step before the planned resection (during the same anesthetic procedure), rather than as a separate procedure.
  - A separate staging procedure adds time, costs, coordination of care, inconvenience, and an additional anesthetic risk.
  - Preoperative invasive mediastinal staging may be appropriate for a strong clinical suspicion of N2 or N3 nodal disease or when intraoperative cytology or frozen section analysis is not available.
- In patients with suspected NSCLC, many techniques are available for tissue diagnosis.
  - Diagnostic tools that should be routinely available include:
    - Sputum cytology
    - Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)
    - Image-guided transthoracic needle aspiration (TTNA)
    - Thoracentesis
    - Mediastinoscopy
    - Video-assisted thoracic surgery (VATS) and open surgical biopsy
  - Diagnostic tools that provide important additional strategies for biopsy include:
    - Endobronchial ultrasound (EBUS)–guided biopsy
    - Navigational bronchoscopy

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

PRINCIPLES OF DIAGNOSTIC EVALUATION

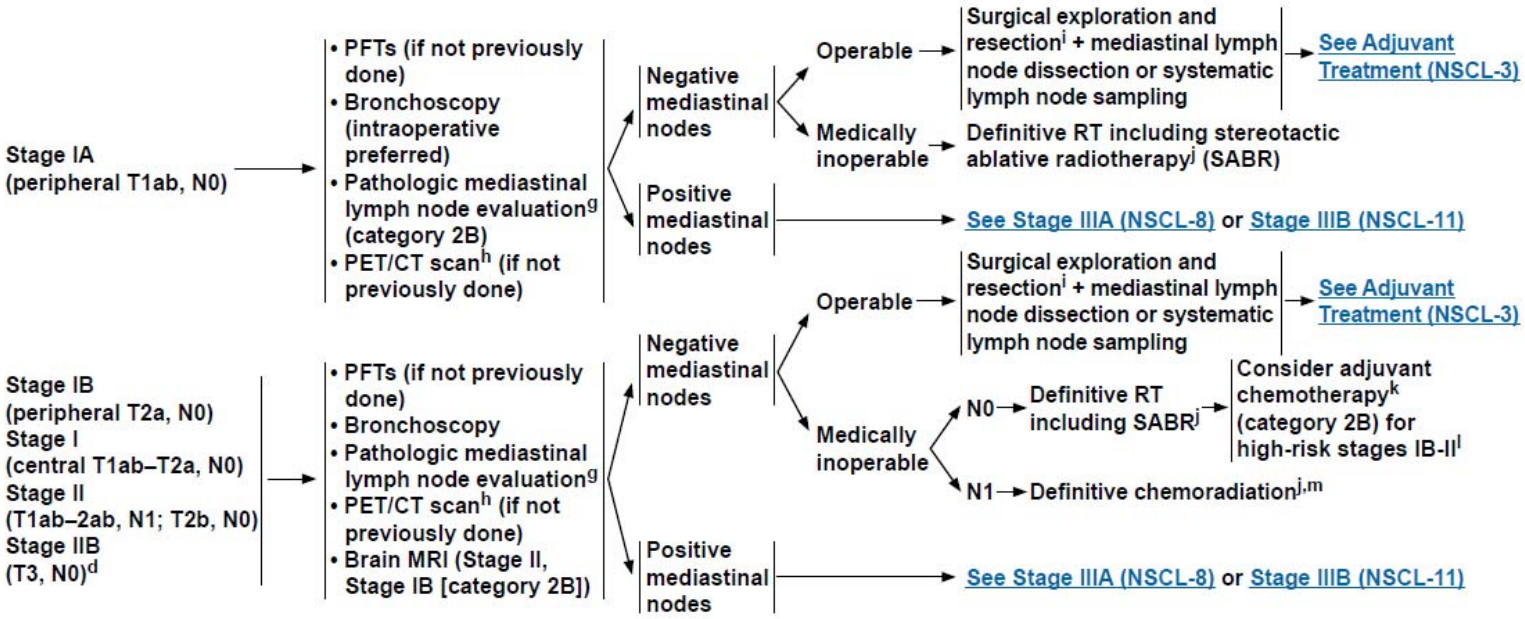
- The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.
  - Factors to be considered in choosing the optimal diagnostic step include:
    - ◊ Anticipated diagnostic yield (sensitivity)
    - ◊ Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (ie, true negative)
    - ◊ Adequate volume of tissue specimen for diagnosis and molecular testing
    - ◊ Invasiveness and risk of procedure
    - ◊ Efficiency of evaluation
      - – Access and timeliness of procedure
      - – Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (ie, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion).
    - ◊ Technologies and expertise available
  - Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and board-certified thoracic surgeons who devote a significant portion of their practice to thoracic oncology. Multidisciplinary evaluation may also benefit from involvement of a pulmonologist with experience in advanced bronchoscopic techniques for diagnosis, depending on local expertise.
  - The least invasive biopsy with the highest yield is preferred as the first diagnostic study.
    - ◊ Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.
    - ◊ Patients with peripheral (outer one-third) nodules should have navigational bronchoscopy, radial EBUS, or TTNA.
    - ◊ Patients with suspected nodal disease should be biopsied by EBUS, navigational bronchoscopy, or mediastinoscopy.
      - – Esophageal ultrasound (EUS)–guided biopsy provides additional access to station 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.
      - – TTNA and anterior mediastinotomy (ie, Chamberlain procedure) provide additional access to anterior mediastinal (station 5 and 6) lymph nodes if these are clinically suspicious.
    - ◊ Lung cancer patients with an associated pleural effusion should undergo thoracentesis and cytology. A negative cytology result on initial thoracentesis does not exclude pleural involvement. An additional thoracentesis and/or thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy.
    - ◊ Patients suspected of having a solitary site of metastatic disease should preferably have tissue confirmation of that site if feasible.
    - ◊ Patients suspected of having metastatic disease should have confirmation from one of the metastatic sites if feasible.
    - ◊ Patients who may have multiple sites of metastatic disease—based on a strong clinical suspicion—should have biopsy of the primary lung lesion or mediastinal lymph nodes if it is technically difficult or very risky to biopsy a metastatic site.

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

National Comprehensive Cancer Network®

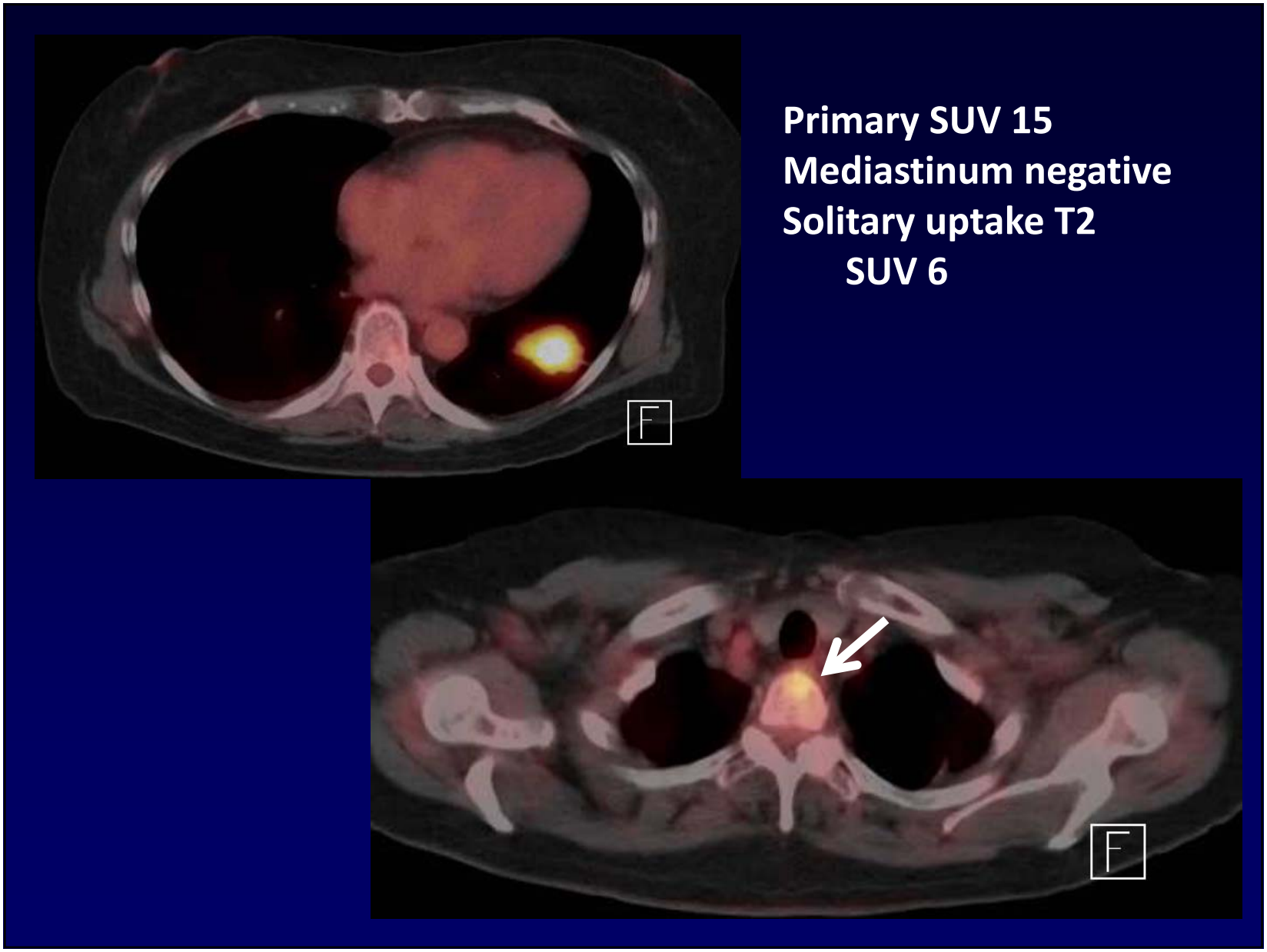
NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion



[d]T3, N0 related to size or satellite nodules.
[f]Testing is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.
[g]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[h]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[i]See Principles of Surgical Therapy (NSCL-B).
[j]See Principles of Radiation Therapy (NSCL-C).
[k]See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[l]Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.
[m]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

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



Lung Cancer Evaluation

The most appropriate next step in workup is:

a) **Lung biopsy**
b) **Vertebral body biopsy**
c) **Spine MRI**
d) **Brain MRI**

LUNG CANCER STAGING
Modalities

Non-invasive staging

- History and exam
- CXR +/- old x-rays
- Chest CT
- PET
- MRI
- Bone scan
- Brain MRI

Invasive staging

- Bronchoscopy
- Mediastinoscopy
- EBUS
- Needle biopsy
- EUS + biopsy
- Chamberlain
- Thoracoscopy
- Thoracotomy

LUNG CANCER STAGING

Modalities

T stage

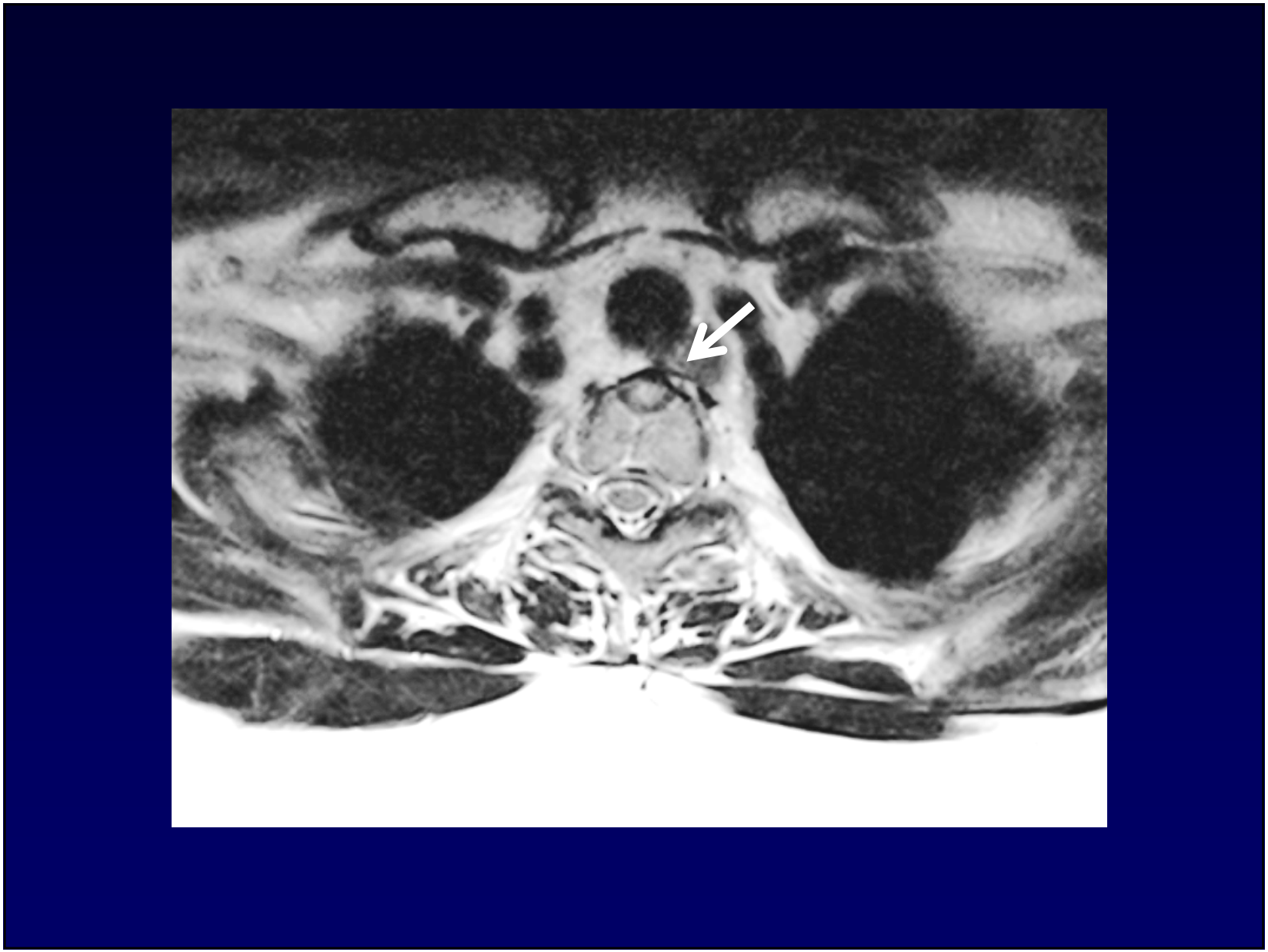
- History/physical
- Chest CT
- MRI
- Bronchoscopy
- Mediastinoscopy
- Chamberlain
- Thoracoscopy
- Thoracotomy

N stage

- Chest CT
- PET
- Needle biopsy
- EUS + biopsy
- Mediastinoscopy
- EBUS
- Chamberlain
- Thoracoscopy
- Thoracotomy

M stage

- Chest CT
- PET
- Brain MR
- Bone scan
- MRI
- Biopsy



Lung Cancer Evaluation

Radiologist states T2 vertebral body not accessible for percutaneous biopsy

CT guided needle biopsy of the lung
Adenocarcinoma – ICC suggestive of lung primary
Insufficient tissue for EGFR or ALK testing

Lung Cancer Evaluation

The next step in management is:

a) **Repeat lung biopsy for molecular testing**
b) **Vertebral biopsy**
c) **Mediastinoscopy**
d) **Initiate systemic therapy for stage IV disease**
e) **Perform lobectomy for stage I disease**

LUNG CANCER STAGING
Goals

- Avoid overstaging
  - Tragedy of palliative rather than curative intent therapy
- Avoid overstaging
- Avoid understaging
  - Non-therapeutic thoracotomy
  - Morbidity and mortality
  - Delay of appropriate treatment
- Provide prognosis to patient and family

Lung Cancer Evaluation

- Strong suspicion of oligometastatic disease
  - Yet solitary metastatic site unusual
- Stage I versus stage IV disease
- Performed surgical biopsy
  - Transcervical T2 vertebral body biopsy
  - Mediastinoscopy
  - Minimally invasive outpatient procedure
- Pathology
  - Mediastinal LNs negative
  - T2 vertebral body positive
  - Exon 19 deletion of EGFR gene

Lung Cancer Evaluation

Appropriate management for this patient is:

a) **Cisplatin based chemotherapy**
b) **Erlotinib**
c) **Lobectomy and vertebral body radiation**
d) **Radiation to both lung and vertebral body**

Lung Cancer Evaluation

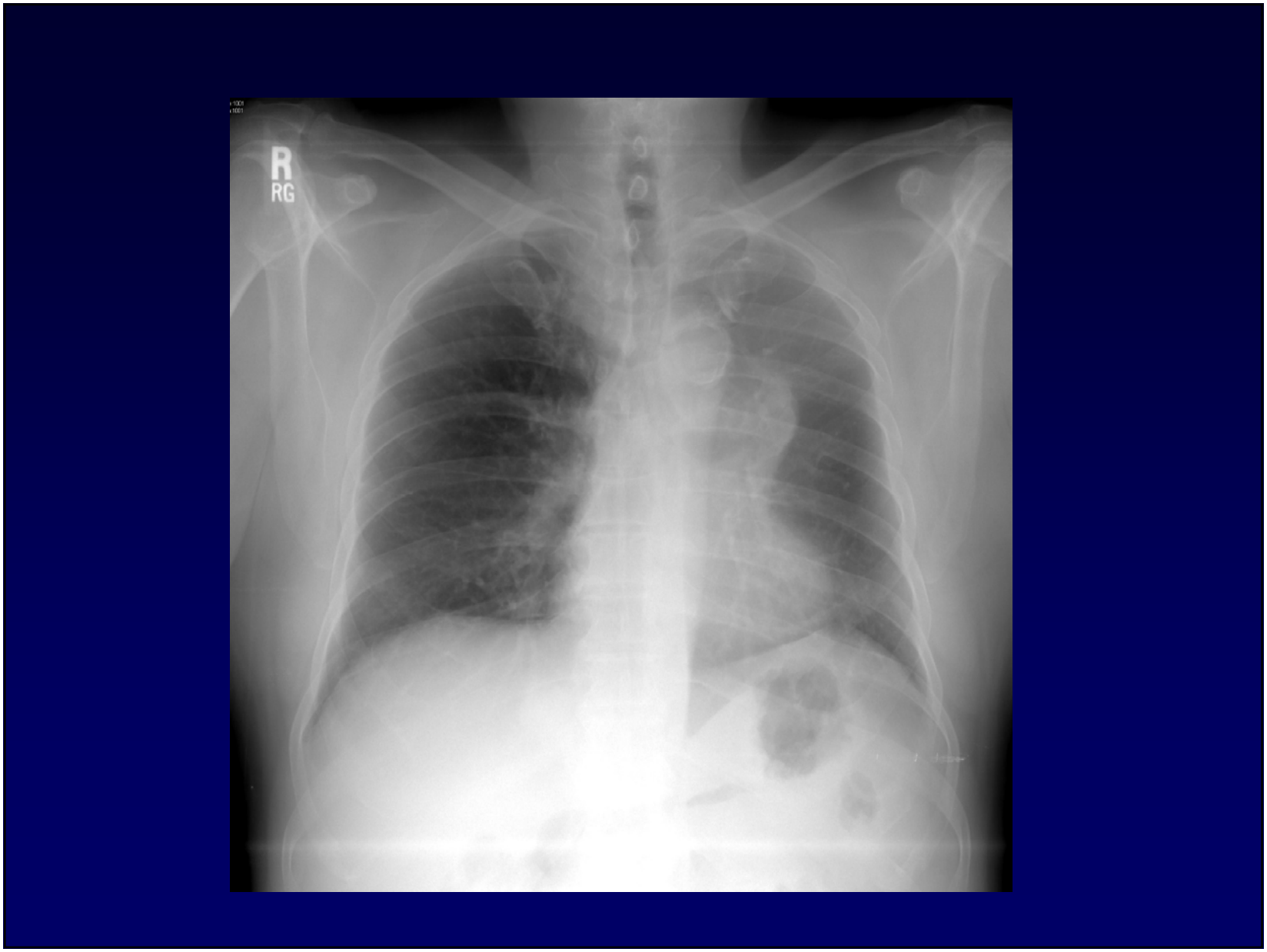
- 73 yo male from Guam with history of heavy smoking admitted with LUL pneumonia
  - Treated with antibiotics : resolution of symptoms
  - Recurrent symptoms 4 months later
  - Diagnosed with LUL mass

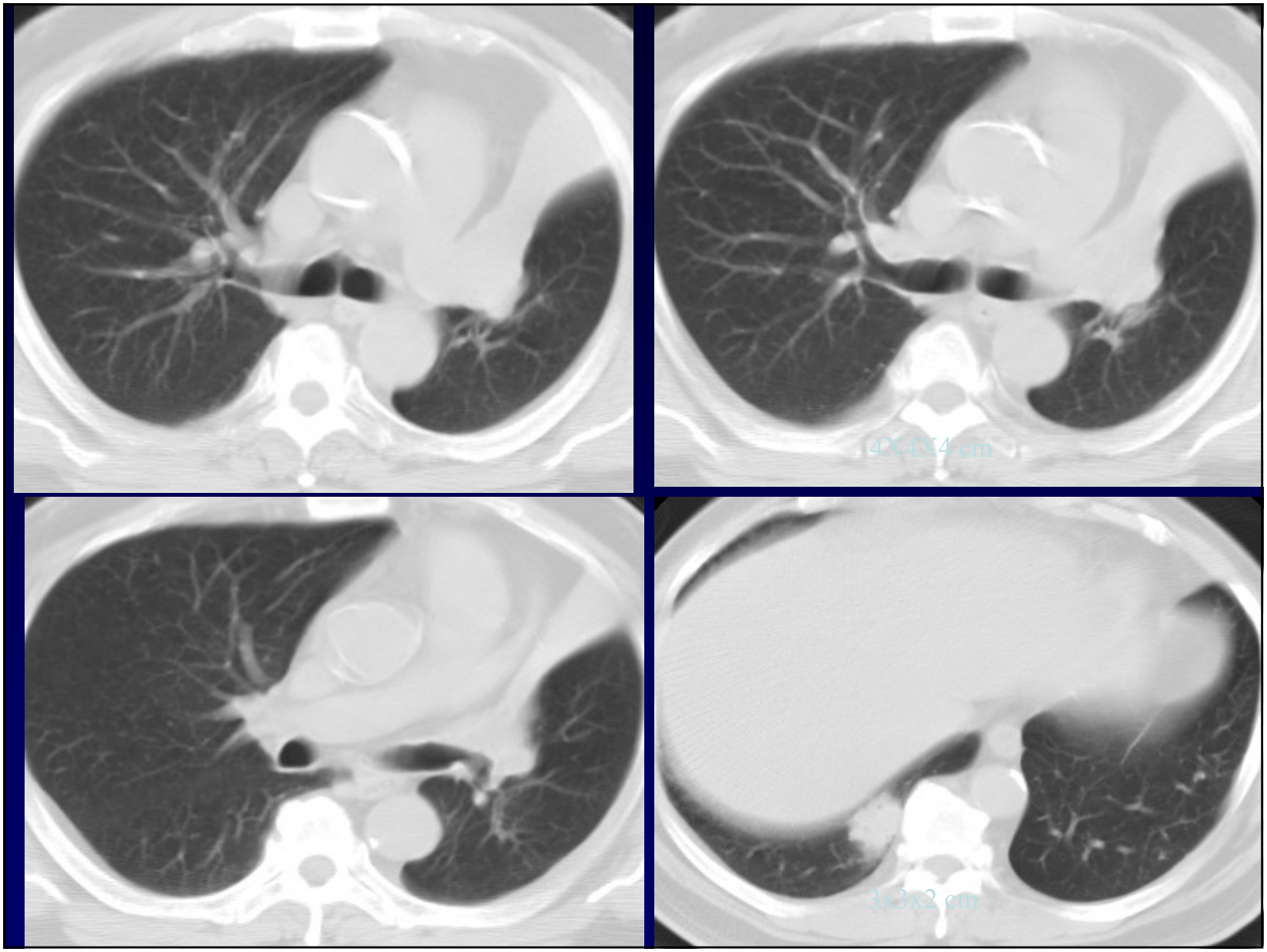
Lung Cancer Evaluation

- PMH
  - Coronary artery disease
  - Diabetes
  - Hypertension

Lung Cancer Evaluation

- Physical exam:
  - Good functional status
  - Afebrile
  - Room air
  - No adenopathy
  - Slight decrease BS in apex of Left lung
  - Exam otherwise normal





Lung Cancer Evaluation

- Both lesions were biopsied:
  - Moderate to poorly differentiated squamous cell CA
- PET positive in only the two lung lesions
- Brain MRI negative

Lung Cancer Evaluation

The appropriate next step in management is:

a) **Initiate systemic therapy for stage IV disease**
b) **Resect both lesions as bilateral stage I disease**
c) **Mediastinoscopy**
d) **Left hilar radiation and right stereotactic radiation**

Lung Cancer Evaluation

- In Guam, diagnosed as Stage IV NSCLC
- Recommended supportive care only

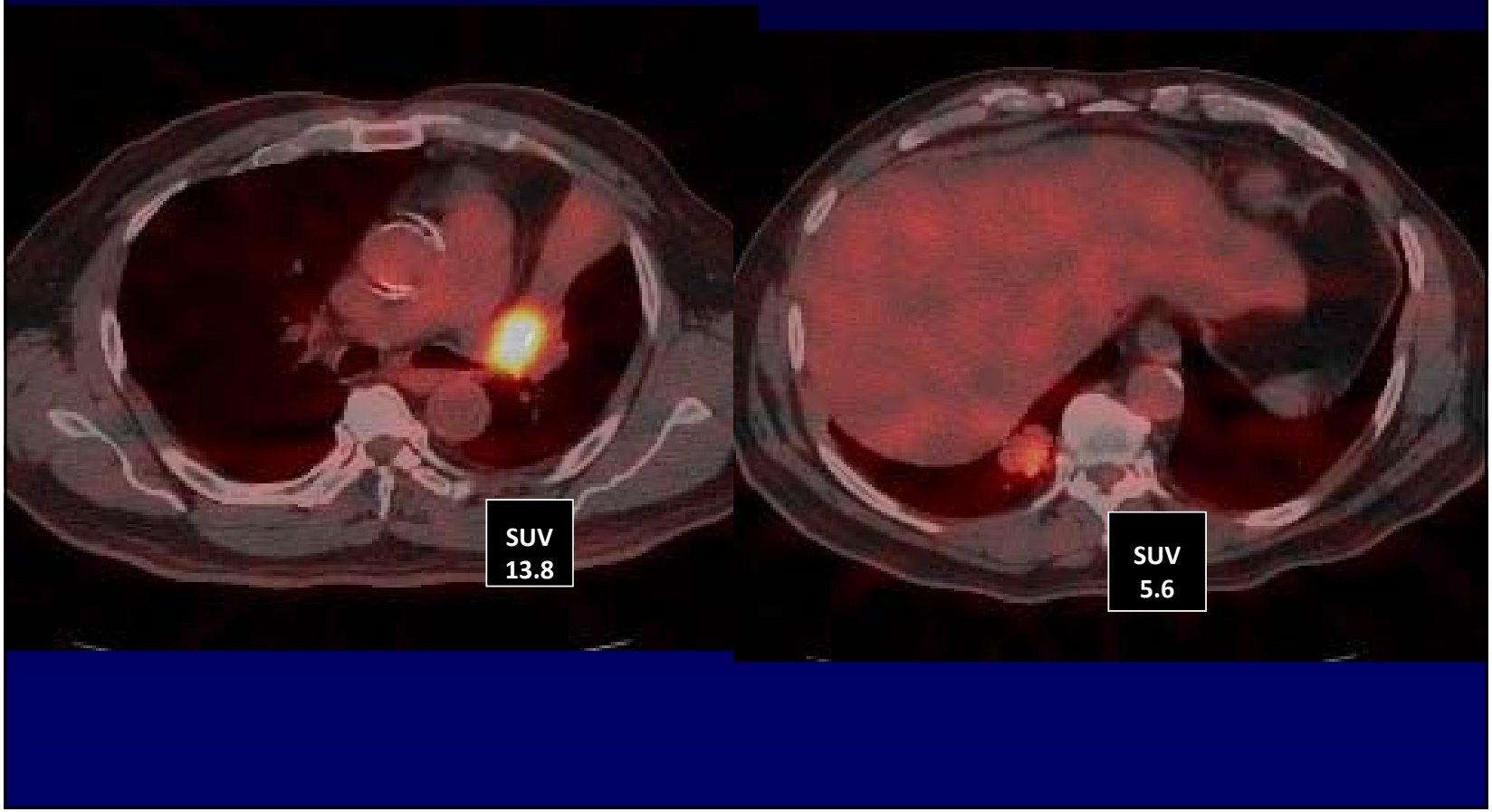
Lung Cancer Evaluation

- Referred to University of Washington
- How to differentiate stage IV lung cancer from simultaneous primary cancers?

Lung Cancer Evaluation

- Two nodules – the University of Washington approach
- Difficult to differentiate synchronous lung cancer from stage IV lung cancer from lung cancer with benign nodule – even with both being biopsied
- Surrogate for stage IV lung cancer
  - presence of mediastinal nodal disease
  - evidence of other metastatic disease
- Absence of nodal or distant metastases implies synchronous primary lung cancer
- Obtained PET scan and brain MRI
- Performed mediastinoscopy

Lung Cancer Evaluation



PET Scan and Brain MRI

- No evidence of hilar or mediastinal adenopathy or FDG uptake
- No evidence of distant metastasis
- Different SUV of right and left sided lesions
- Brain MRI negative
- Appears to imply separate synchronous cancers

Bilateral Lung Cancer

- Pulmonary function test
  - FEV1 : 1.94 (65% predicted)
  - DLCO 70% predicted
- Bronchoscopy
  - LMSB open until distal main stem
  - Endoluminal tumor involving the posterolateral aspect of LMSB, occluding the orifice of LUL
  - Encroaching upon the superior segment orifice

Bilateral Lung Cancer Procedure

- Mediastinoscopy (negative)
- R thoracoscopic wedge resection
  - LN sampling
- Left thoracotomy
  - LUL sleeve lobectomy and L superior segmentectomy, PA resection and reconstruction

Bilateral Lung Cancer

- Pathology
  - Well differentiated squamous cell CA
    - LUL: T2N0M0 (stage IB)
    - RLL: T2N0M0 (stage IB)

Bilateral Lung Cancer

- Tolerated the procedure well
- Discharged POD #7 with no complications

Bilateral Lung Cancer

- Adjuvant therapy?

Lung Cancer Evaluation

59 yo woman with cough, dyspnea

Admitted with pneumonia

Past smoker

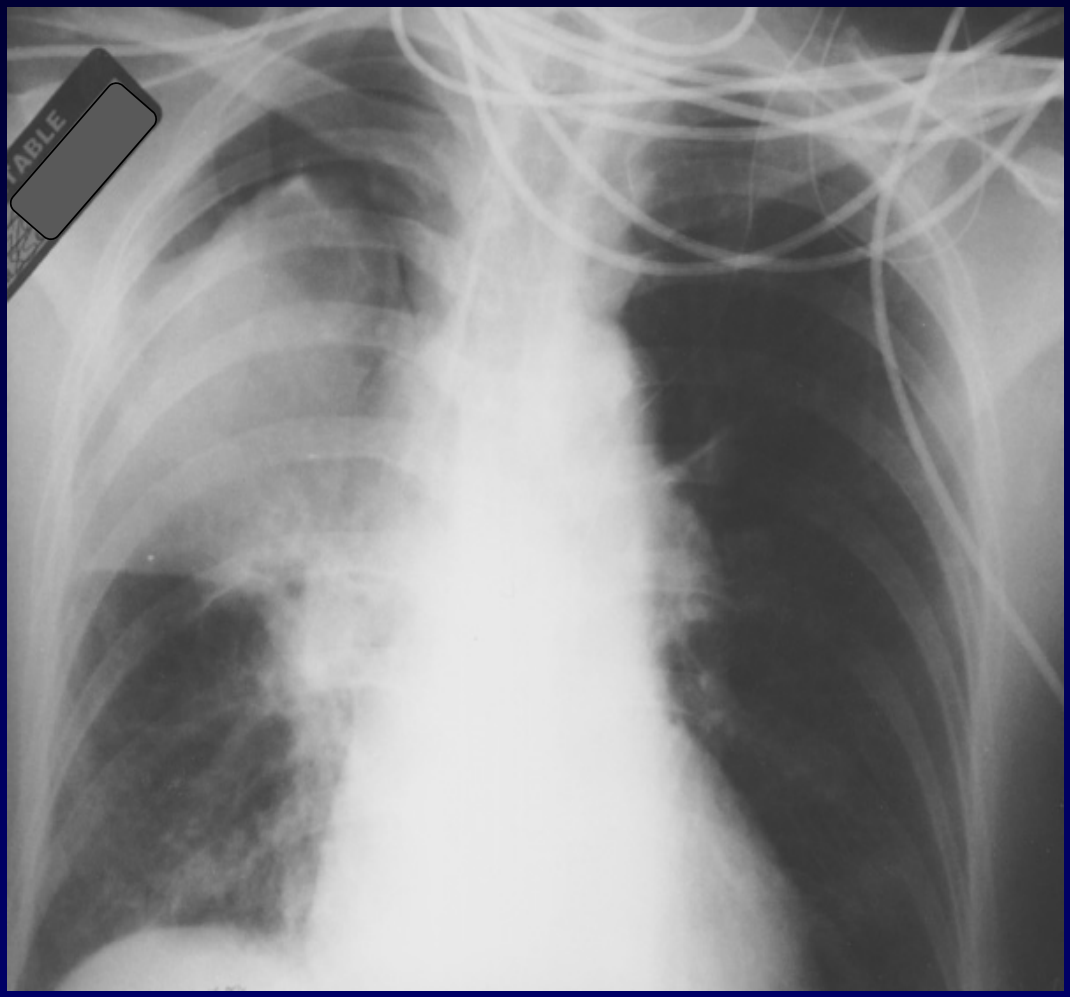
No significant medical or surgical history

T 102, P 115, BP 128/82

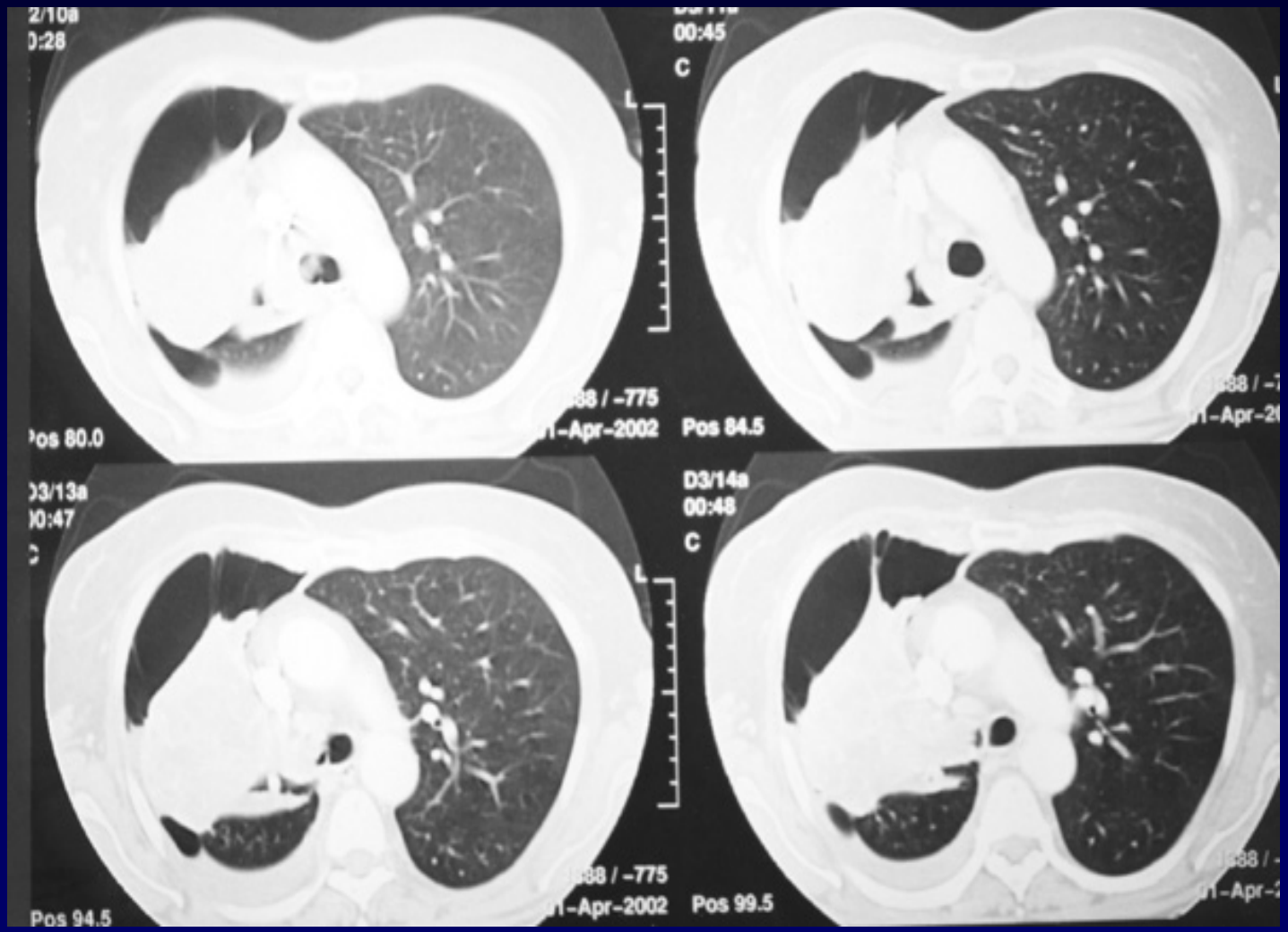
Dyspneic, diaphoretic, mild distress

No right side breath sounds

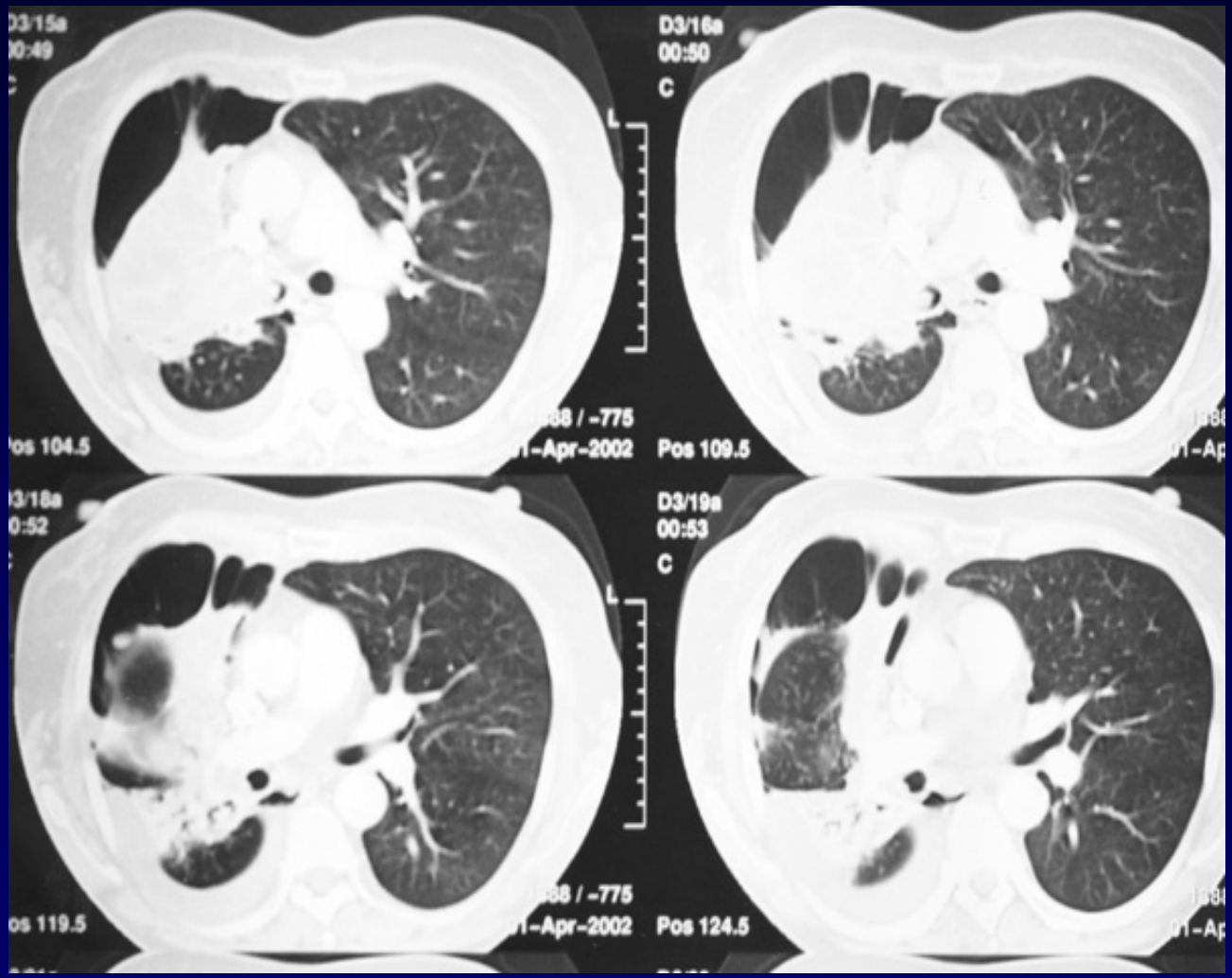
Lung Cancer Evaluation



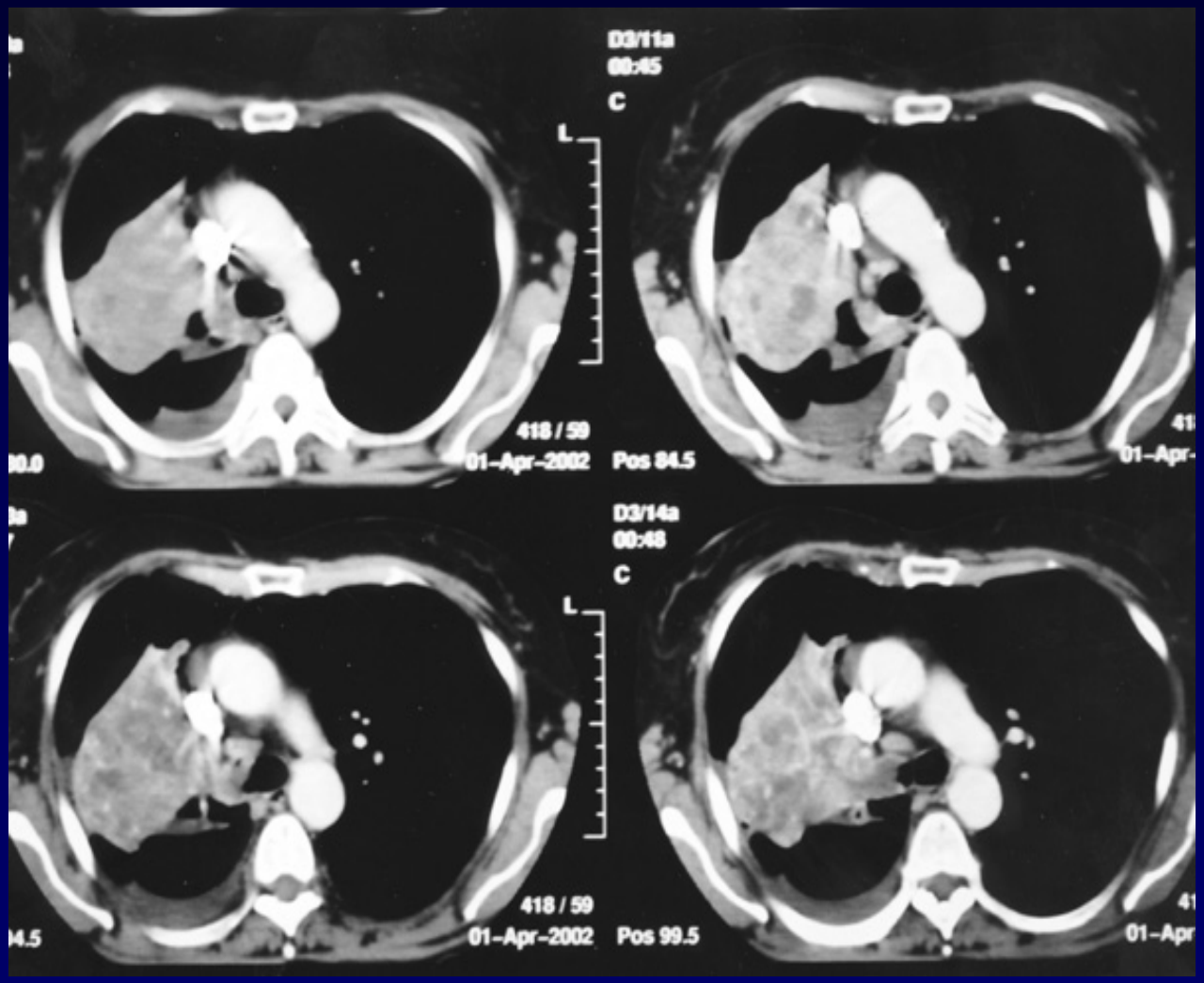
Lung Cancer Evaluation



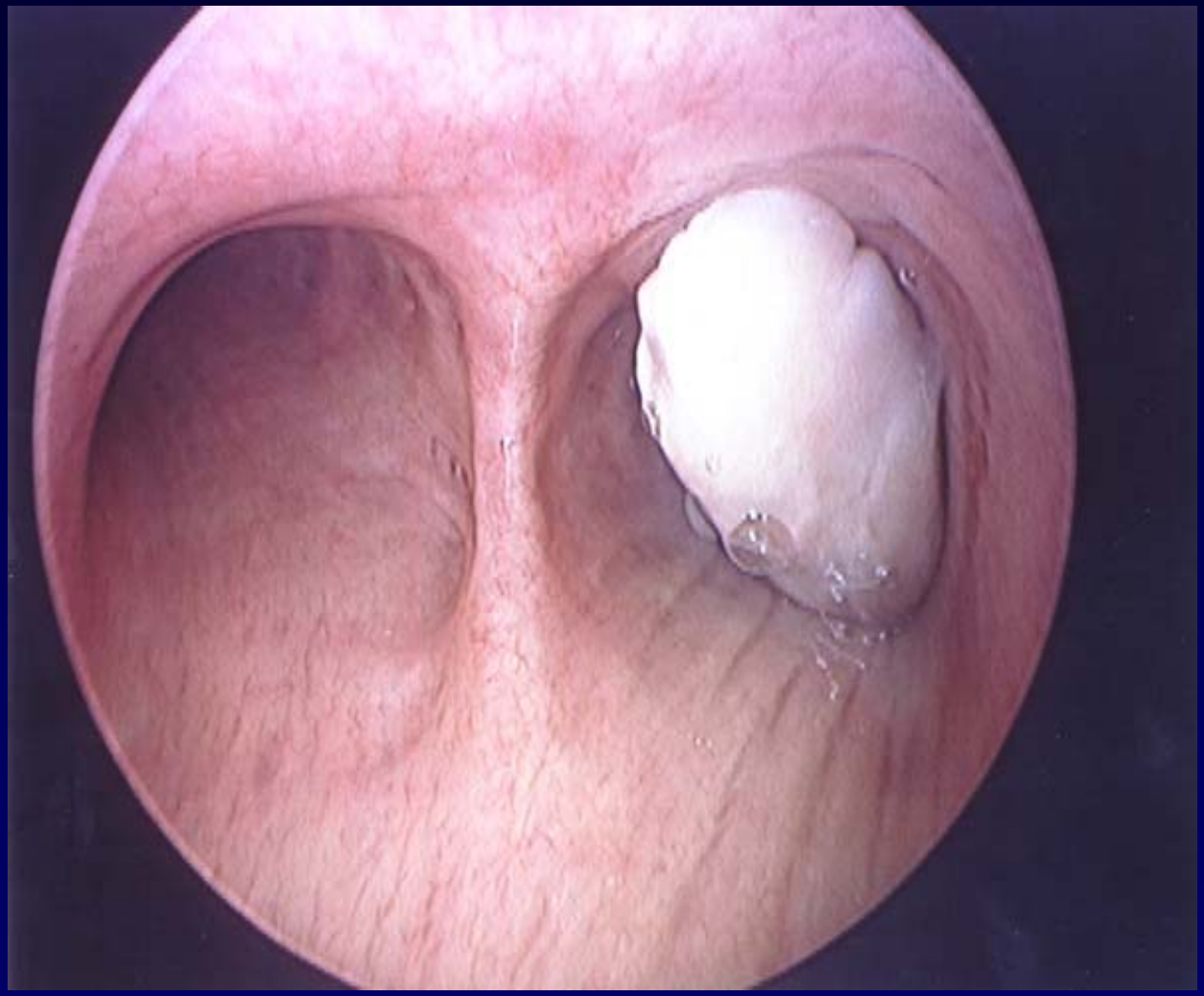
Lung Cancer Evaluation



Lung Cancer Evaluation



Lung Cancer Evaluation



Lung Cancer Evaluation

What is the apparent clinical stage?

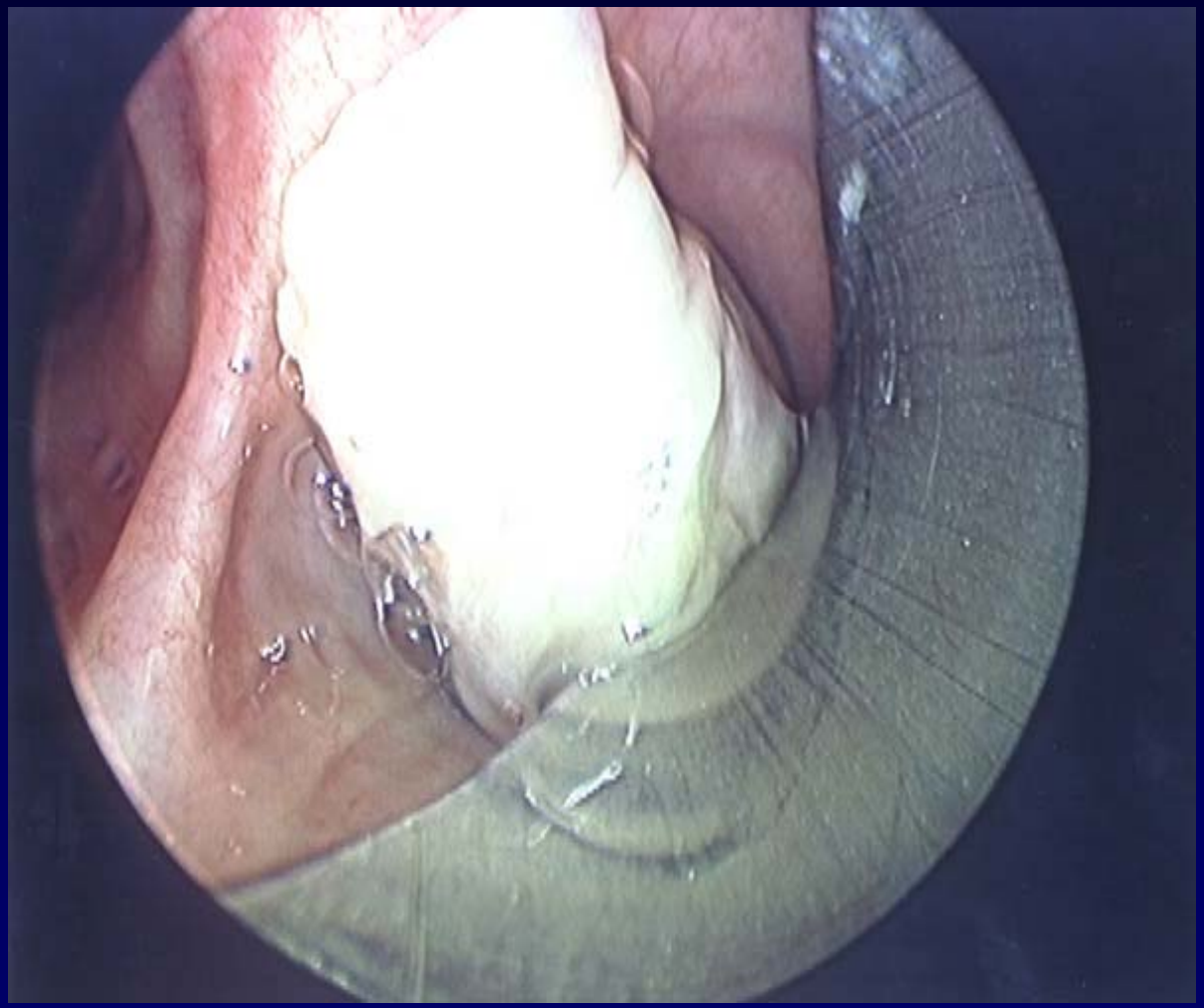
a) Stage IIA
b) Stage IIB
c) Stage IIIA
d) Stage IIIB
e) Stage IV

Lung Cancer Evaluation

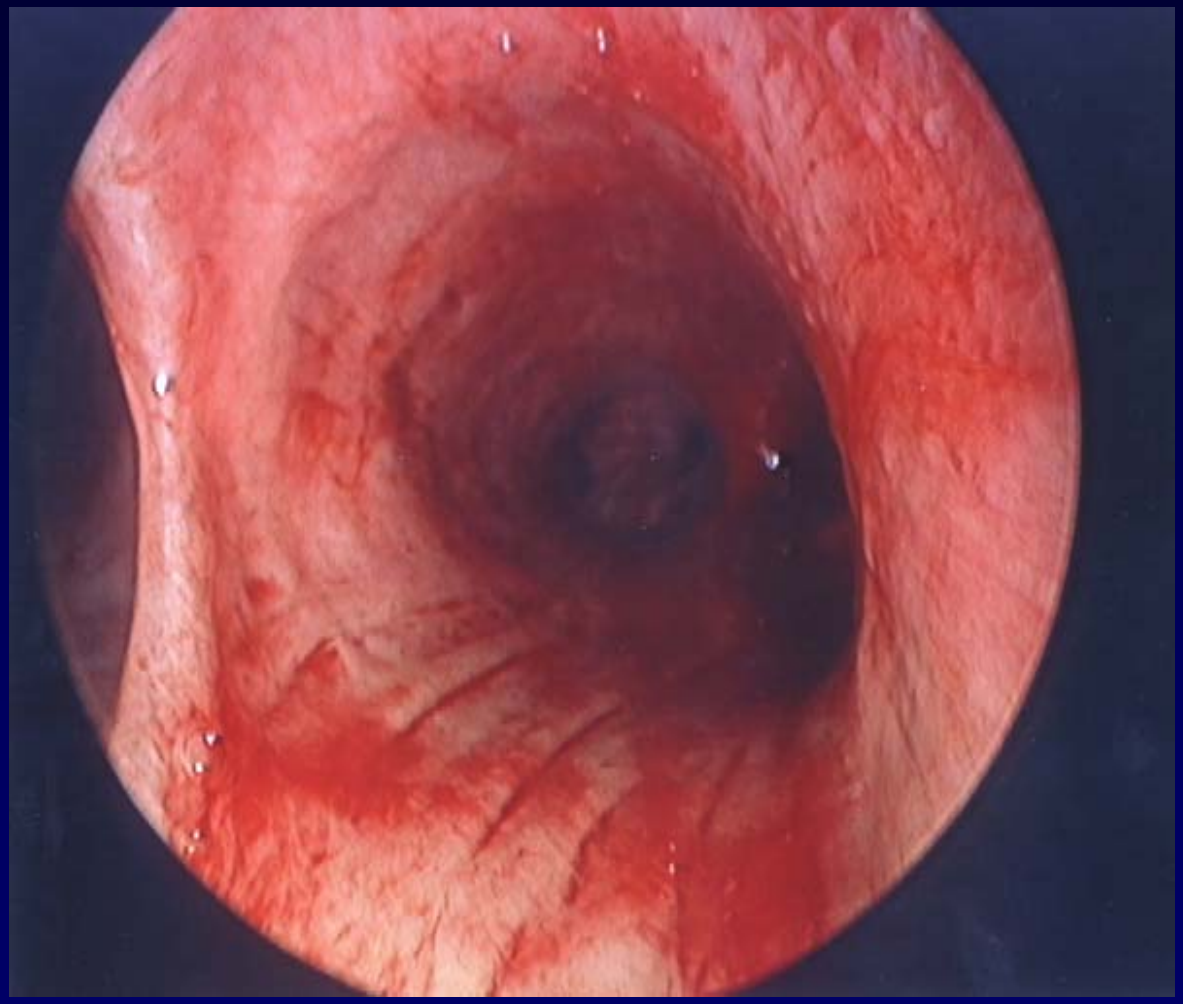
What is the next step in management?

a) Urgent radiation
b) Palliative pneumonectomy
c) Therapeutic bronchoscopy
d) Chemoradiation followed by possible surgery
e) Chemotherapy

Lung Cancer Evaluation



Lung Cancer Evaluation



Lung Cancer Evaluation

Which form of advanced disease would not preclude a curative resection?

a) T4N0 - malignant pleural effusion
b) T3N2 - ipsilateral mediastinal lymph nodes
c) T4N0 - tumor invasion of carina
d) T3N1M1 - isolated brain metastasis

Lung Cancer Evaluation

What is the most efficient staging work-up?

a) Thoracentesis, PET, mediastinoscopy
b) Brain MRI, bone scan, thoracoscopy
c) Mediastinoscopy, thoracoscopy, PET
d) PET, bone scan, brain MRI

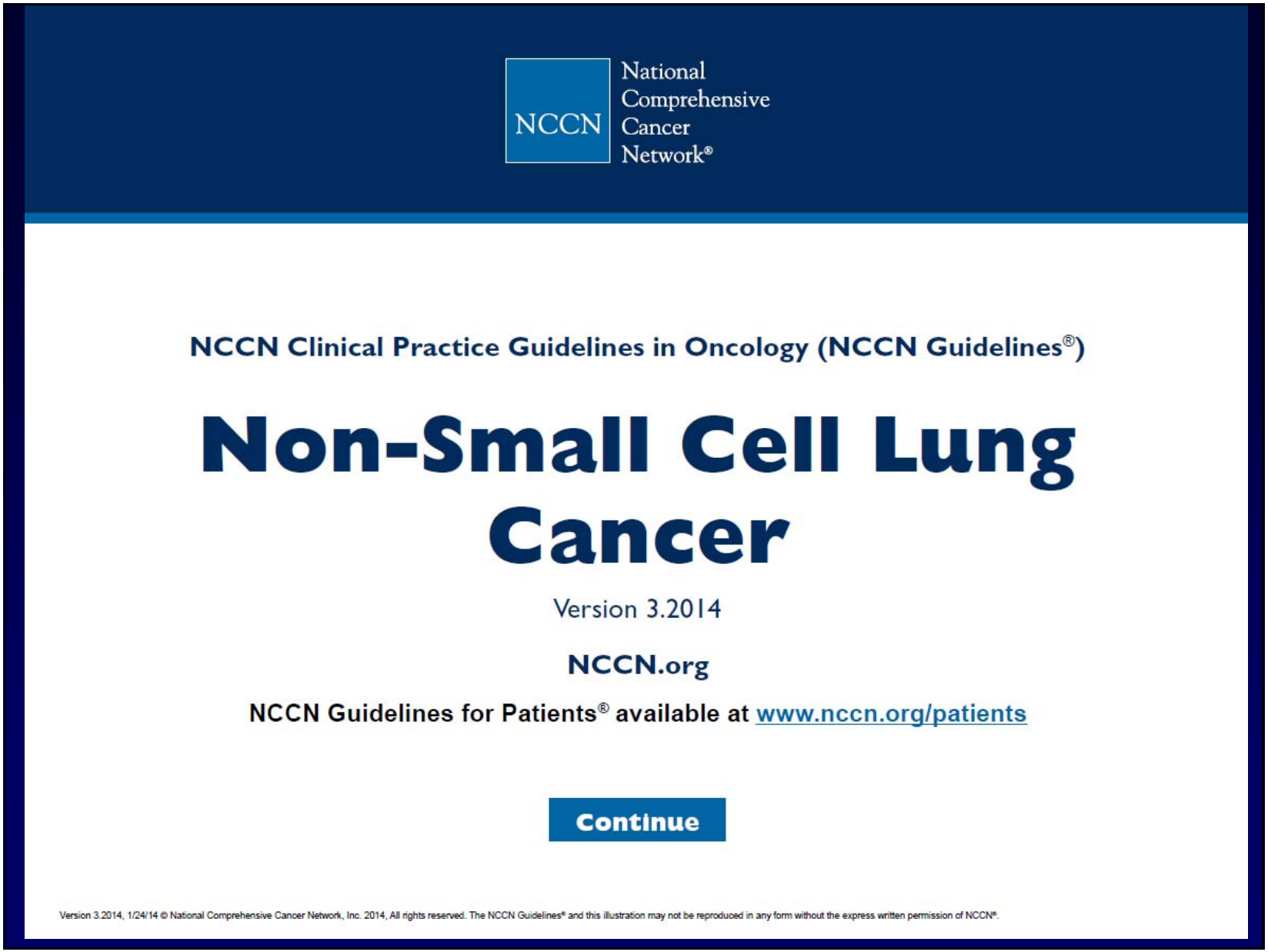
Lung Cancer Evaluation

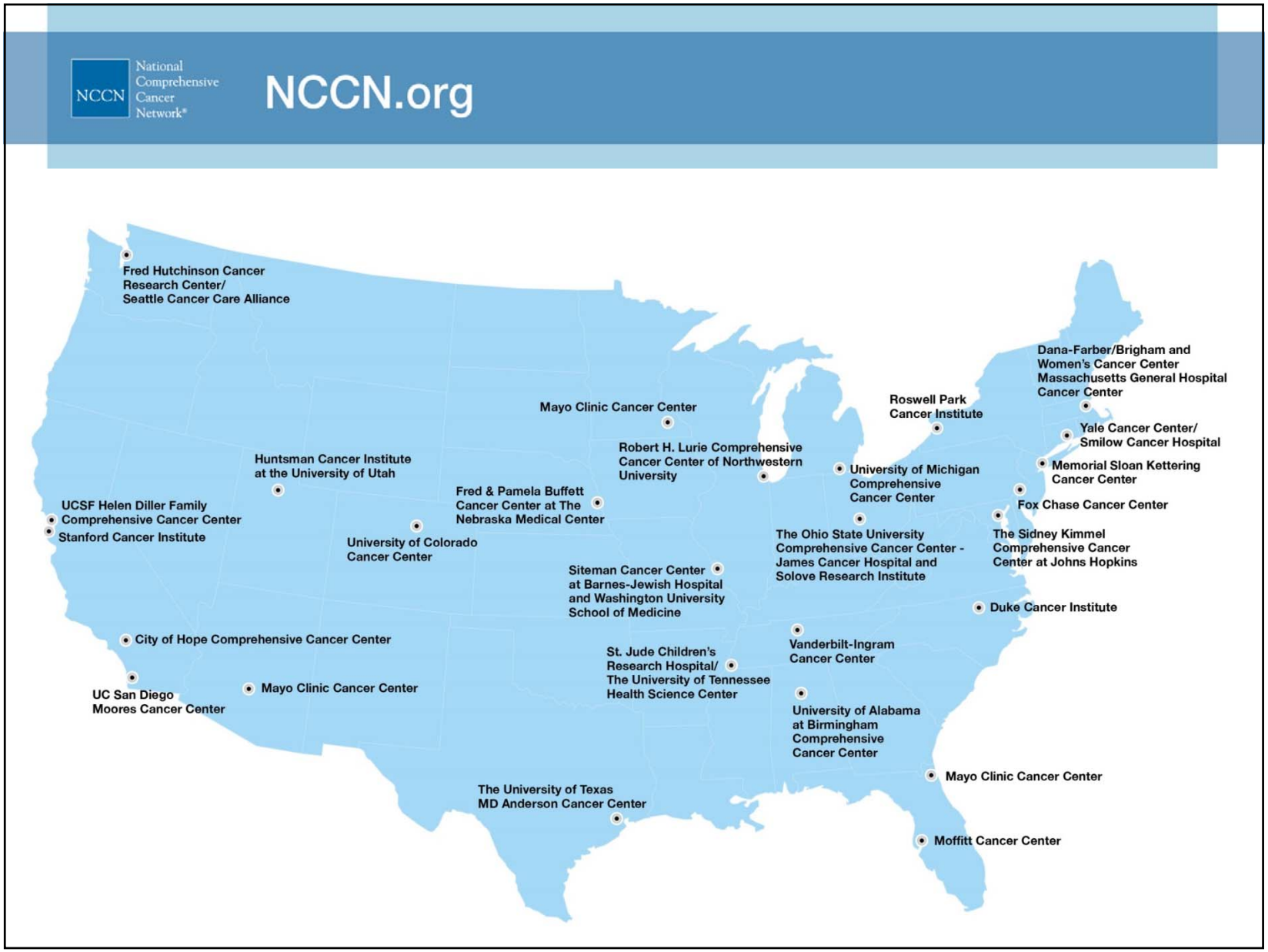
- Thoracentesis - negative cytology
- Bronchoscopy - core-out of obstructing tumor, uninvolved right mainstem and bronchus intermedius, resolution of obstructive pneumonia
- PET - primary tumor SUV 9.6, remaining lung, pleura and all lymph nodes inflammatory only
- Mediastinoscopy - negative N2/N3 lymph nodes

Lung Cancer Evaluation

What is the best treatment plan?

a) Definitive chemoradiotherapy
b) Induction chemoradiotherapy followed by surgery
c) Right upper lobectomy
d) Right upper sleeve lobectomy
e) Right pneumonectomy





NCCN Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer
Appropriate Selection of Therapy in NSCLC Using Biomarker Data

Presented live on April 1, 2014

by:

Gregory A. Otterson, MD
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research

A recording of this live webinar is available at http://education.nccn.org/node/49247 until June 17, 2015.

Intended Audience and Learning Objectives

Intended Audience:

This slide deck is designed to meet the educational needs of medical oncologists, radiation oncologists, surgical oncologists, pathologists, nurses, pharmacists, and other healthcare professionals who manage patients with non-small cell lung cancer.

Learning Objectives:

Following this section, participants should be able to:

- Describe the appropriate selection of therapies for patients with NSCLC using biomarker data

Progressive ALK Positive Adenocarcinoma

- 32 yo never smoker, presented in February 2009 with back pain
  - Progressive weight loss, LE weakness
  - Imaging revealed extensive bony and brain metastatic disease
  - Biopsy of supraclavicular node showed adenocarcinoma
    - TTF1, CK7 positive
  - Radiation to brain and lumbar spine
  - Queued up for platinum based chemo, but ALK testing performed - positive

J Thorac Oncol. 2013 Jan;8(1):e3-5.

ALK positive Adenocarcinoma

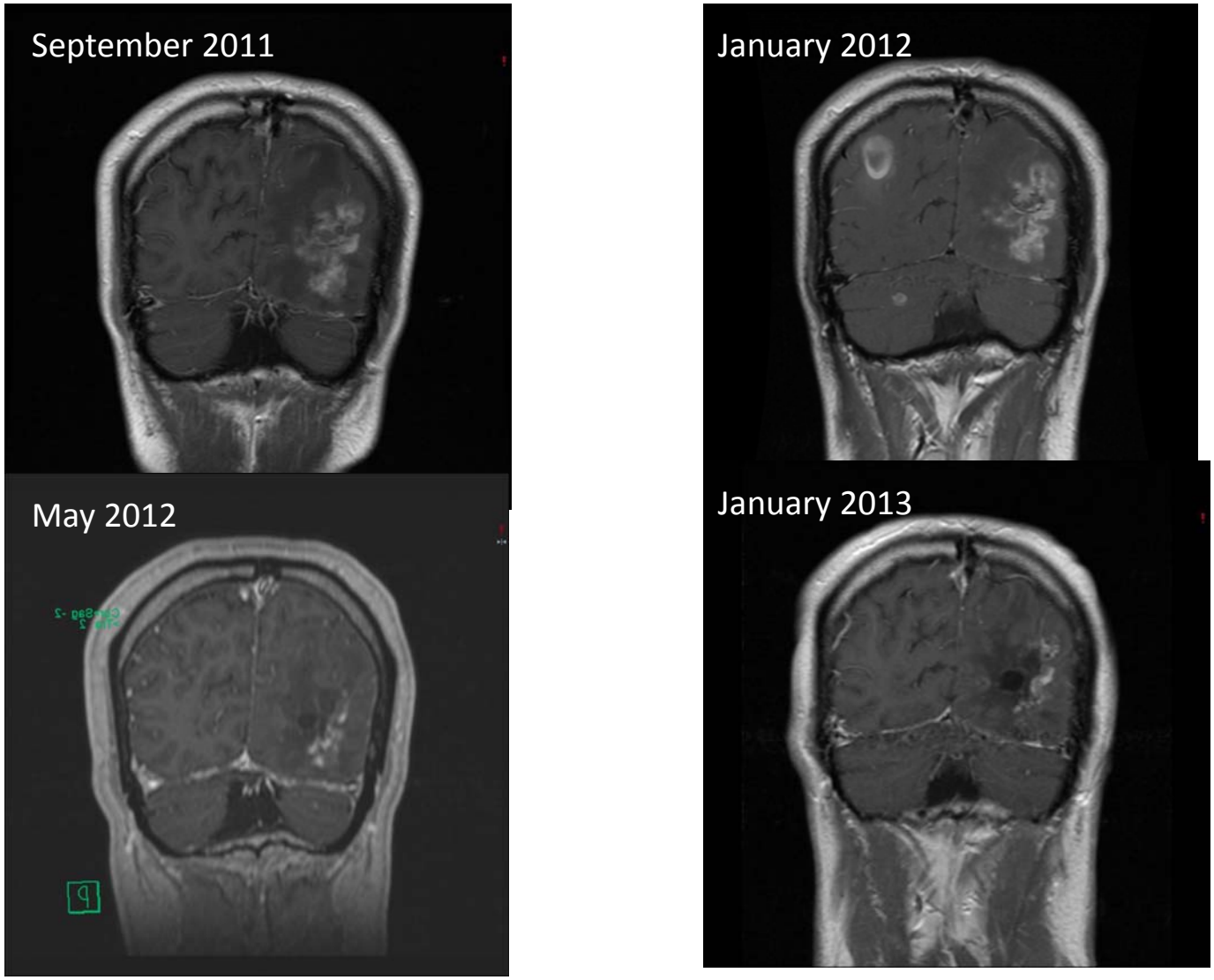
- Started on phase I study of crizotinib in March 2009
- Moved to Columbus in 2010, continued crizotinib
  - mild ophthalmologic effects, mild nausea
- July 2010, LLL lung lesion
  - Biopsy at DFCI showed MAC residual focus of cancer
- November 2010, isolated brain lesion
  - Gamma knife radiosurgery
- June 2011, growing right axillary lesion
  - Biopsy adenocarcinoma

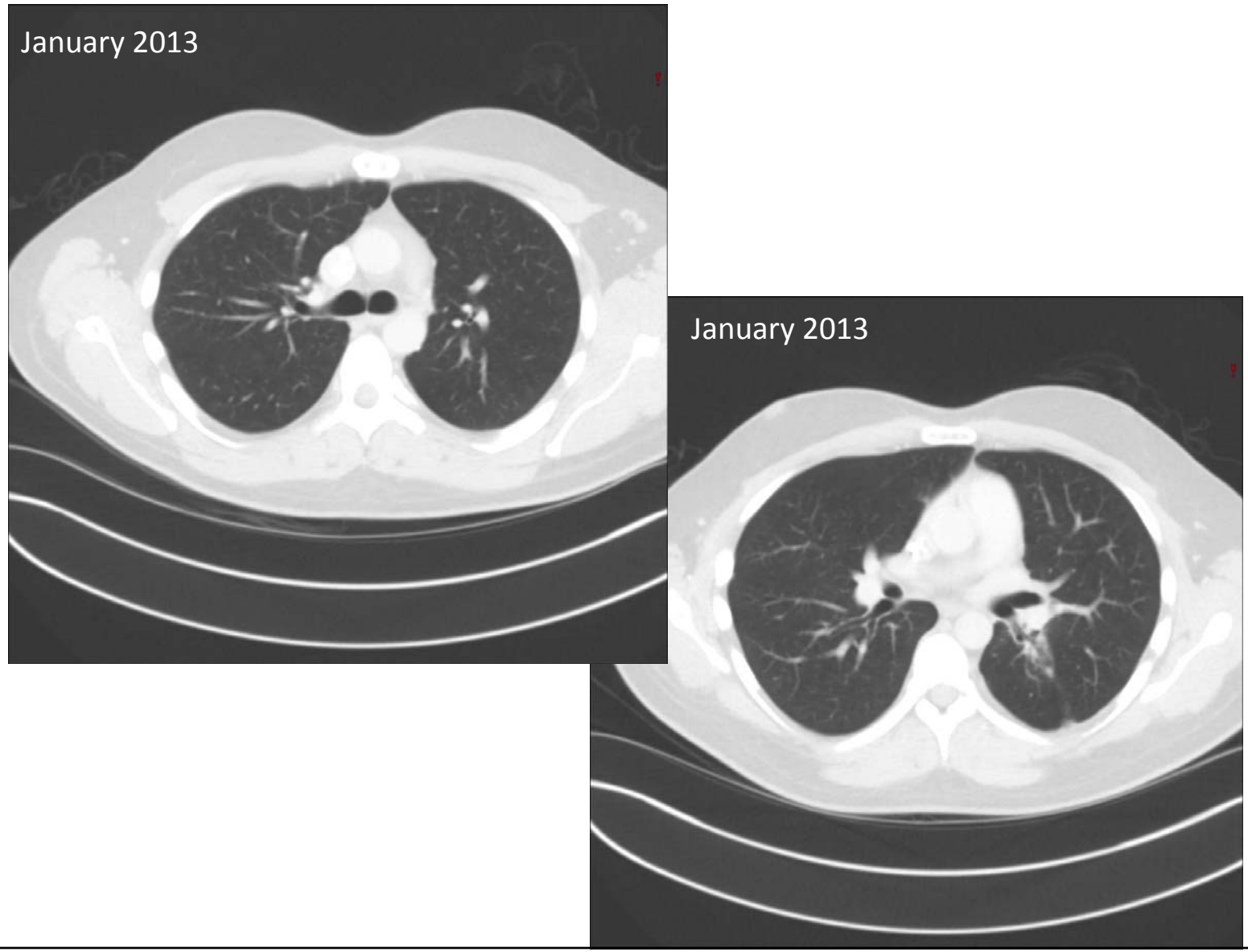
J Thorac Oncol. 2013 Jan;8(1):e3-5.

ALK positive Adenocarcinoma

- Received radiation to axilla
- January 2012, extensive brain progression with > 30 new lesions
- Initiated chemotherapy with pemetrexed, continued crizotinib
  - Pemetrexed 900 mg/m2
  - Crizotinib 600 mg once daily

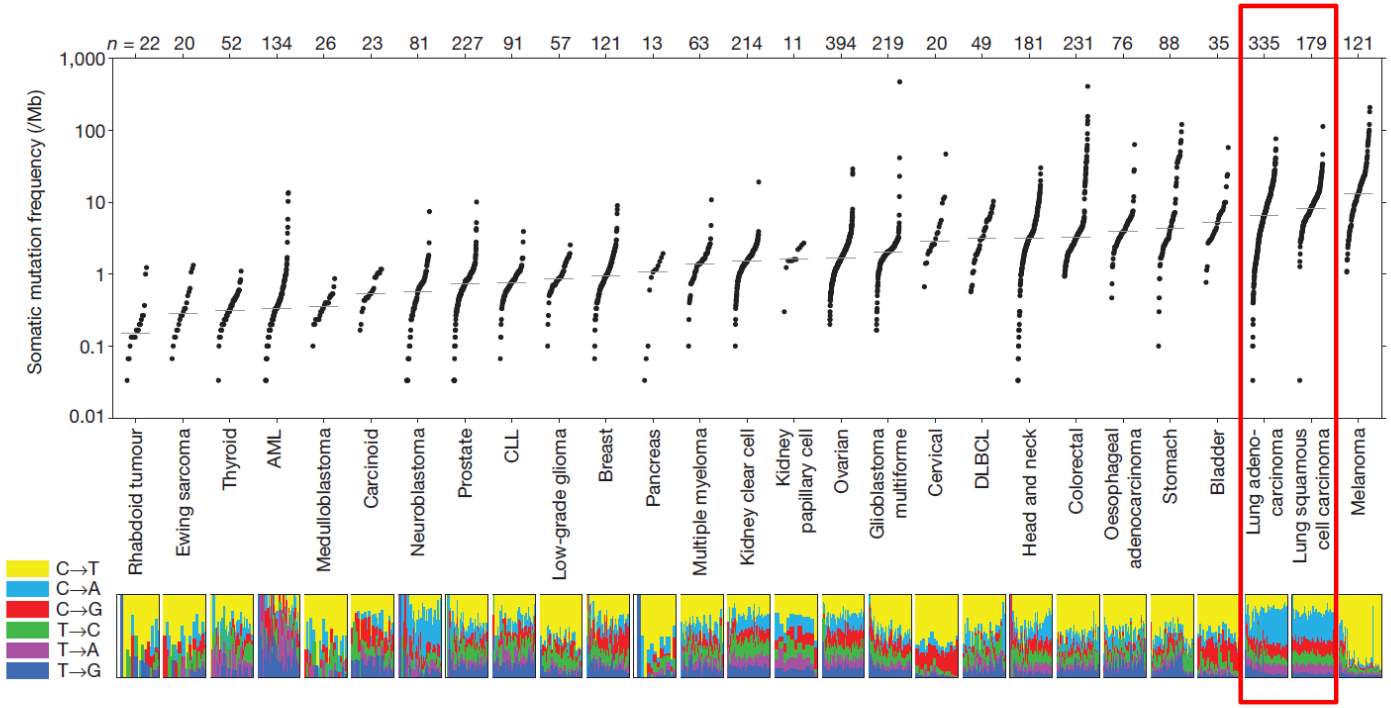
J Thorac Oncol. 2013 Jan;8(1):e3-5.



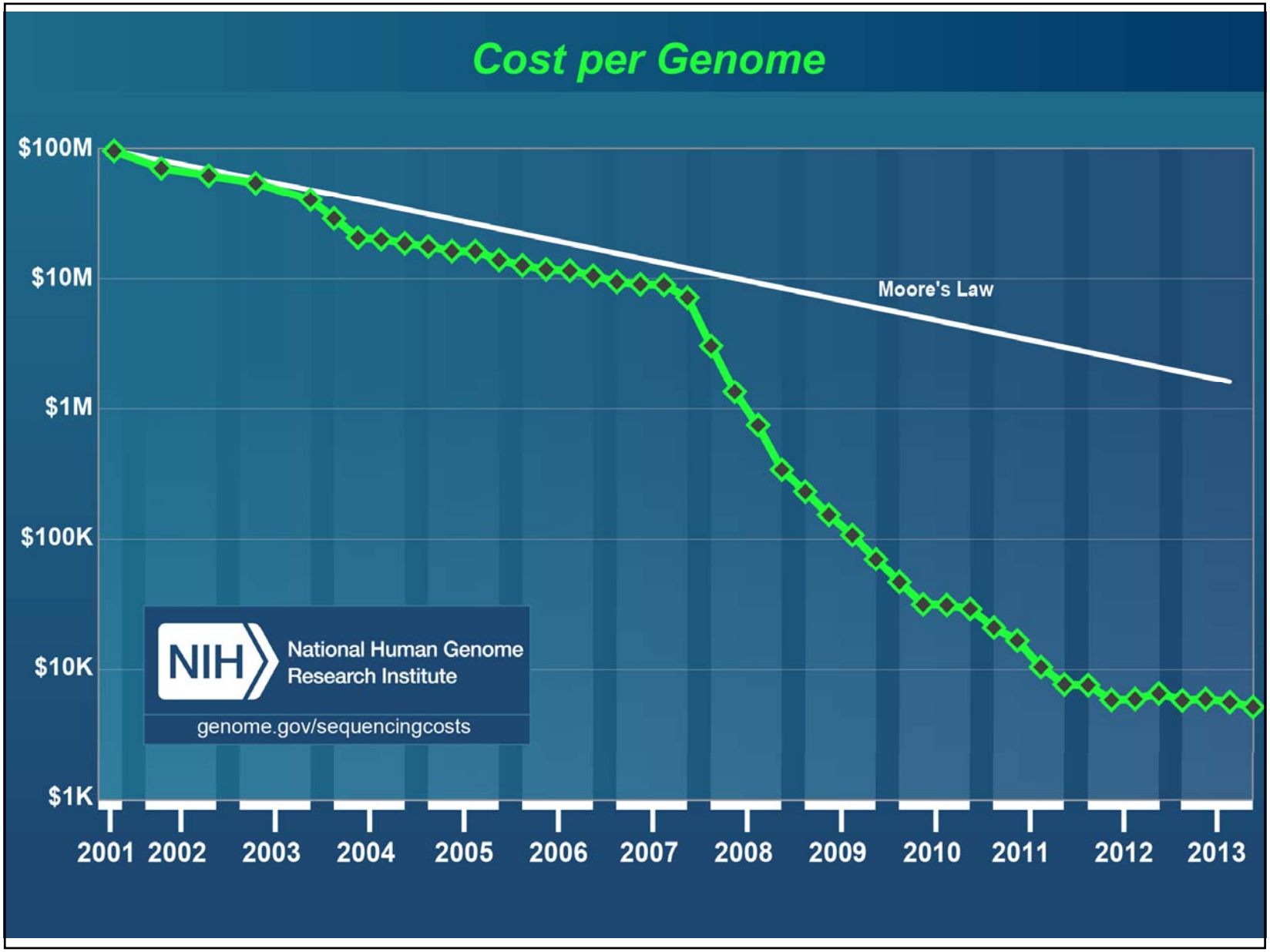


Lung Cancer is Complicated

Somatic Mutation Frequencies

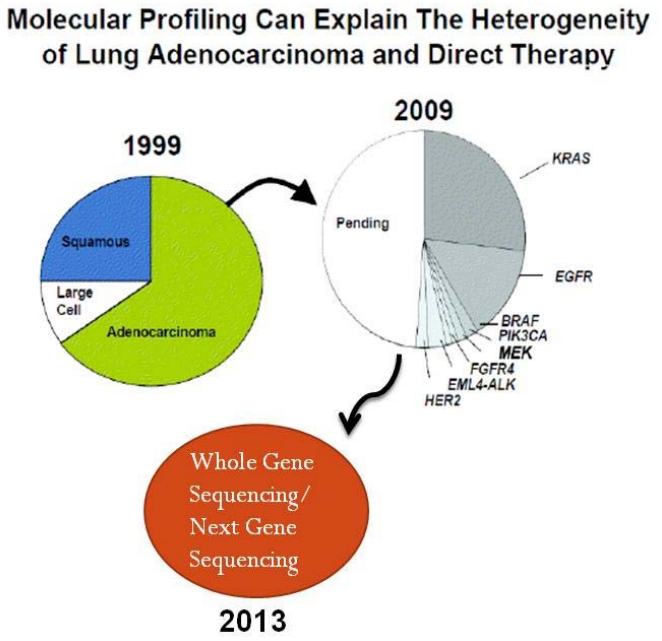


Nature 2013; 499:214-18

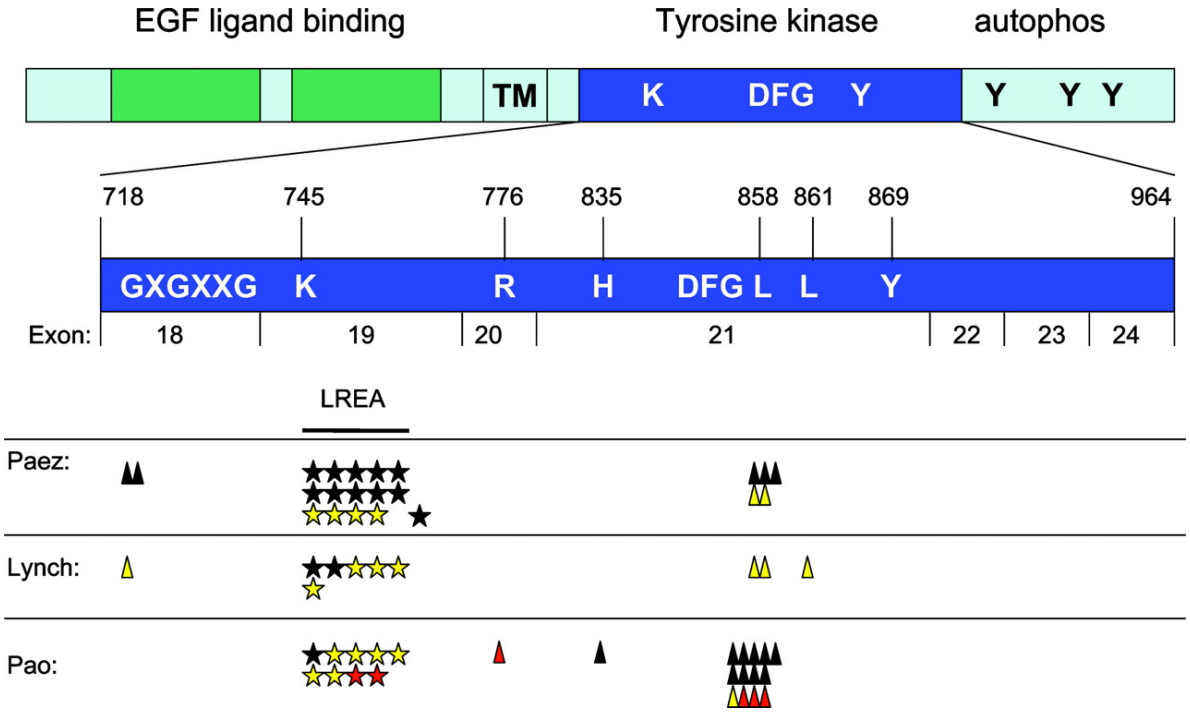


Lung Adenocarcinoma Features

- Lung cancer is the leading cause of death in United States
- There are multiple different histologic types of lung cancers
- Adenocarcinoma, the most common histotype of NSCLC, is diagnosed in 130,000 patients in the United States and one million persons worldwide each year
- It is also the type of lung cancer with the highest frequency of actionable oncogenic drivers



Summary of mutations in the TK domain of EGFR in NSCLCs



Pao, William et al. (2004) Proc. Natl. Acad. Sci. USA 101, 13306-13311

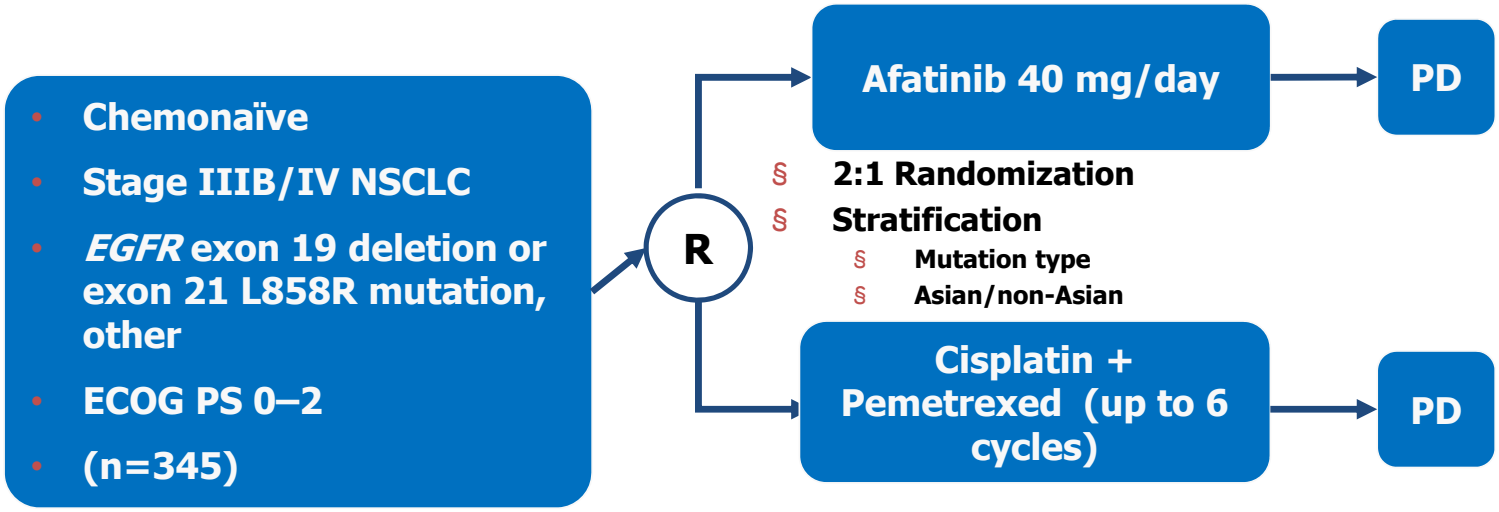
Patients With EGFR Mutations Are Particularly Responsive to EGFR Inhibitors

Prospective trials of lung cancer patients with EGFR mutations treated with EGFR tyrosine kinase inhibitors

Author	No. Screened	EGFR Mutations	Agent	RR, %	TTP, mo
Inoue et al[1]	99	16	Gefitinib	75	9.7
Paz-Ares et al[2]	1047	127	Erlotinib	82	13.3
Okamoto et al[3]	118	32	Gefitinib	75	ND
Sutani et al[4]	100	38	Gefitinib	78	9.4
Morikawa et al[5]	123	46	Gefitinib	62	9.7
Sequist et al[6]	98	31	Gefitinib	55	11.4

1. Inoue A et al. *J Clin Oncol.* 2006;24:3340-3346. 2. Paz-Ares L et al. *J Clin Oncol.* 2006;24(suppl). Abst. #7020. 3. Okamoto I et al. *J Clin Oncol.* 2006;24(suppl). Abst. #7073. 4. Sutani A et al. *J Clin Oncol.* 2006;24(suppl). Abst. #7076. 5. Morikawa N et al. *J Clin Oncol.* 2006;24(suppl). Abst. #7077. 6. Sequist LV et al. *J Clin Oncol.* 2008;26:2442-2449.

LUX-Lung 3 Study Design



Primary endpoint

- Progression-free survival (PFS) by independent review

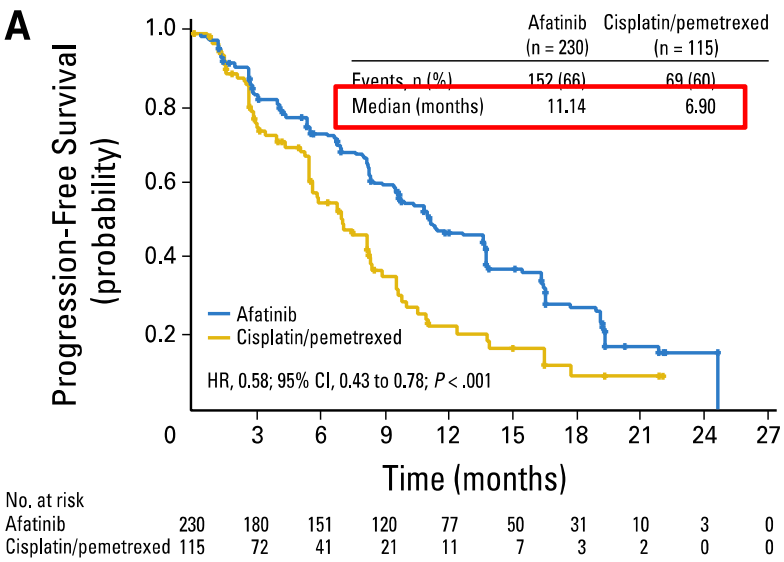
Secondary endpoints

- Objective response rate
- Overall survival (OS)
- AEs
- PROs

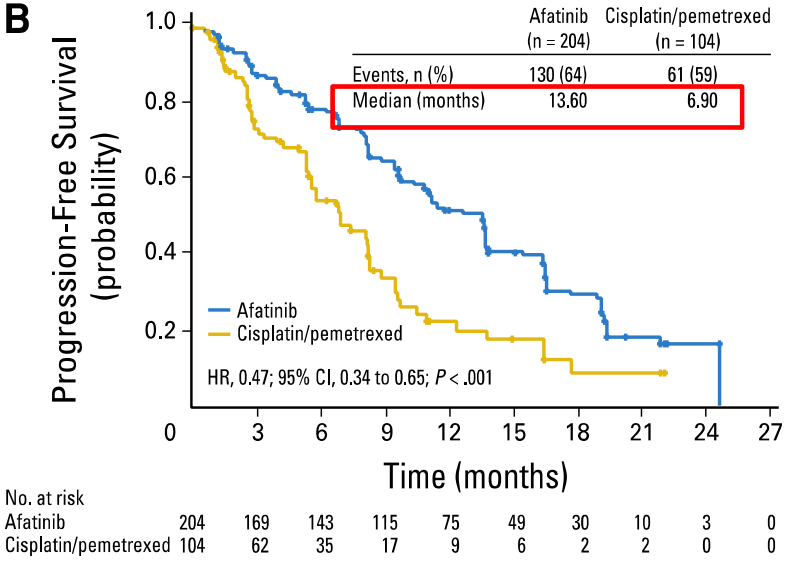
JCO 2013; 31:3327-34

PFS

ITT population (345)



Canonical Mutations (308)



More diarrhea, rash, paronychia in Afatinib
More fatigue and Heme toxicity with chemo
? Toxicity Afatinib > Erlotinib

JCO 2013; 31:3327-34

EGFRi vs Chemo

- Six + phase III first line studies
- In mutation positive patients (exon 19 deletion, L858R)
  - Superior response
  - Superior PFS (as initial treatment)
  - Probably equivalent OS
  - Improved QoL

1) IPASS: NEJM 2009; 361:947-57, 2) WJTOG 3405: Lancet Oncol 2010; 11:121-28, 3) OPTIMAL: Lancet Oncol 2011; 12:735-42, 4) EURTAC: Lancet Oncol 2012; 13: 239-46, 5) NEJSG: NEJM 2010; 362:2380-88, 6) LUX-Lung 3: JCO 2013; 31:3327-34

Subsequent Treatment

Study (n= mutation pts)	TKI/Chemo	2nd line after TKI	2nd line after chemo
IPASS* (n=261 EGFRmt)	Gefitinib / PC	39% to PC 10% other	40% EGFR TKI 14% other
NEJSG^ (Maemondo n=230)	Gefitinib / PC	68% PC 21% other	95% gefitinib
EURTAC # (n=174)	Erlotinib / Cis or Carbo + Gem or Docetaxel	37% cis/carbo 22% EGFR TKI	76% erlotinib

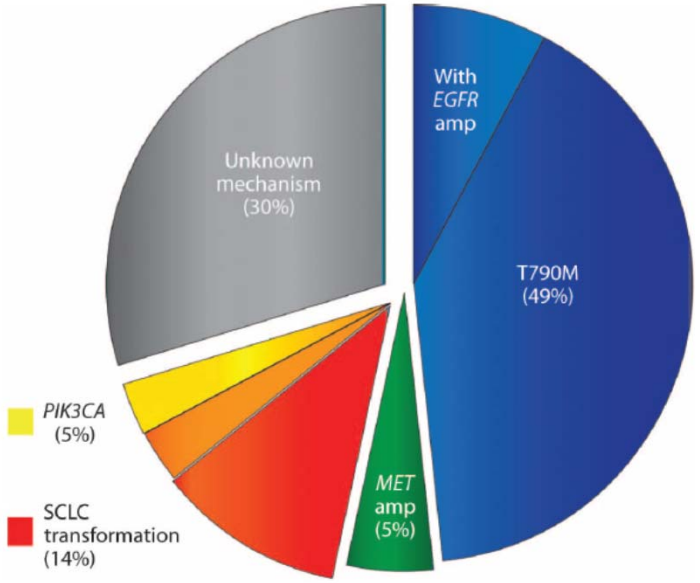
*IPASS: NEJM 2009; 361:947-57,
^NEJSG: NEJM 2010; 362:2380-88
#EURTAC: Lancet Oncol 2012; 13: 239-46,

RESEARCH ARTICLE

CANCER

Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors

- 37 pts rebiopsied
- 49% with T790M
  - ? Treat with irreversible EGFR TKI
- 5% with MET amp (how many with MET IHC?)
  - ? Treat with MET inhibitor
- 14% with SCLC transformation!



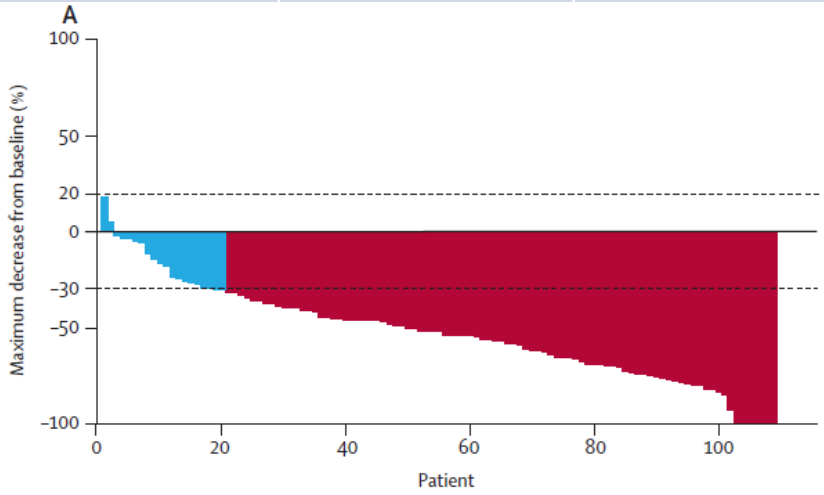
ScienceTranslationalMedicine 2011;75:1

Subsequent Treatment: Novel TKI

- Two agents furthest along
  - Afatinib (BIBW2992) – approved in August 2013
  - Dacomitinib (PF-00299804)
- In vitro promise
  - Irreversible binding to EGFR
  - Pan-HER inhibitor (HER 1-4)
  - More potent against non-canonical sensitivity mutants

Phase II Testing TKIs

Study	ORR (%)	PFS (mos)	OS (mos)	Toxicity (Gr 3 / 4 %)
Afatinib (EGFRmt) 50 mg (n=99) 40 mg (n=30)	ITT: 61% 50 mg: 62% 40 mg: 60%	ITT: 10.1 1st line: 12.0 2nd line: 8.0	ITT: 24.8 1st line: NA 2nd line: 23.3	Diarrhea 50 mg: 22% 40 mg: 7% Rash 50mg: 28% 40 mg: 7%



Lancet Oncol 2012; 13:539-548

Phase II Testing TKIs

Dacomitinib vs. Erlotinib in unselected pts

	ORR (%)	PFS (mos)	OS (mos)	Gr 3 / 4 tox (%)
Dacomitinib (n=94, 19 EGFR mt)	17	2.86	9.53	Diarrhea: 11.8 Rash: 10.8
Erlotinib (n=94, 11 EGFR mt)	5.3	1.91	7.44	Diarrhea: 4.3 Rash: 6.4

JCO 2012; 30:3337- 3314

Phase III Novel TKI testing

- Multiple trials
  - Afatinib following Erlotinib/Gefitinib progression failed to meet OS benefit (improvement in PFS)
    - LUX-LUNG 1
  - Afatinib vs. chemo in EGFR mutant first line
    - LUX-LUNG 3 and 6 (vs. Pem/Cis or Gem/Cis)
  - Dacomitinib phase III in unselected NSCLC second line

Subsequent Treatment: METi

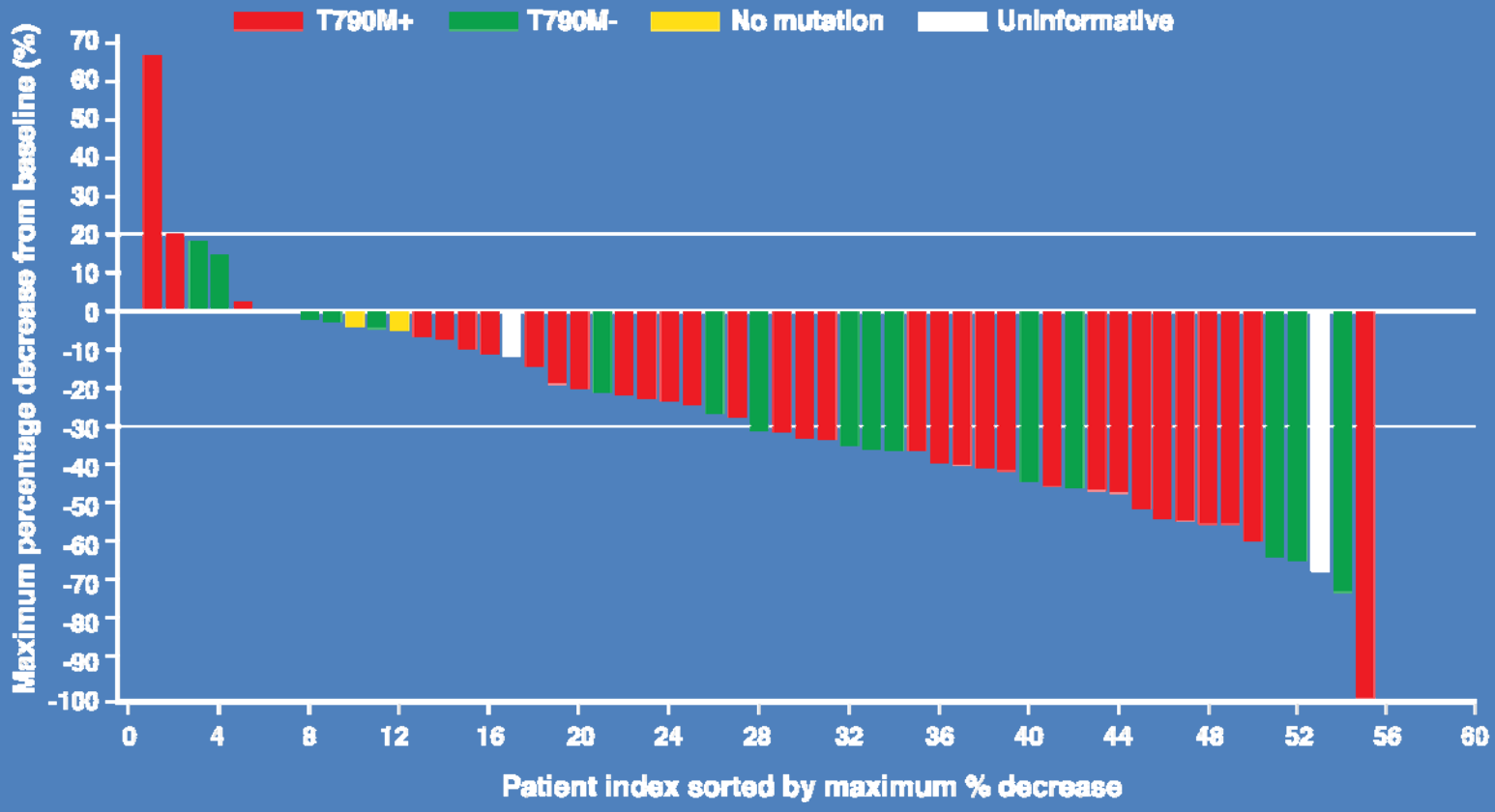
- Hypothesis: if MET amplification is a cause of EGFR TKI resistance, then addition of METi either up front or upon resistance makes sense
- TKI vs. Monoclonal antibody
  - Unfortunately, TKI phase III (MARQUEE trial) recently reported negative
  - Similarly, METMAB phase III trial also negative (even in selected patients)

Afatinib (BIBW 2992) + Cetuximab in Patients With Acquired Resistance to Erlotinib or Gefitinib

- Background: T790M resistance common
- Methods: 61 NSCLC with "acquired resistance" received oral afatinib 40 mg qd + biweekly cetuximab 250 or 500 mg/m^2
- Results (of 55 evaluable):
  - 100% disease control w/500 mg/m^2 dose: 51% PR
  - 11/35 PR in T790M+ patients
  - No dose-limiting toxicities, 8% Gr 3 rash
- Based upon interesting in vitro and murine work

Horn L et al. WCLC Annual Meeting. Abstract O19.07
JCI 2009; 119:3000-3010

Tumor Regression by T790M Mutation Status at Recommended Dose



Horn L et al. WCLC 2011. Slide courtesy of Dr. Horn.

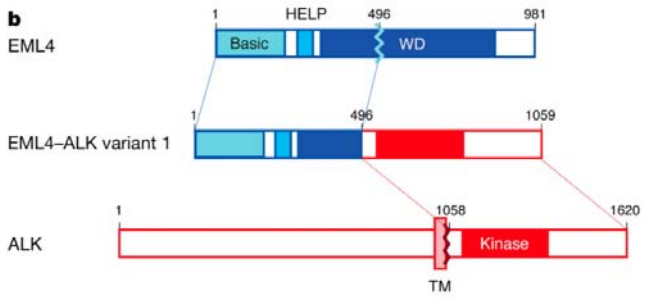
Summary

- Initial treatment
  - If you know Ex 19 deletion or L858R, erlotinib (or other appropriate TKI) as initial therapy
  - Erlotinib and Afatinib recently received FDA approval for first line treatment in EGFR mutant NSCLC
- Subsequent treatment
  - Chemotherapy (if not already given) with platinum based doublet or single agent
  - Unclear role of second generation TKIs
  - Unclear role of MET inhibitors (TKI or antibody)
  - ? Afatinib + cetuximab (need more data)
    - Planned ECOG and SWOG studies

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

- Echinoderm microtubule-associated protein-like 4 (*EML4*) becomes fused with the anaplastic lymphoma kinase (*ALK*)
  - Inversion within chromosome 2p
- First identified in 2007 from a resected lung adenocarcinoma specimen
- Clinical evaluation
  - Young
  - Never/light smokers
  - ?Male predominance
  - Adenocarcinoma histology



Nature 2007;448:561
J Clin Oncol 2009;27:4247

The NEW ENGLAND JOURNAL of MEDICINE

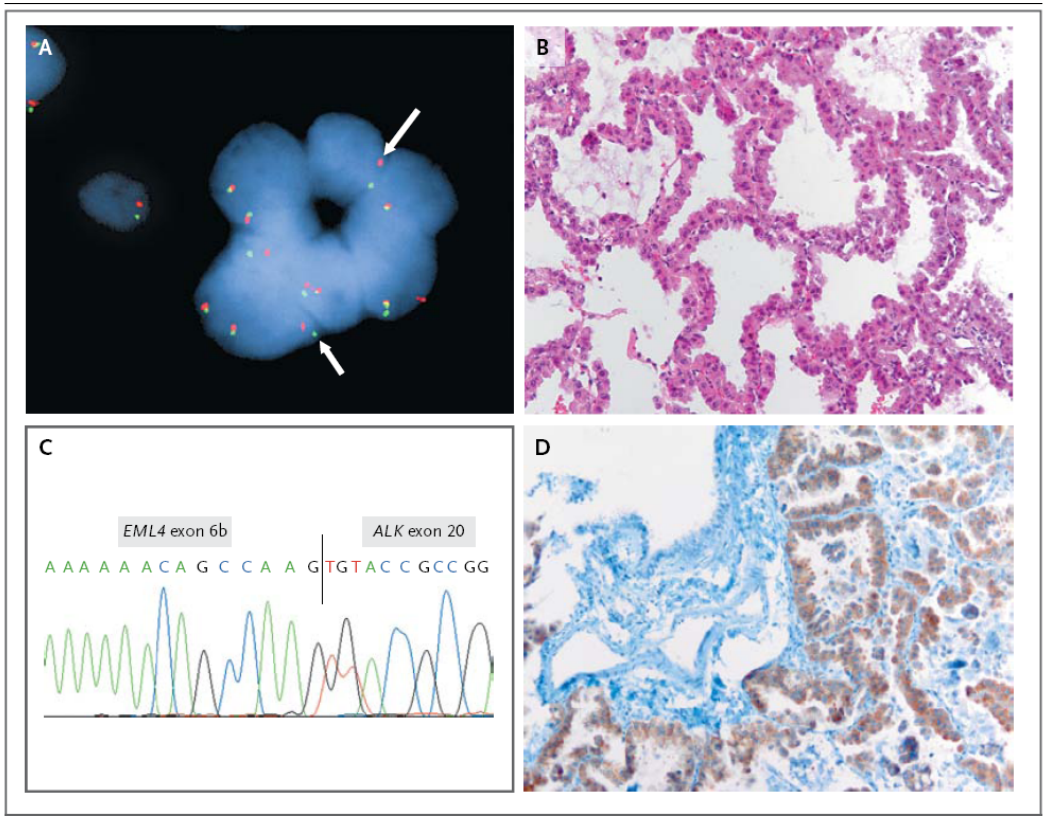
ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

- 1500 pts screened
- 82 ALK positive pts identified
- Enrolled on phase I expansion (most at MTD of 250 mg bid)

Diagnostic Studies

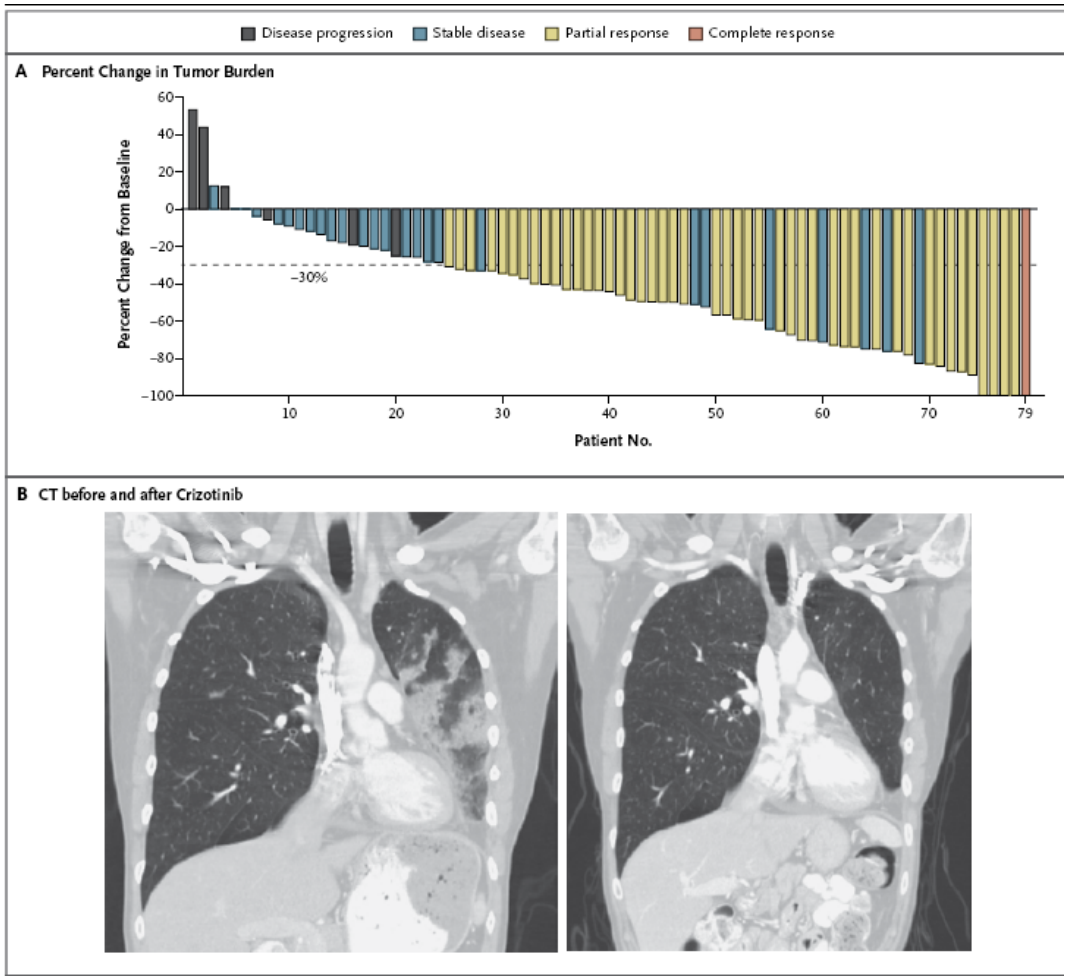
- A) FISH Break apart
- B) H&E
- C) Sequencing
- D) IHC



NEJM 2010;363:1693

Responsiveness

- 57% response
- 90% Benefit
- Estimated 6 month PFS 72% (median not reached)
- OS not reached



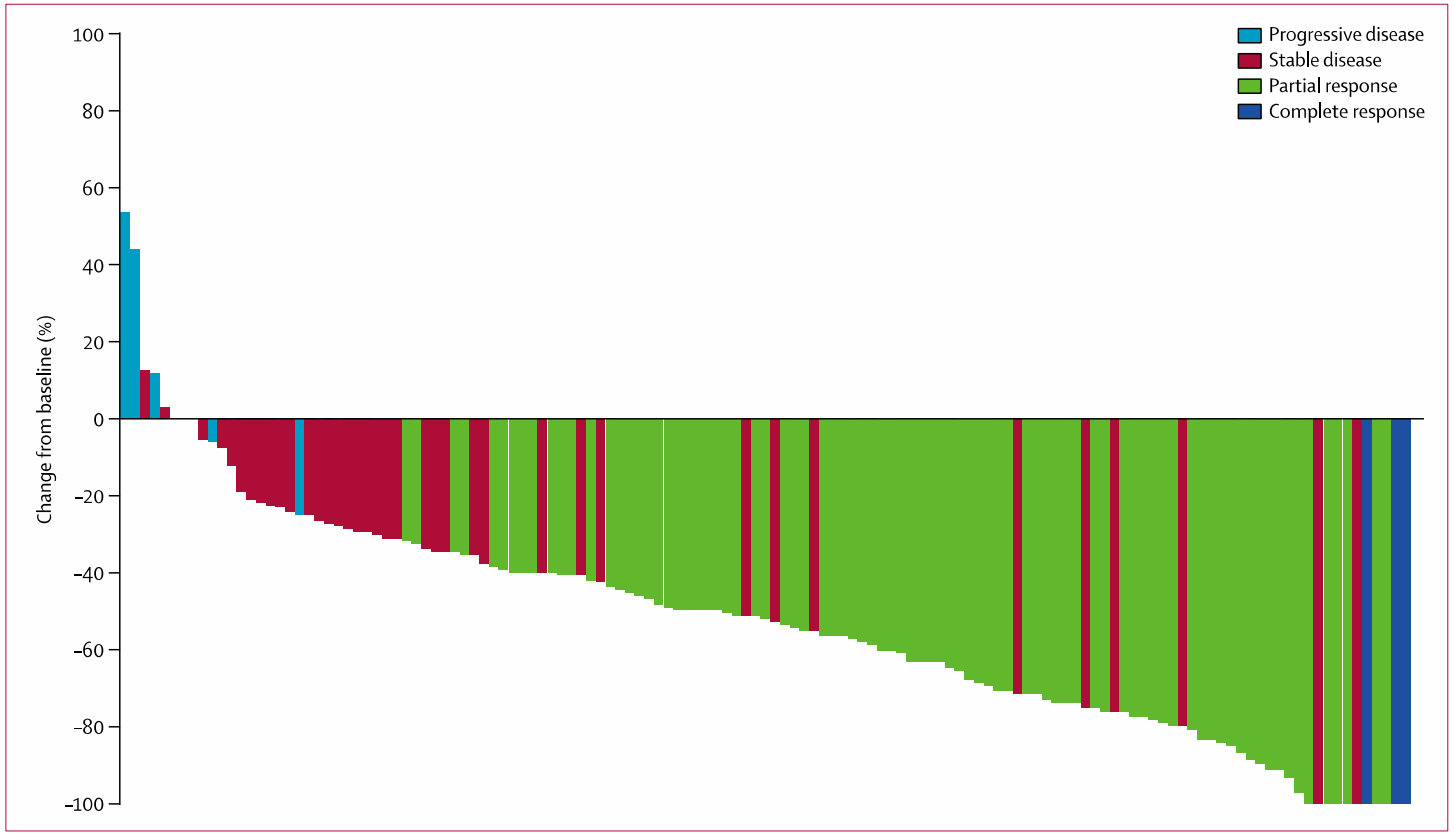
NEJM 2010;363:1693

Updated Phase I Results

- Additional follow up of 149 patients
  - 60.8% ORR (77% Asian, 55% non-Asian)
  - Median time to response 7.9 weeks
  - Median PFS 9.7 months
- 69 pts with disease progression
  - 39 continued crizotinib beyond progression (for > 2 weeks)
  - 10 brain, 5 lung, 3 liver

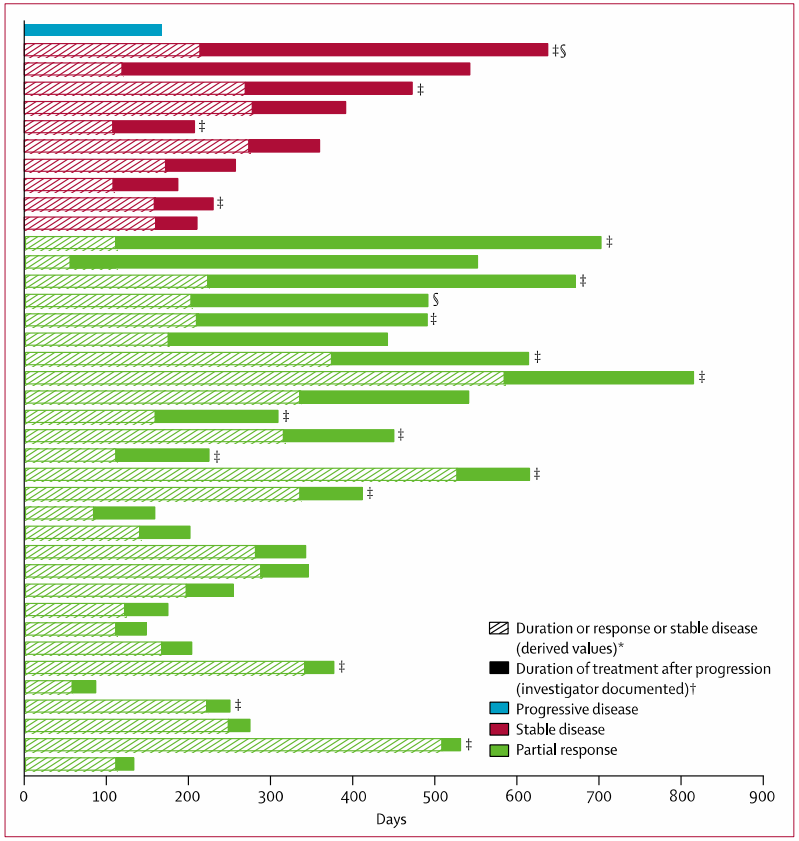
Lancet Oncol 2012; 13:1011-19

Waterfall Plot



Lancet Oncol 2012; 13:1011-19

Continued Crizotinib Beyond PD



Lancet Oncol 2012; 13:1011-19

Treatment Upon Progression

- Mechanism of progression
  - Pharmacokinetic – Brain
  - Genetic resistance
- “Oligo”-progressive disease
  - Consider stereotactic radiation (brain or elsewhere)
- Diffuse metastatic progression
  - Chemotherapy
  - Clinical trials

Predictive Biomarkers and Personalized Medicine

Clinical Cancer Research

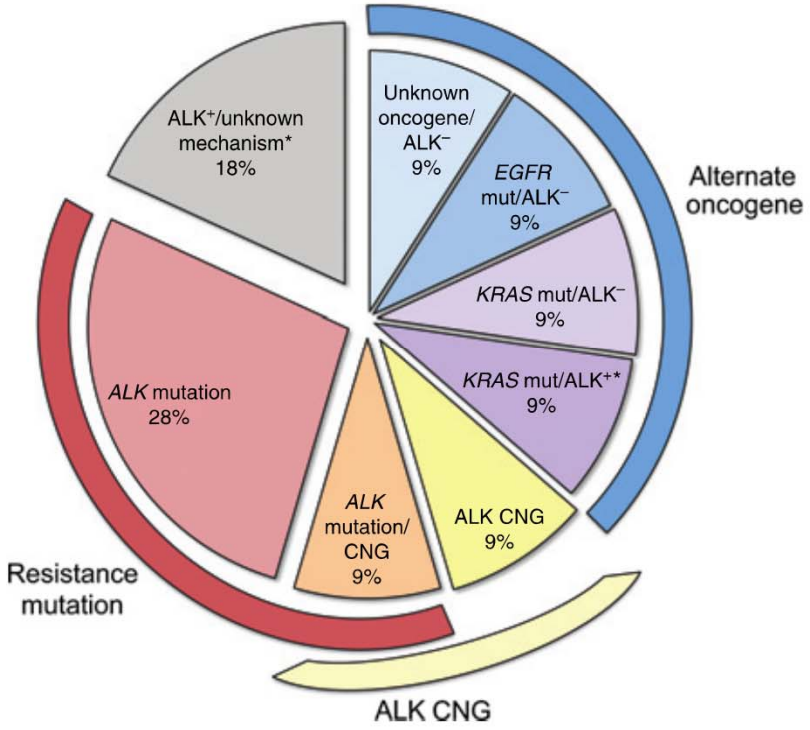
Mechanisms of Resistance to Crizotinib in Patients with *ALK* Gene Rearranged Non–Small Cell Lung Cancer

Robert C. Doebele[1], Amanda B. Pilling[1], Dara L. Aisner[2], Tatiana G. Kutateladze[3], Anh T. Le[1], Andrew J. Weickhardt[1], Kimi L. Kondo[4], Derek J. Linderman[6], Lynn E. Heasley[5], Wilbur A. Franklin[2], Marileila Varella-Garcia[1], and D. Ross Camidge[1]

- Re-biopsy study of 14 pts (11 usable)
  - 4 secondary ALK mutations
  - 2 ALK CNG
  - 1 EGFR L858R mutation
  - 2 KRAS mutations
  - 2 none identified

Clin Cancer Res 2012; 18:1472-82

ALK Resistance



Clin Cancer Res 2012; 18:1472-82

Second Generation ALKi

- Numerous compounds in phase I/II/III testing
  - Improved CNS penetration
  - Activity against ALK resistance mutants
- Testing questions
  - Prior to crizotinib?
  - Following initial response to crizotinib?

Second Generation ALKi

The NEW ENGLAND JOURNAL of MEDICINE

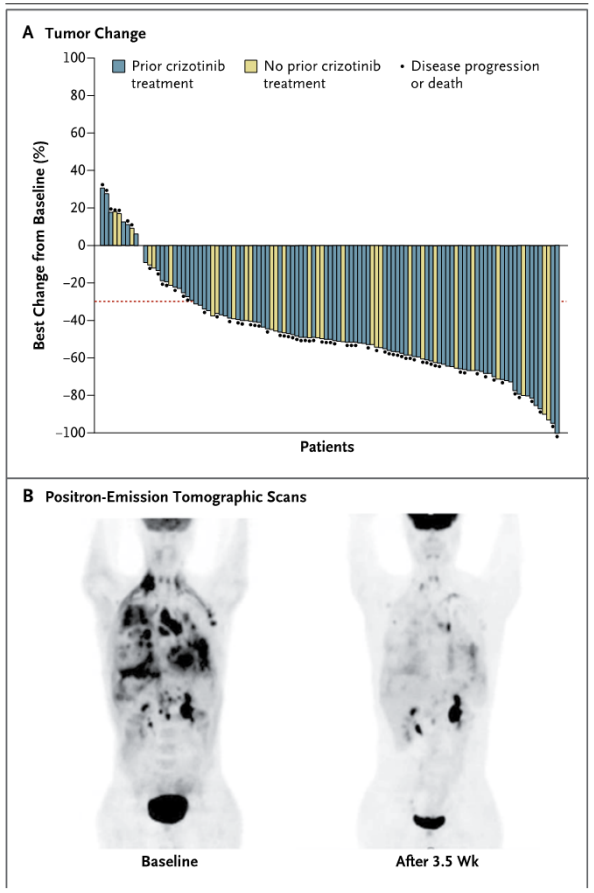
ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

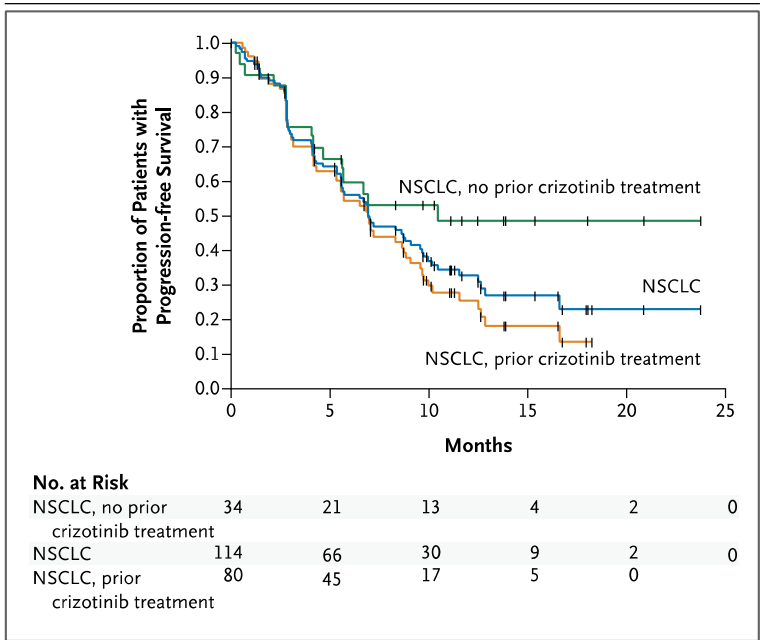
Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

NEJM, March 27, 2014; 370:1189-97

Ceritinib (LDK378) Phase I





No. at Risk

NSCLC, no prior crizotinib treatment	34	21	13	4	2	0
NSCLC	114	66	30	9	2	0
NSCLC, prior crizotinib treatment	80	45	17	5	0	

NEJM, March 27, 2014; 370:1189-97

LDK 378 Preliminary Results

- Potent activity seen at doses ≥ 400 mg/day
  - ORR 58% in 114 NSCLC pts
  - ORR 56% in crizotinib treated pts
  - Median PFS 7 months
- Significant activity seen in CNS
- Activity seen regardless of resistance mechanism
- Most frequent toxicities GI
  - Nausea, vomiting, diarrhea

NEJM, March 27, 2014; 370:1189-97

Second Generation ALKi

- CH5424802 (Chugai/Roche)
  - Phase I/II study (24 pts phase I, 46 pts phase II)
  - Doses 20-300 mg bid, MTD 300 mg bid
    - 43/46 pts treated at MTD had response
    - Mild grade 3 toxicity, no grade 4 toxicities reported

Seto et al, Lancet Oncol 2013 Jun;14(7):590-8.

Non-ALKi Strategies

- Phase II study of Ganetespib monotherapy (HSP90 inh) in genotypically defined NSCLC
  - 3 cohorts – EGFR mutant, KRAS mutant, neither
  - 99 pts
    - 15 EGFR – PFS @ 16 wks 13.3%
    - 17 KRAS – PFS @ 16 wks 5.9%
    - 66 neither – PFS @ 16 wks 19.7%
  - 4 PRs, all ALK positive (of 8 ALK patients, crizotinib naïve)

Socinski MA et al. Clin Cancer Res. 2013 Jun 1;19(11):3068-77.

Summary

- Initial Treatment
  - Crizotinib is appropriate as initial treatment for ALK translocated NSCLC
  - Expected RR ~ 60%, PFS ~ 10+ months
  - Phase III of crizotinib vs. chemo in 2nd line + therapy crizotinib superior
  - Recent press release of positive 1st line trial
- Subsequent treatment
  - Chemotherapy (if not already given) with platinum based doublet or single agent
  - ?Rebiopsy – although subsequent response not dependent upon mechanism of resistance
  - Second generation ALKi?
    - LDK378 with "breakthrough" designation in March
    - Others
  - HSP90 inhibitors?

Challenges

- Insufficient biopsy material
  - Consider re-biopsy
  - CTCs and serum/plasma analysis not ready
- Time delay?
  - Needs to be team effort with pulmonary docs, interventional radiologists, surgeons and pathologists
- Where to test?
  - Institutional
  - Core lab
- What is the best test?
  - FISH
  - IHC
  - Next Gen Sequencing?

Other Molecular Markers

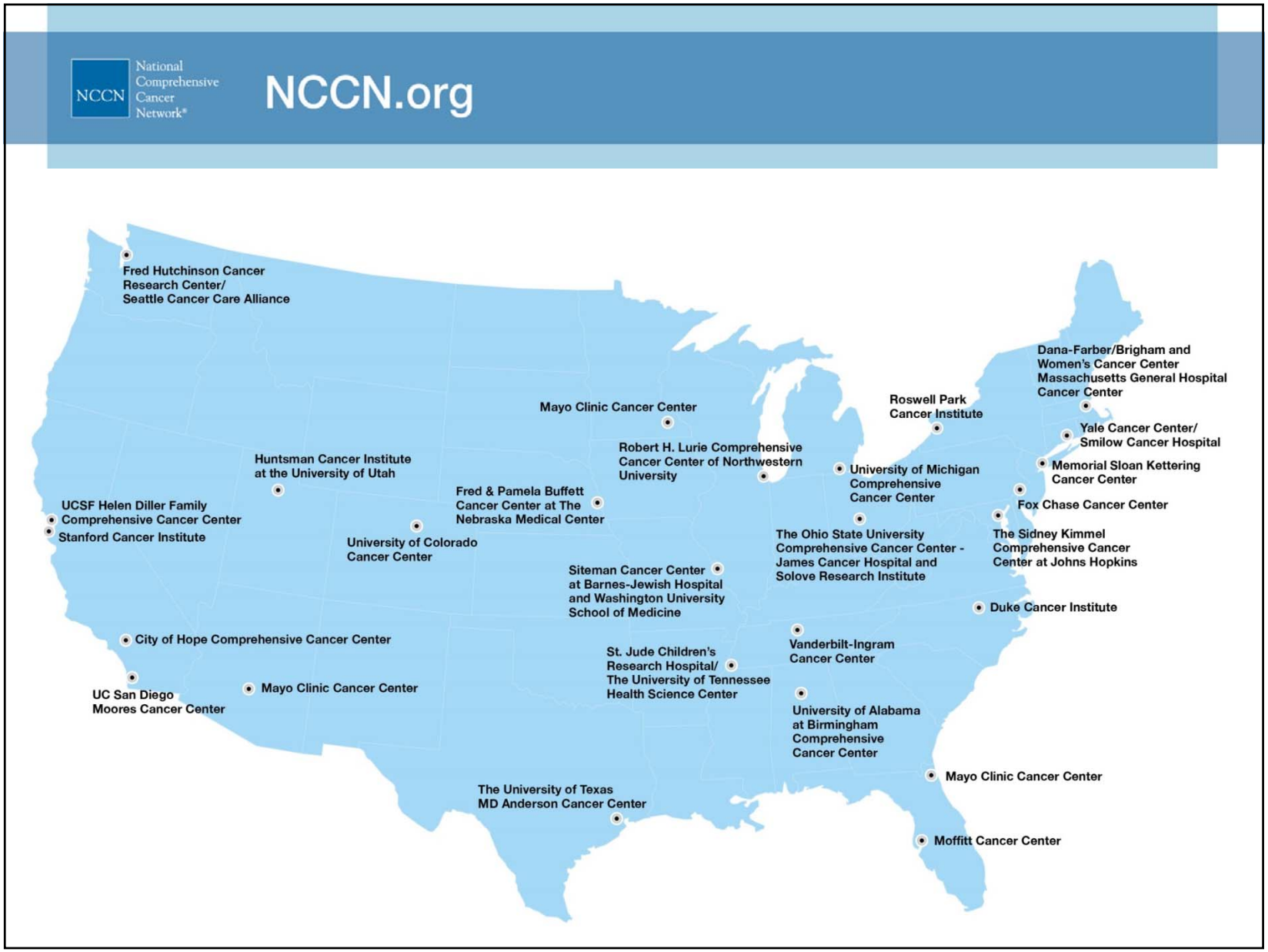
- EGFR – atypical mutations, Exon 20, others
- ROS1 – initial responsiveness to crizotinib
- MET amplification or mutations – stay tuned to ASCO 2014
- BRAF - < 5% of NSCLC patients, ~ 50% of the mutations seen are V600E
- HER2 mutations
- FGFR mutations and amplifications
- Other tumors –Squamous?

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

- Mutation testing guidelines
  - All advanced non-squamous histology
    - Not restricted by age, sex, smoking history, ethnicity
  - Select squamous cancers
    - Small biopsy of larger tumor
    - Possibly guided by smoking history

JTO 2013; 8:823-59



NCCN Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer
Patient Navigation: Role in Molecular Testing in NSCLC

Presented live on April 8, 2014

by:

Teresa Knoop, MSN, RN, AOCN
Assistant Director, Clinical Trials Shared Resource
Vanderbilt-Ingram Cancer Center

A recording of this live webinar is available at http://education.nccn.org/node/49250 until June 17, 2015.

Intended Audience and Learning Objectives

Intended Audience:

This slide deck is designed to meet the educational needs of medical oncologists, radiation oncologists, surgical oncologists, pathologists, nurses, pharmacists, and other healthcare professionals who manage patients with non-small cell lung cancer.

Learning Objectives:

Following this section, participants should be able to:

- Develop core communication messages for use with patients in advance of testing decision making

Objective

- Develop core communication messages for use with patients with non-small cell lung cancer (NSCLC) in advance of testing decision making.

Core Communication Messages

- Stage/current disease state/histology
- What does molecular tumor testing mean?
- Is molecular testing appropriate for every patient's case? Why or why not?

Core Communication Messages

- What information will molecular testing provide and what will it not provide?
- How is molecular testing done?
- Why might additional biopsies be required and what will be entailed?

Core Communication Messages

- How long is the waiting time for molecular testing results?
- How are the results interpreted and how will those results drive treatment decisions?
- How does molecular testing help drive available standard of options and clinical trial options?
- What does this information mean now and what might it mean for the future?

Stage/Current Disease State/Histology

- Stage at diagnosis
- Current disease state
  - Newly diagnosed
  - Recurrence/metastasis
- Histology of NSCLC
  - Adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified (NOS)
  - Squamous cell carcinoma
- Goal of current treatment

What does molecular testing mean?

- Molecular testing is a way to look at the tumor at a molecular level to determine if there are any biomarkers that can predict whether the patient will receive therapeutic benefit from a drug. (predictive biomarkers)

- Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements are 2 commonly recommended molecular tests for non-small cell lung cancer

NCCN.org 2014

Is molecular testing appropriate for every patient's case? Why or why not?

- Decisions to do molecular testing may depend on:
  - Where patient is in disease trajectory
  - What the sub-type is for their NSCLC
    - Adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified (NOS): EGFR and ALK
    - Squamous cell carcinoma: if it is squamous cell, then the recommendation is to only do EGFR/ALK testing if the patient is a never smoker, has mixed adeno-squamous histology or if only a small specimen (not a resection) was done for histology testing (with small specimens, it could be a mixed adeno-squamous and be missed due to the small size of the specimen)

NCCN.org 2014

What information will molecular testing provide and what will it not provide?

- Molecular testing for NSCLC will provide:
  - Information about gene alterations (mutations or alterations) in the patient's tumor that predict whether the cancer will be sensitive to certain drugs or whether those drugs are not likely to help in that patient's situation due to a lack of gene alterations

- Molecular testing for NSCLC will not provide:
  - A guarantee that the drugs given for the genetic alterations will cure the cancer; tumors often develop resistance to these drugs after a period of time
  - Information about hereditary risk for other members of the family

NCCN.org 2014

How is molecular testing done?

- To perform molecular testing on patients with NSCLC currently it:
  - Must be done via a sample of the patient's tumor tissue; can be done on archived tissue
  - Cannot be done on a blood sample
  - May be done on the primary site of the tumor or on a metastatic site
  - Must be done on a large enough specimen of tissue. Fine needle aspirations often do not provide enough tissue for molecular testing
  - Should be done with an effort in pathology to use enough tissue to accurately diagnose the case, while conserving enough tissue to perform molecular testing

NCCN.org 2014

Why might additional biopsies be required and what will be entailed?

- If a patient needs molecular testing done to be able to choose the most appropriate treatment plan, then an additional biopsy may be needed. Common in the clinical trial setting
- Additional tissue may be needed if the initial biopsy did not yield enough tissue for both histologic diagnosis and molecular testing
- The least invasive biopsy type that can yield the amount of tissue needed will be chosen
- Types of procedures may include: biopsy of lymph node or an organ such as liver; bronchoscopy; mediastinoscopy

NCCN.org 2014

How long is the waiting time for results?

- Waiting time variable and can be anxiety producing
- What can alter the waiting time?
  - Will the testing be done in your institution or sent out to an independent lab?
  - Is enough tumor tissue available in your pathology department?
    - If not, the archived tumor tissue may have to be obtained from a different institution which increases time frame
  - Is enough tumor tissue available?
    - If not, the patient may need another biopsy which will increase time frame

How are the results interpreted and how will those results drive treatment decisions?

- EGFR results are interpreted by looking at the tumor DNA via multiplex polymerase chain reaction (PCR) systems
- EGFR is often done together with a mutation screening assay panel that looks at a multitude of biomarkers simultaneously for point mutations
- PCR systems do not detect gene rearrangements so ALK has to be tested differently through a procedure known as FISH (fluorescence in situ hybridization) and may be done by a different lab
- Having these results for EGFR and ALK will help the MD and patient make the best treatment decisions

NCCN.org 2014

How does molecular testing drive available standard of options and clinical trial options?

- In NSCLC, there are currently FDA approved drugs that target gene alterations present in the patient's tumor. Presence or absence of these gene alterations can help determine what drugs may be most efficacious for each patient and which drugs are not likely to be effective

- FDA approved drugs for patients with EGFR mutations
  - erlotinib
  - afatinib
  - gefitinib (not widely available in the United States)

- FDA approved drug for patients with ALK rearrangements
  - crizotinib

NCCN.org 2014

How does molecular testing drive available standard of options and clinical trial options?

- In NSCLC there are many clinical trials being conducted across the United States exploring other driver mutations or alterations that can be targeted by drugs (druggable targets)

- Targets of interest for NSCLC include:
  - HER2 (ERRB2)
  - BRAF
  - ROS1 and RET gene rearrangements
  - MET amplifications

- Next generation gene sequencing is looking at large numbers of genes

NCCN.org 2014

What does this information mean now and what might it mean for the future?

- Molecular testing many mean little in terms of immediate treatment options to some patients, particularly if their disease is not advanced. However, may be needed for the future in case of disease recurrence

- Molecular testing results may mean immediate treatment options for some patients in terms of:
  - Standard treatment
  - Clinical trials

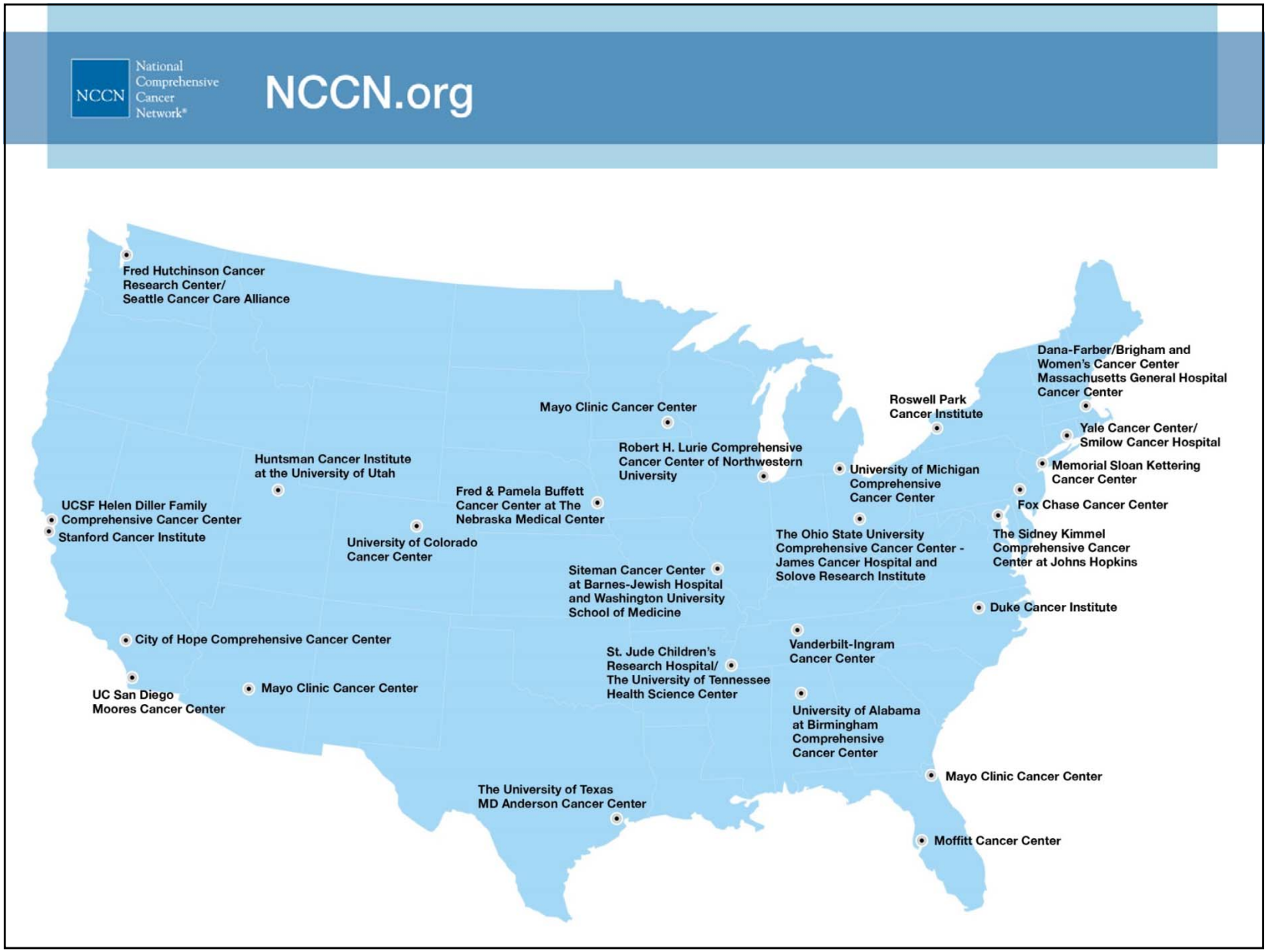
NCCN.org 2014

Resources for Health Care Professionals

- Genetics/Genomics Competency Center (G2C2) developed by the National Human Genome Research Institute (NHGRI)
  - http://www.g-2-c-2.org/
- International Society of Nurses in Genetics (ISONG)
  - *www.**isong**.org*
- Mycancergenome.org
  - http://mycancergenome.org
- National Comprehensive Cancer Network
  - http://NCCN.org
- Oncology Nursing Society
  - http://ONS.org

Reference

- National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Guidelines. Version 3.2014. http://NCCN.org. Retrieved April 6, 2014.



NCCN Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer
Tissue Acquisition in NSCLC: Surgical and Interventional Radiology Perspectives

Presented live on April 23, 2014

by

Richard Cheney, MD
Roswell Park Cancer Institute

Todd Demmy, MD
Roswell Park Cancer Institute

Peter Loud, MD
Roswell Park Cancer Institute

A recording of this live webinar is available at http://education.nccn.org/node/49243 until June 17, 2015.

Intended Audience and Learning Objectives

Intended Audience:

This slide deck is designed to meet the educational needs of medical oncologists, radiation oncologists, surgical oncologists, pathologists, nurses, pharmacists, and other healthcare professionals who manage patients with non-small cell lung cancer.

Learning Objectives:

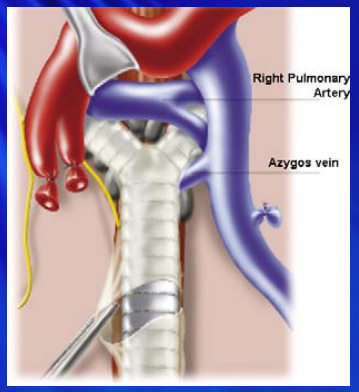
Following this section, participants should be able to:

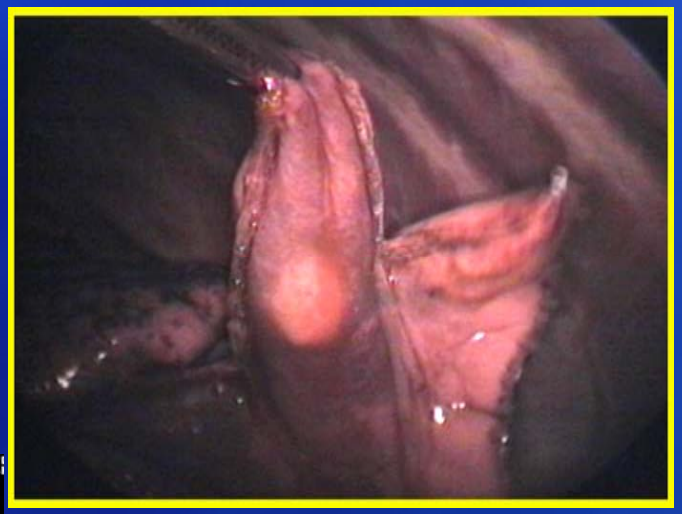
- Discuss the considerations and challenges of obtaining appropriate tissue samples

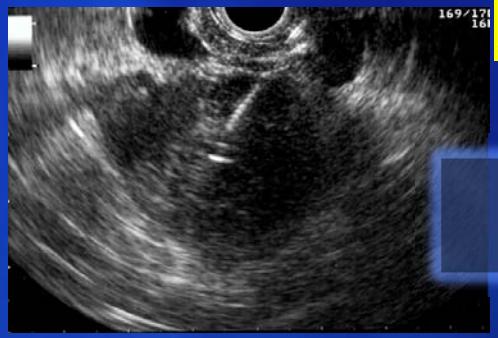
National Comprehensive Cancer Network®

Slides Presented by Dr. Demmy

Methods of Tissue Acquisition
Choosing the Right Balance







Todd L. Demmy

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Objectives

- Endoscopic
  - "Blind" and Ultrasound directed (EBUS/EUS)
  - Navigational Bronchoscopy
- Transcervical
  - Mediastinoscopy & videomediastinoscopy (VMS)
  - Video-Assisted Mediastinal Lymphadenectomy (VAMLA)
  - Transcervical Extended Mediastinal Lymphadenectomy (TEMLA)
- VATS

ROSWELL PARK CANCER INSTITUTE®

Factors Influencing Decision

Pathologic Anatomy

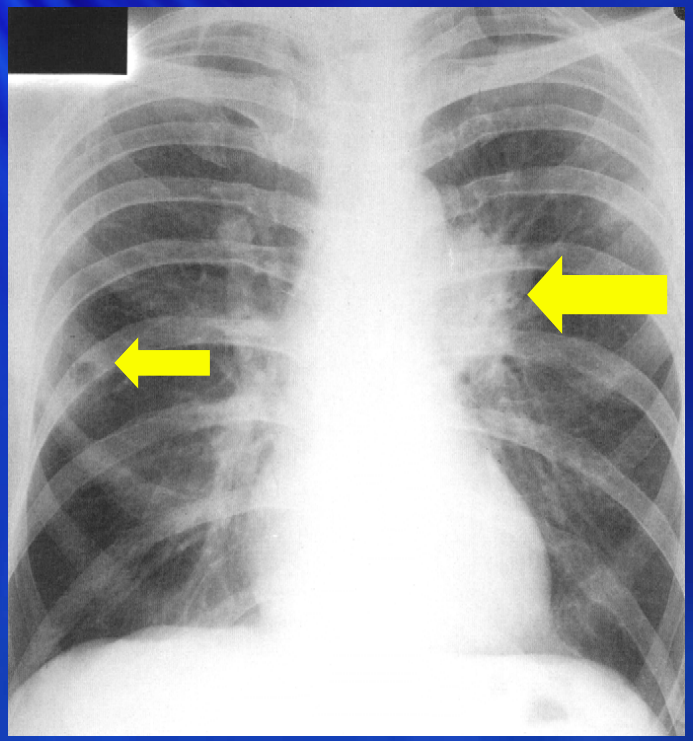
Technology

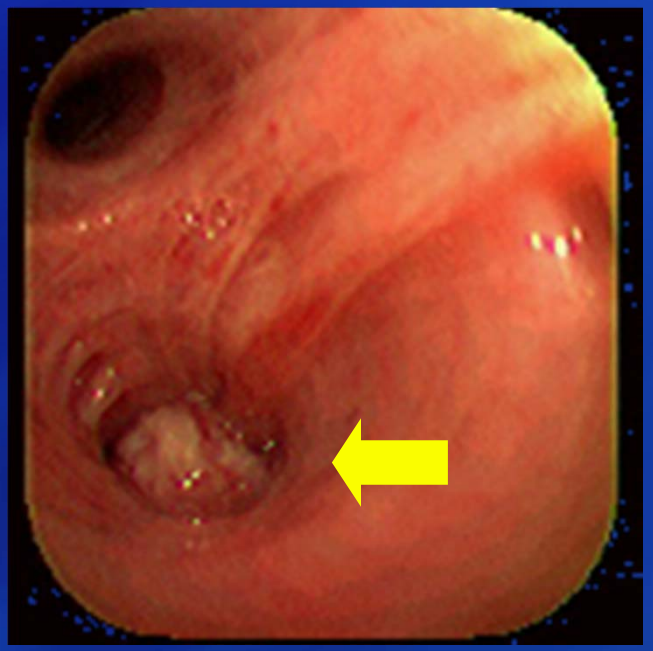
Patient Comorbidities

NCCN Webinar 2014

ROSWELL PARK CANCER INSTITUTE®

VATS for Diagnosis & Staging Lung Cancer

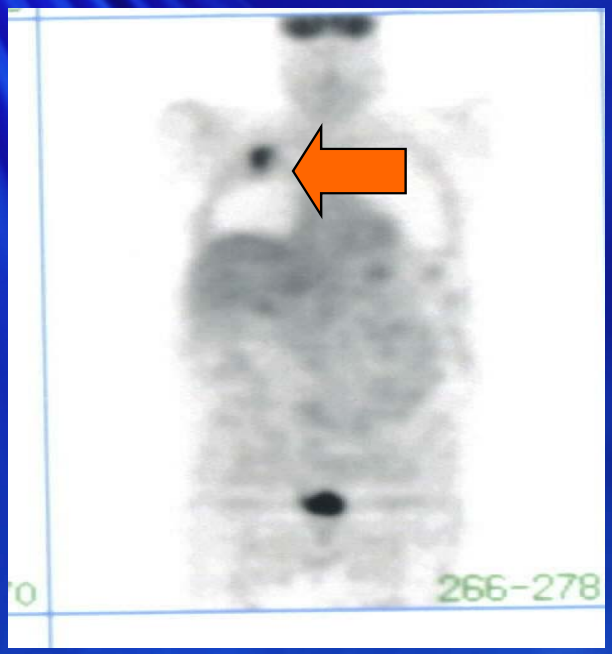


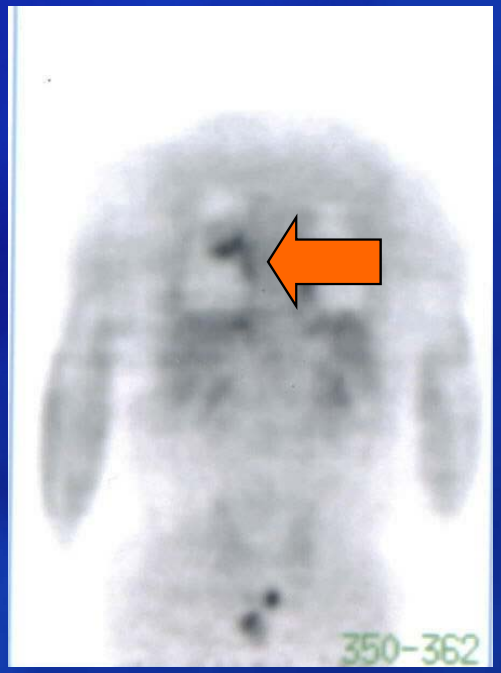


ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

PET Scan Imaging



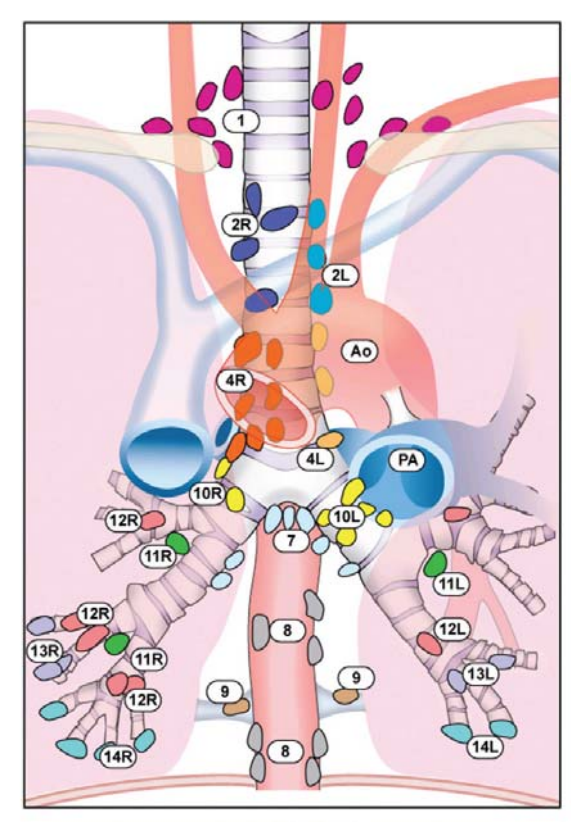


- 97% Sensitive
- 78% Specific
- > 1 cm

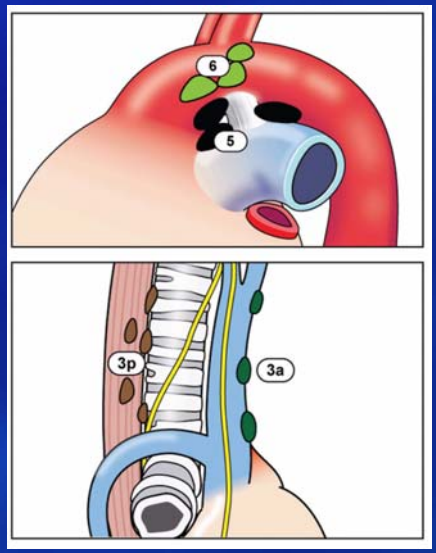
ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

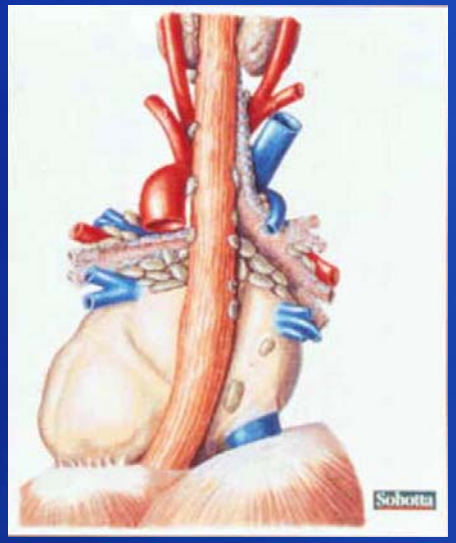
Mediastinal Lymph Nodes



Side



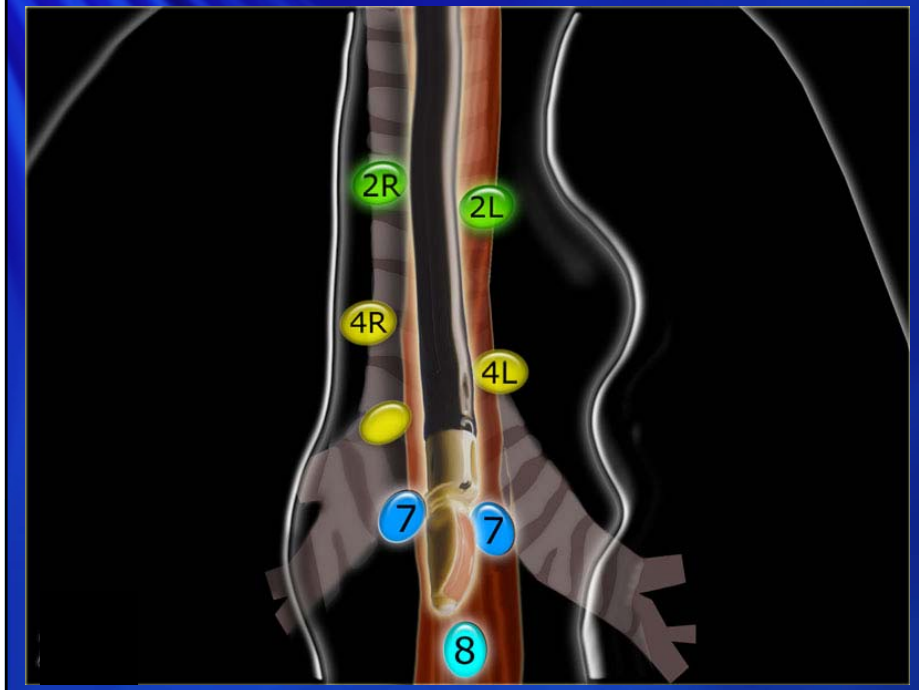
Back

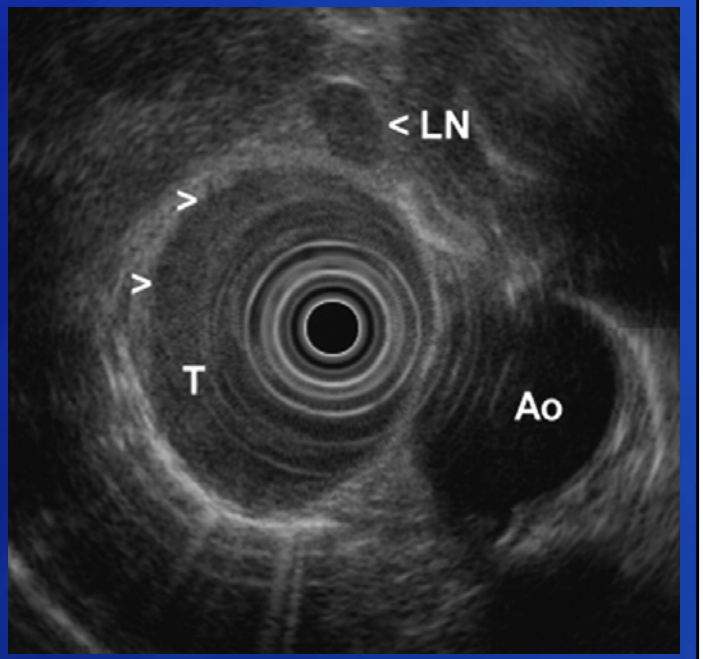


ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

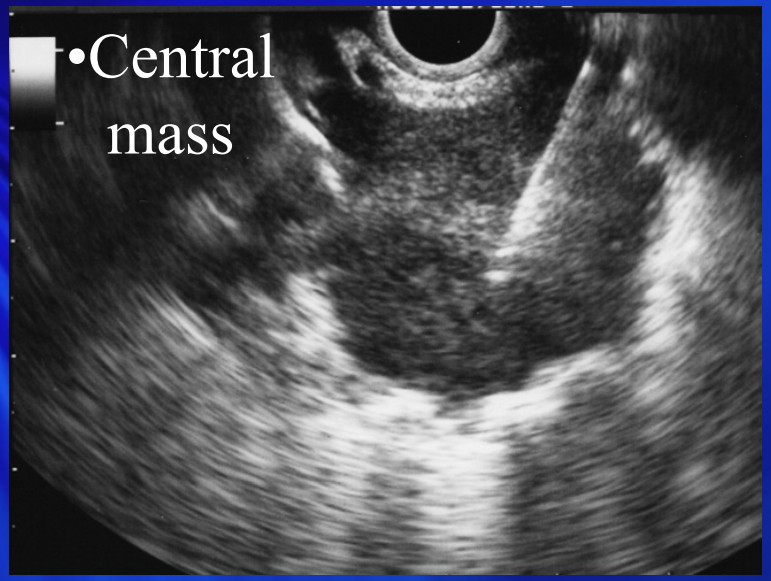
Esophageal Ultrasound (EUS)





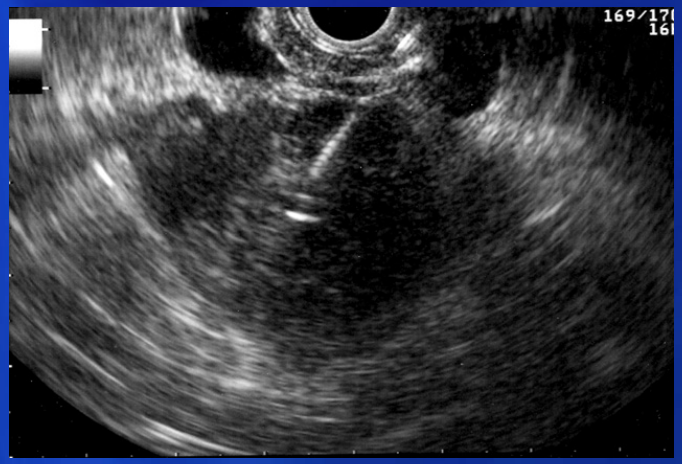
ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014



EUS
FNA

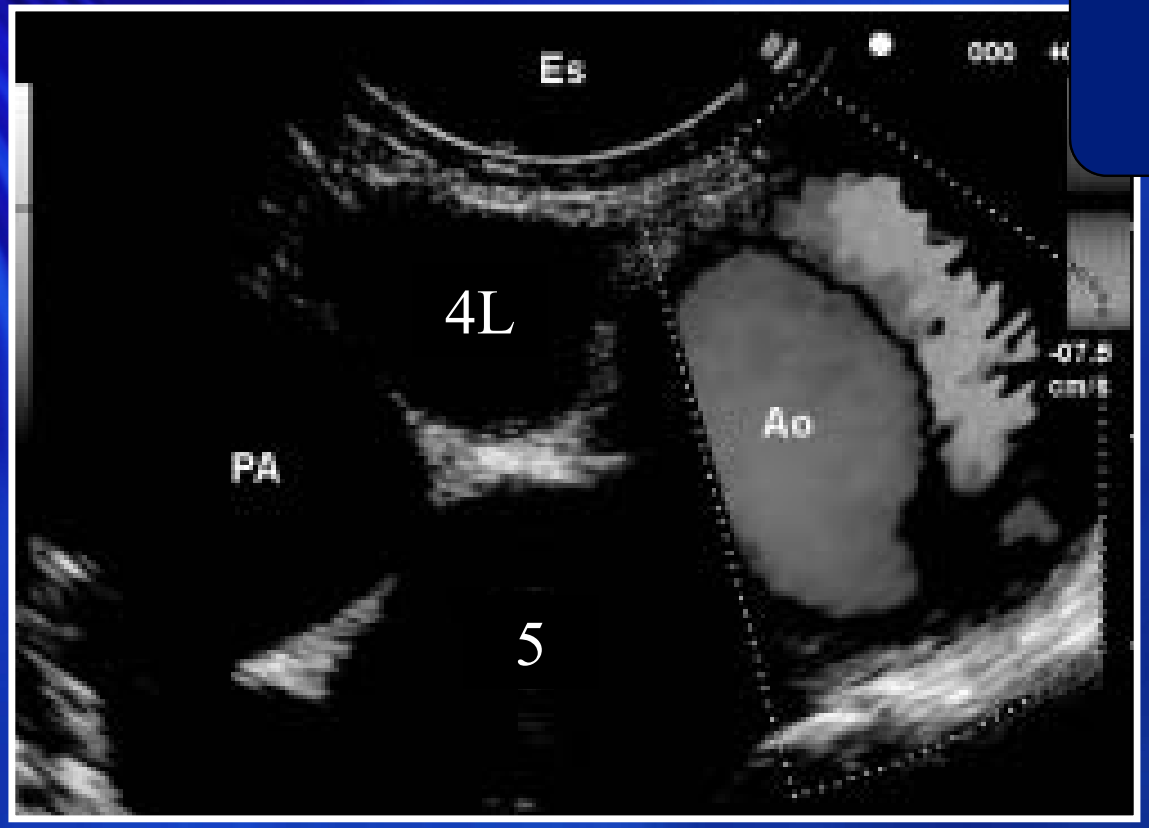
Semin Thorac
Cardiovasc Surg
19:206-211
2007



•L Adrenal gland
97%
accessibility

ROSWELL PARK CANCER INSTITUTE®

EUS FNA



Eur Respir J
2006; 28: 1264–
1275

ROSWELL PARK CANCER INSTITUTE®

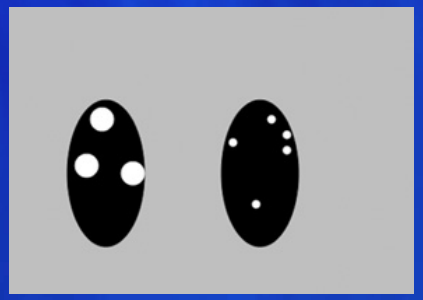
Factors Affecting TBNA Yield

- Presence of LN enlargement on CT scan
- Type of needle
- Site of the tumor or LN
- Number of aspirates performed
- Availability of rapid on-site cytopathologic examination
- Ability and experience of the operators
- Nature of the lesion (malignancy, type of malignancy)

•Eur Respir J 2006; 28: 1264–1275

ROSWELL PARK CANCER INSTITUTE®

Limitation of FNA (EUS)
EUS-FNA sensitivity



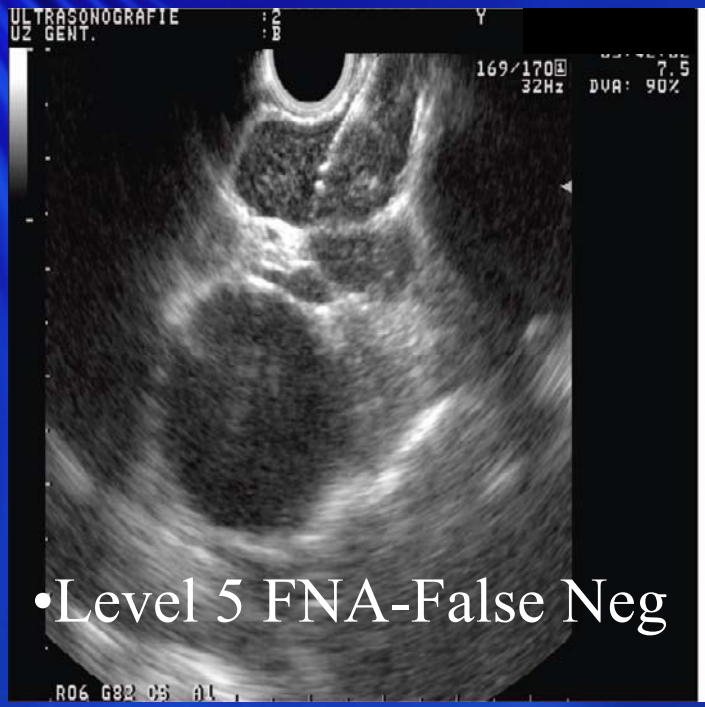
	N	True positive	False negative	Sensitivity (%)
LN size				
Normal	59	7	9	43.8
Enlarged	49	25	7	75
Bulky disease	12	11	1	91.7
Tumor location				
Right	64	16	16	50
Left	46	23	1	95.6
Lymph node station				
7	96	29	7	80.6
5/6	35	15	4	78.9
4R	66	5	16	23.8
4L	49	3	9	25

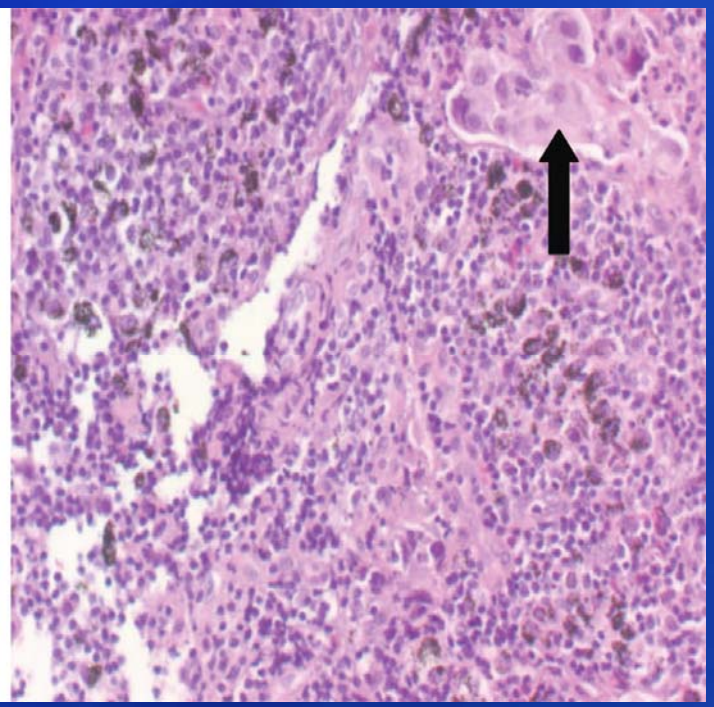
Eur J Cardiothoracic Surgery 33 (2008) 1124—1128

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Limitation of FNA (EUS)





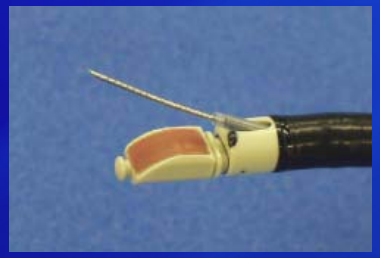
- Level 5 FNA-False Neg

J Thorac Oncol. 2008;3: 245–249

NCCN Webinar 2014

ROSWELL PARK CANCER INSTITUTE®

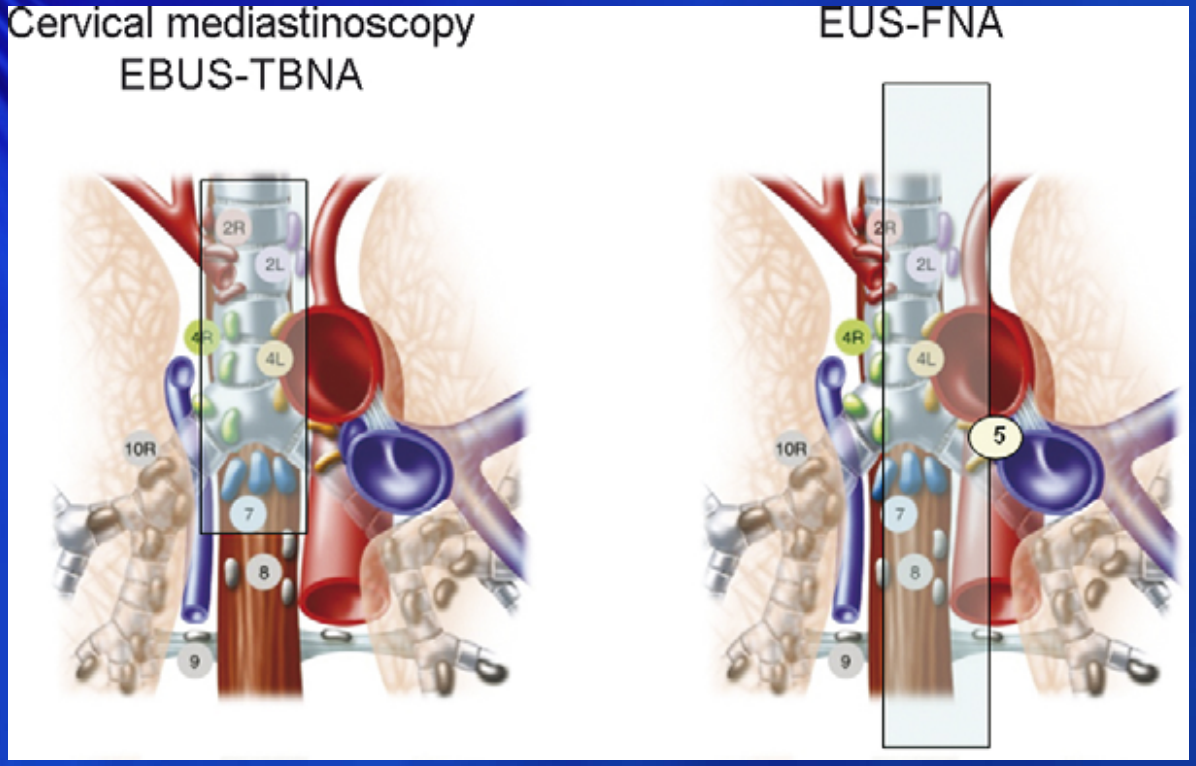
EBUS
FNA



•40s EBUS

ROSWELL PARK CANCER INSTITUTE®

Various Surgical Staging Methods
Comparative Anatomic Access



•European Journal of Cardio-thoracic Surgery 32 (2007) 1—8

ROSWELL PARK CANCER INSTITUTE®

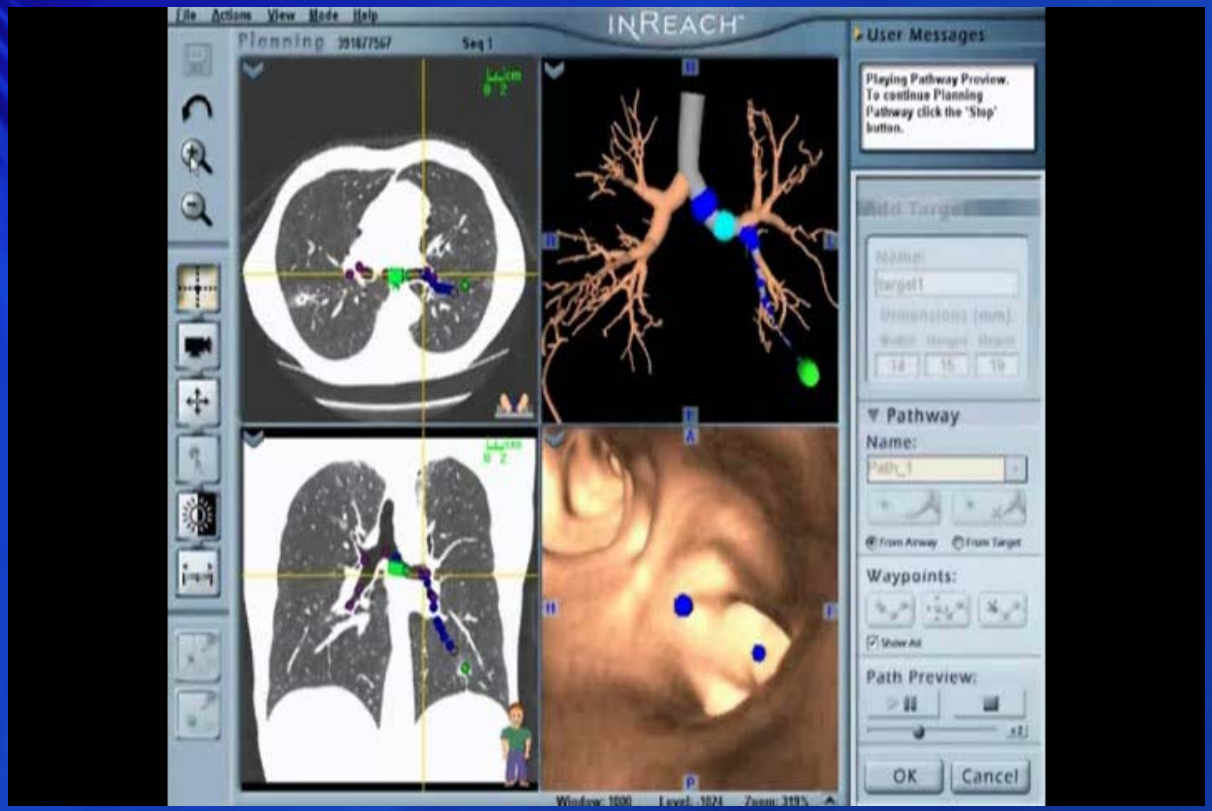
NCCN Webinar 2014

Real-time Location Information

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Navigational Bronchoscopy

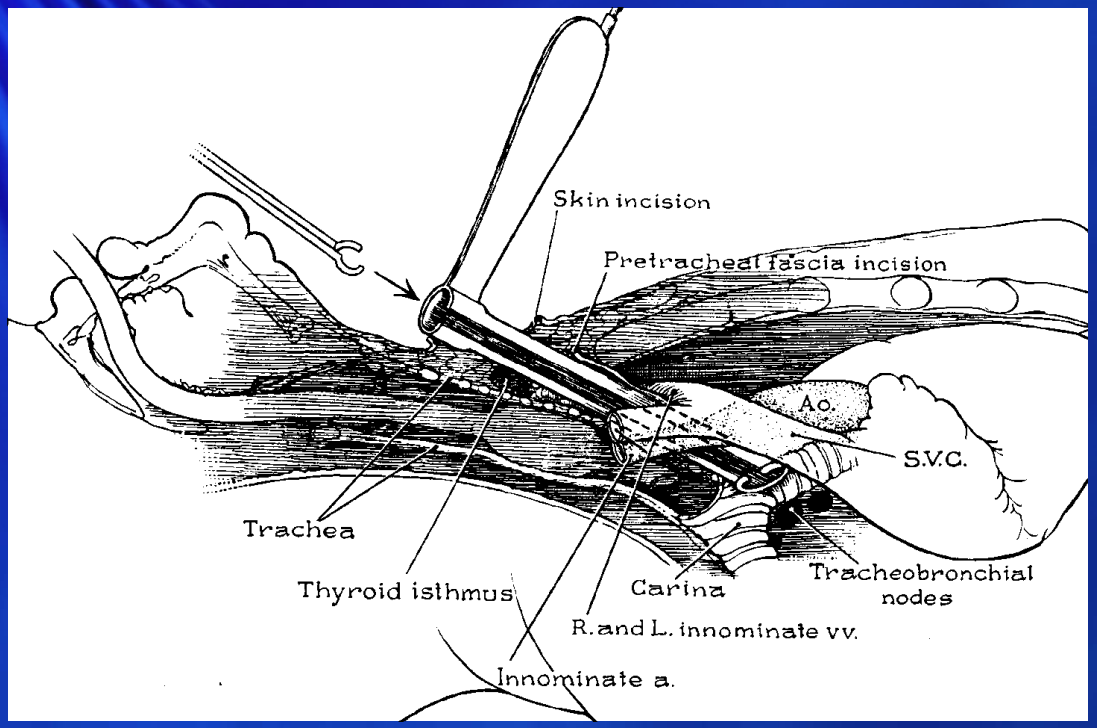


•60Sec SuperDMix

ROSWELL PARK CANCER INSTITUTE®

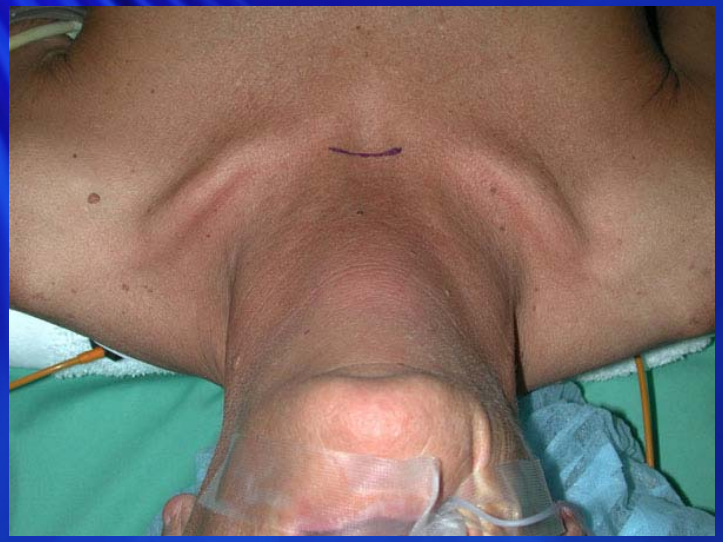
NCCN Webinar 2014

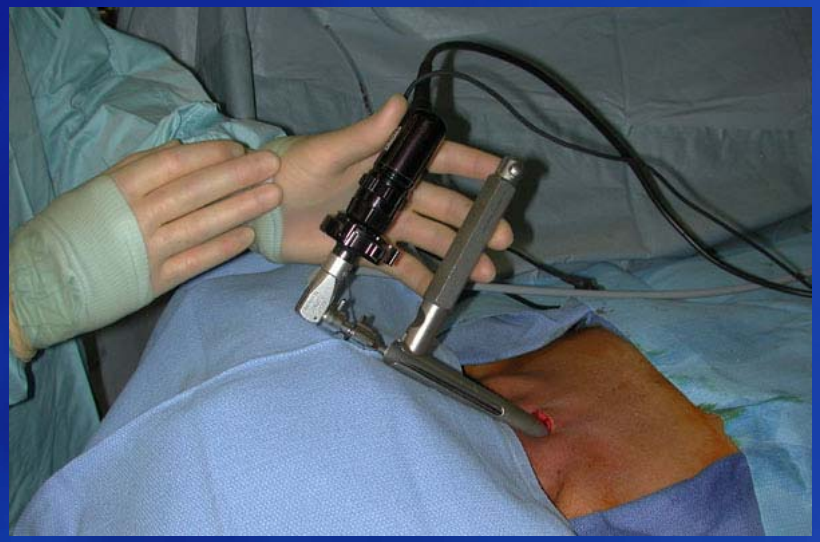
Mediastinoscopy



NCCN Webinar 2014

VideoMediastinoscopy

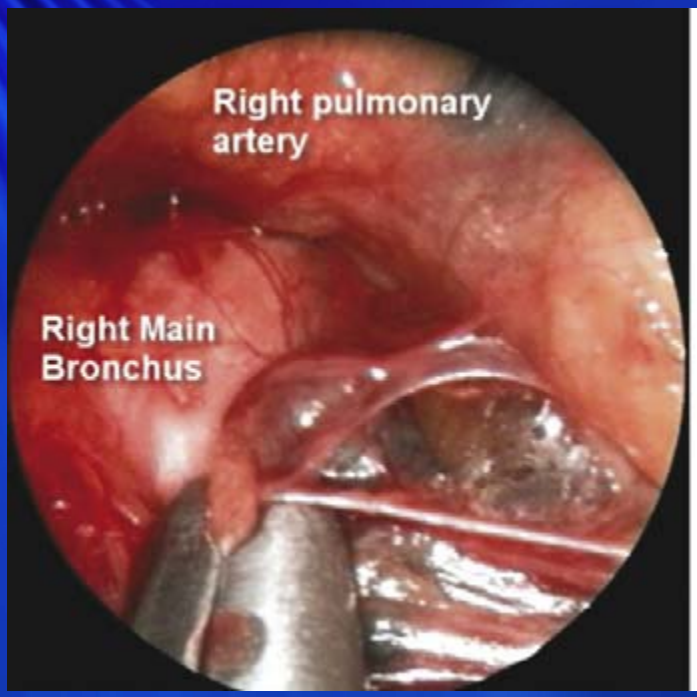


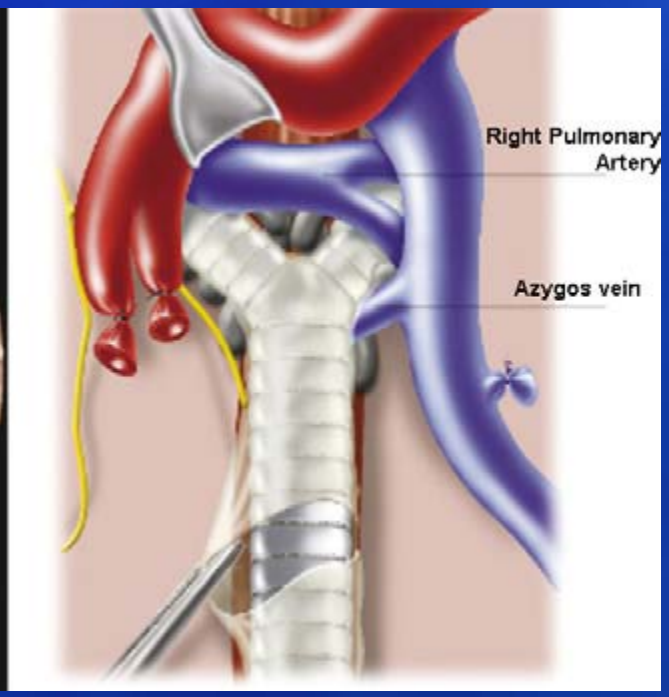


ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Various Surgical Staging Methods
Mediastinoscopic Anatomy



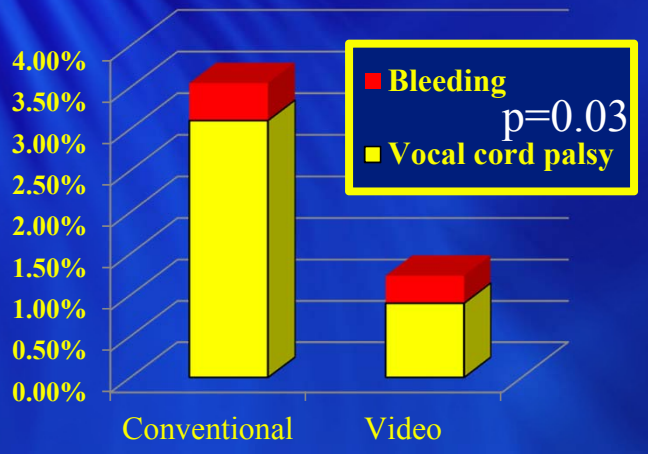


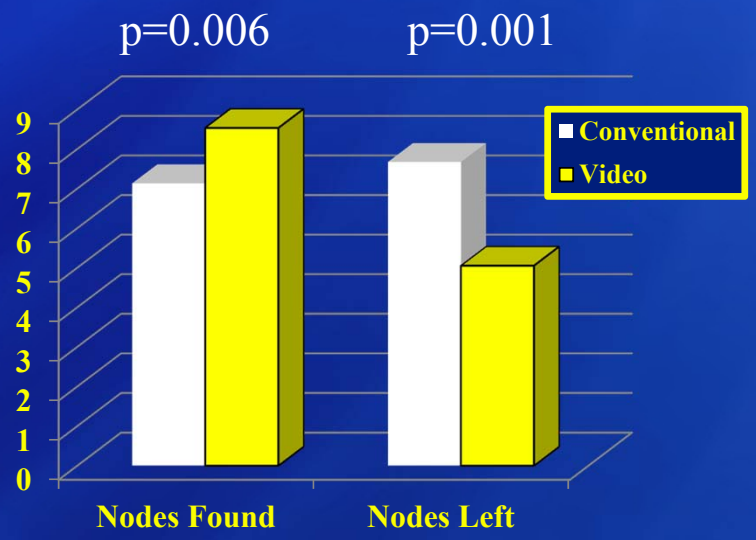
•European Journal of Cardio-thoracic Surgery 32 (2007) 1—8

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

VideoMed vs Traditional Med



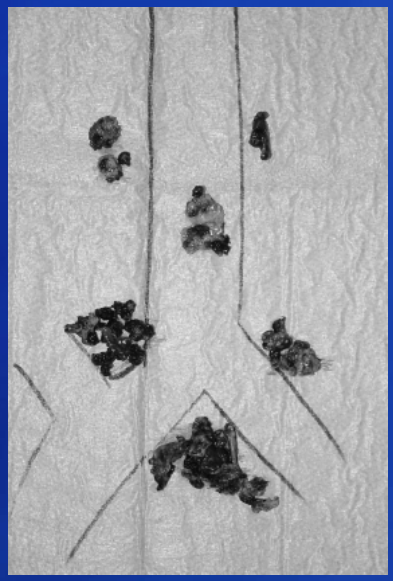


- *Ann Thorac Surg* 2011;92:1007-1011

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

VAMLA

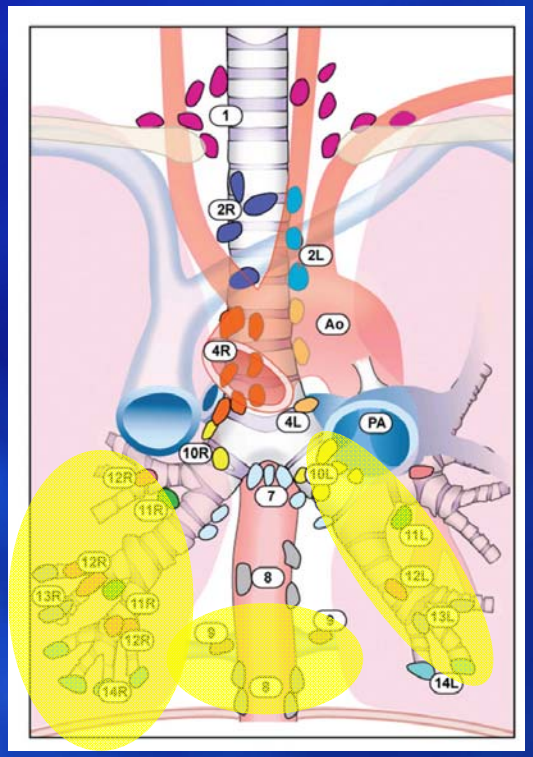


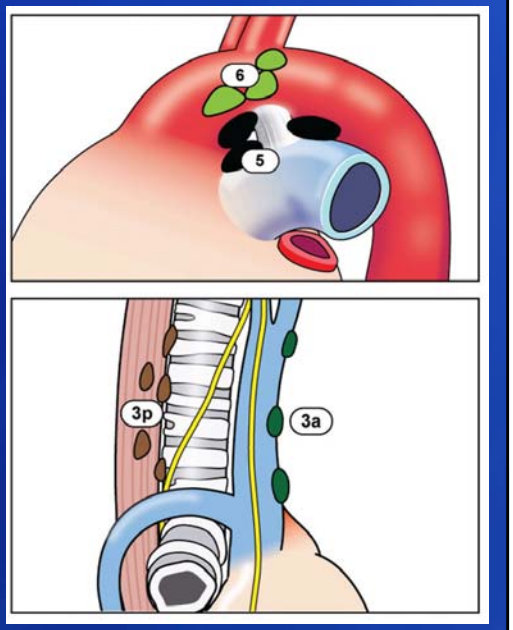
NCCN Webinar '2014

ROSWELL PARK CANCER INSTITUTE®

TEMLA - Technique

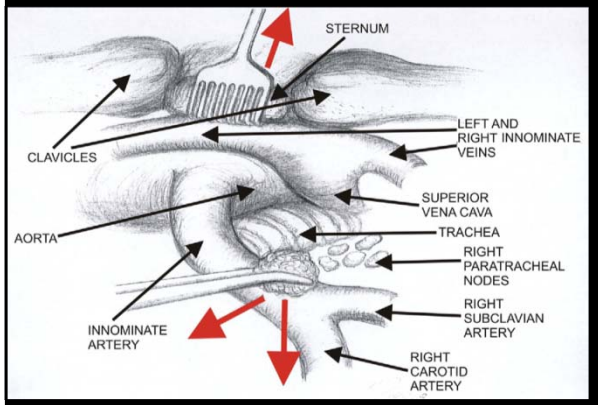
- 5-8cm collar incision
- Elevation sternum
- Nerves visualization
- All nodal stations except:

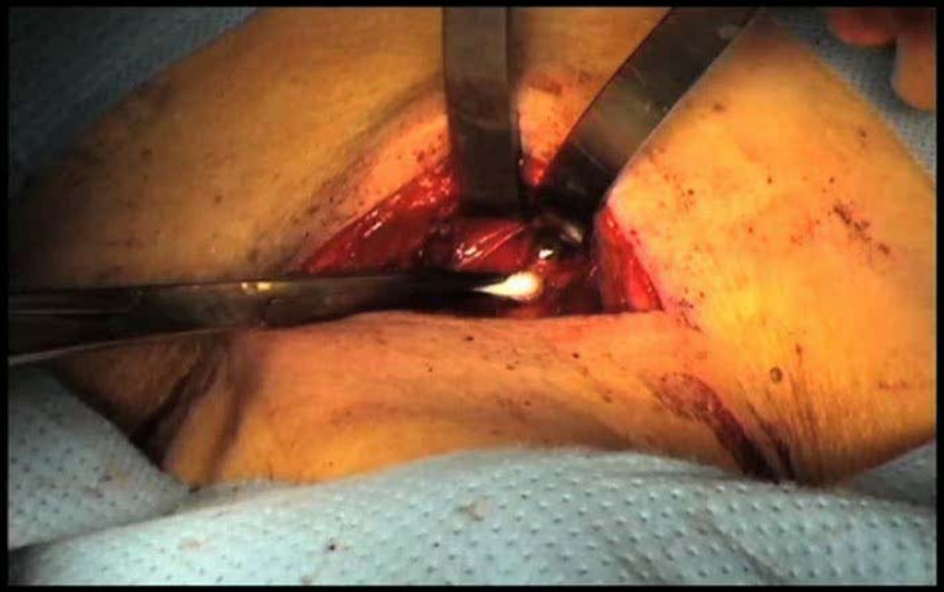




•*J Thorac Oncol. 2007;2: 370–372*

TEMLA





Zielinski Semin Thoracic Surg 22:236-243

•40sTemla

www.ctsnet.org

NCCN Webinar '2014

ROSWELL PARK CANCER INSTITUTE®

Summary

Endoscopic FNA

- Pros
  - Approaches Surgical Accuracy for Targeted Areas
  - Enables access to multiple cavities
  - No incision
- Cons
  - Fewer nodes/stations
  - Miss micro disease
  - Imaging dependent
  - Restaging may be more difficult

Surgical staging

- Pros
  - More nodal resection
  - More cytoreduction
  - Better for restaging
  - Potentially therapeutic
- Cons
  - Excessively invasive for certain stages

ROSWELL PARK CANCER INSTITUTE®

Summary 1

- **Mediastinoscopy is safe and effective for many lung cancer scenarios but not always applied**

•Current preference

Confirmation of Nodal Status before resection in medium risk non-induction patients (+/- EBUS)

Summary 2

- **TEMLA/VAMLA Preferences**

(1) Induction patients:

EBUS for staging,

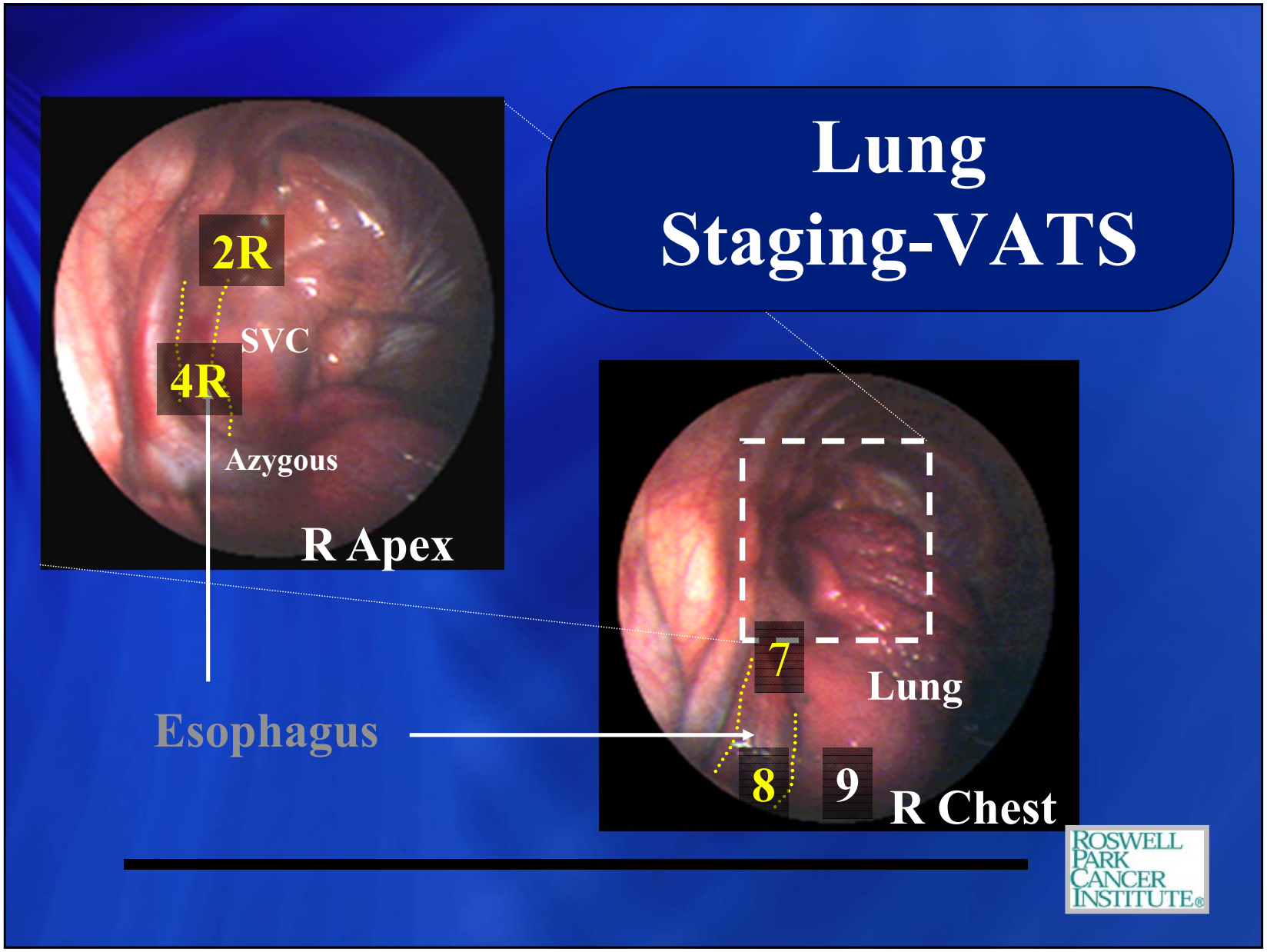
Then Chemo +/- XRT

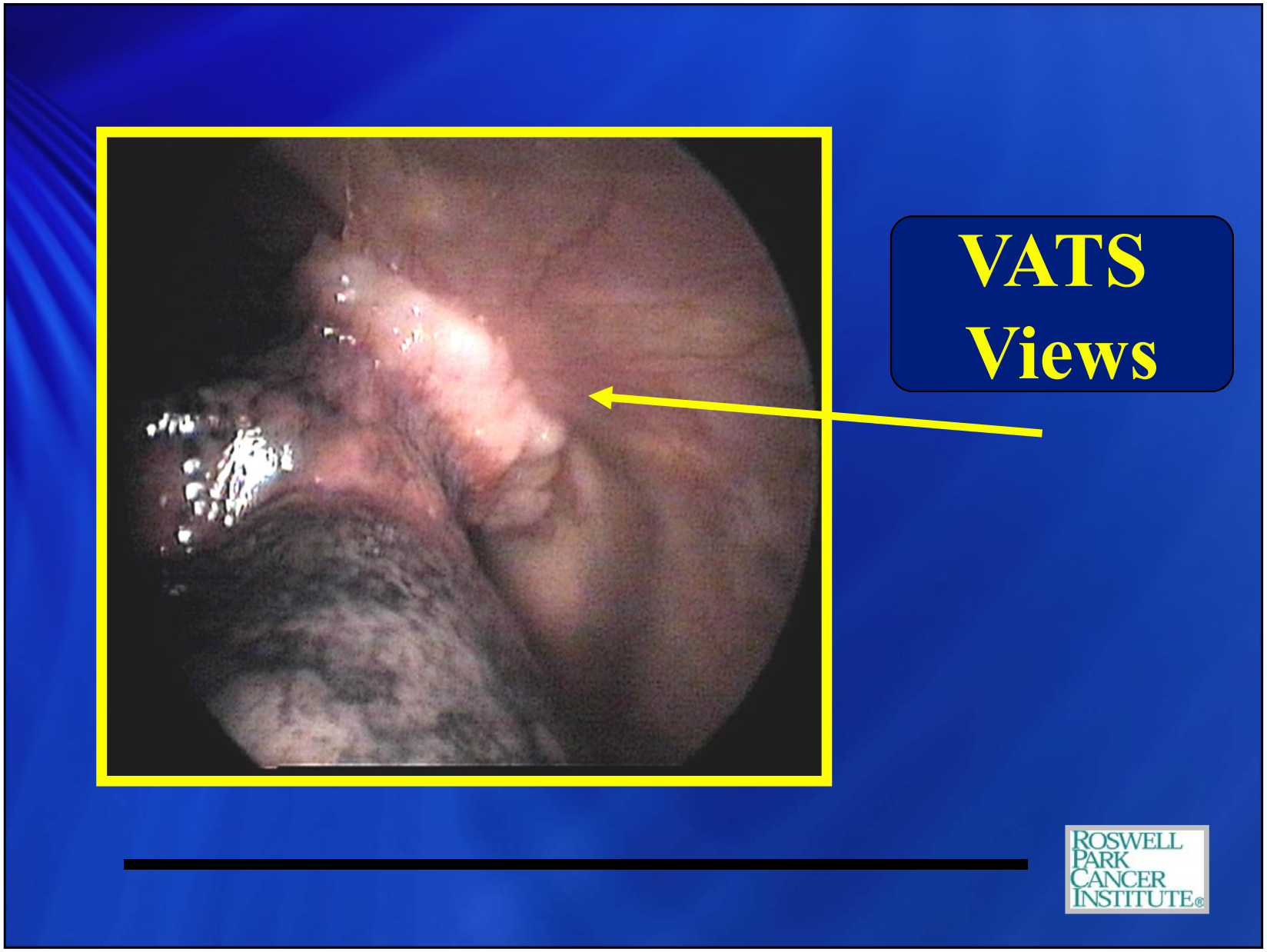
Then TEMLA/VAMLA at time of resection

VATS for the Level 5,6 modes

(2) Unfavorable biology patients

ROSWELL PARK CANCER INSTITUTE®

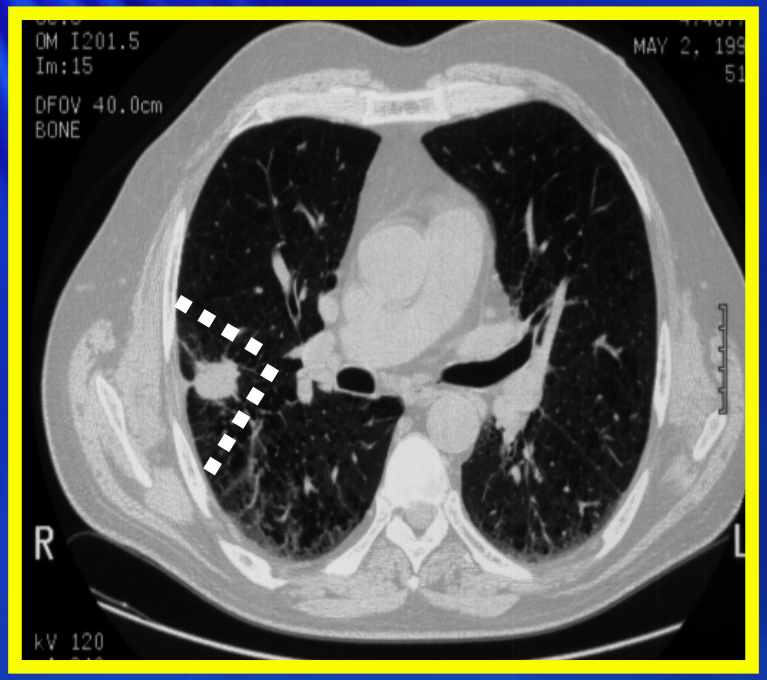


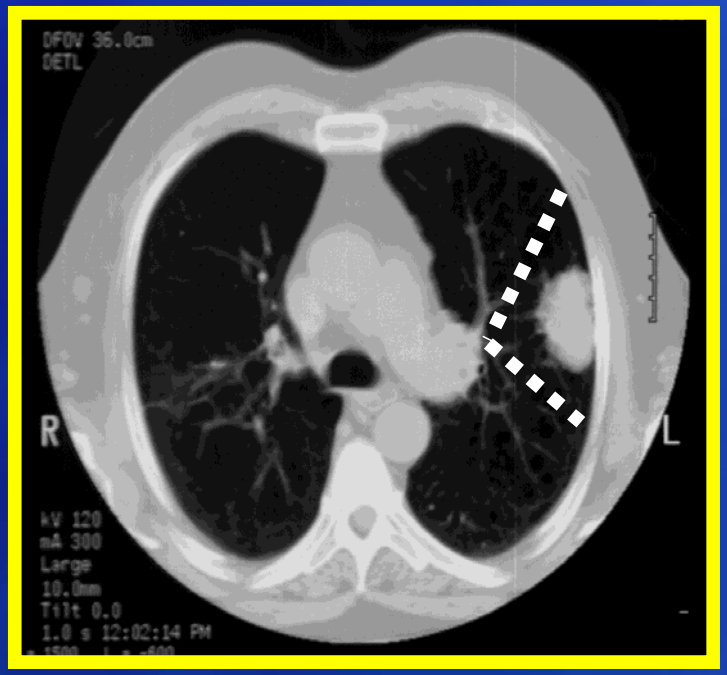


Factors Influencing More Aggressive Resection

- Nodule
  - High SUVmax
  - Large
  - Irregular borders
  - Central
  - Cavitation
- Technology
  - Less invasive
- Patient
  - Good PFTs
  - Anxiety
  - Risk factors

VATS Depth Considerations

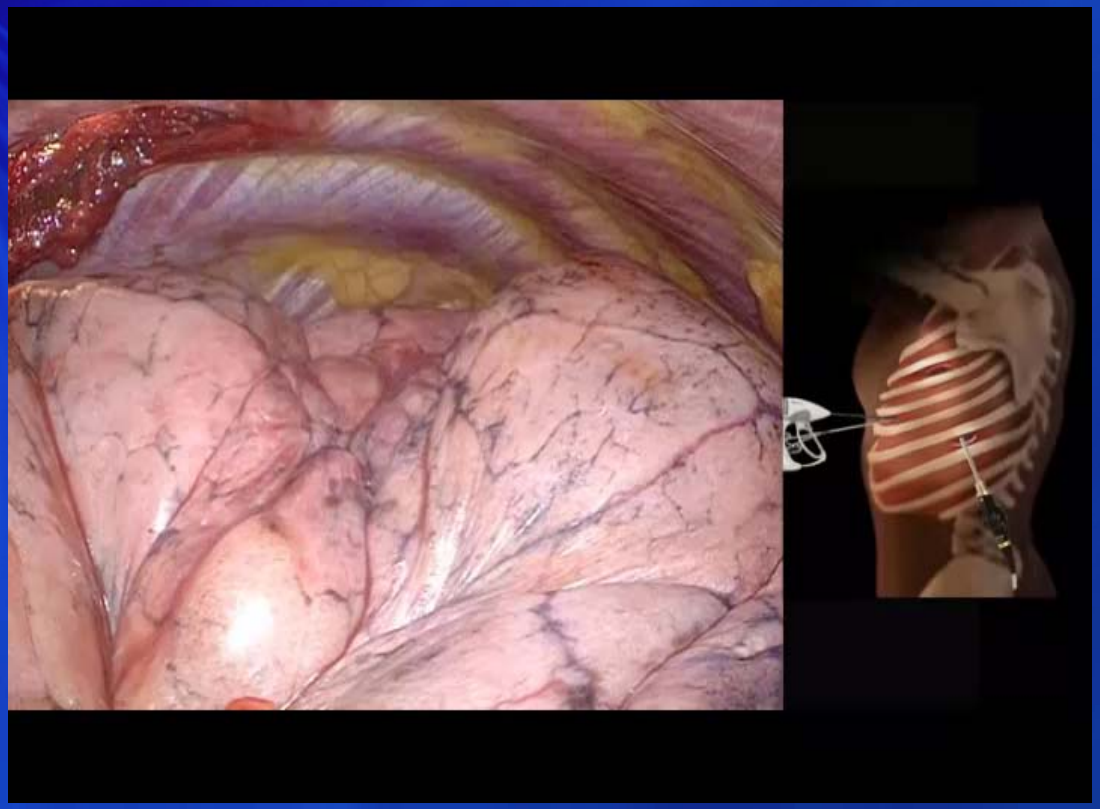




ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Typical Wedge

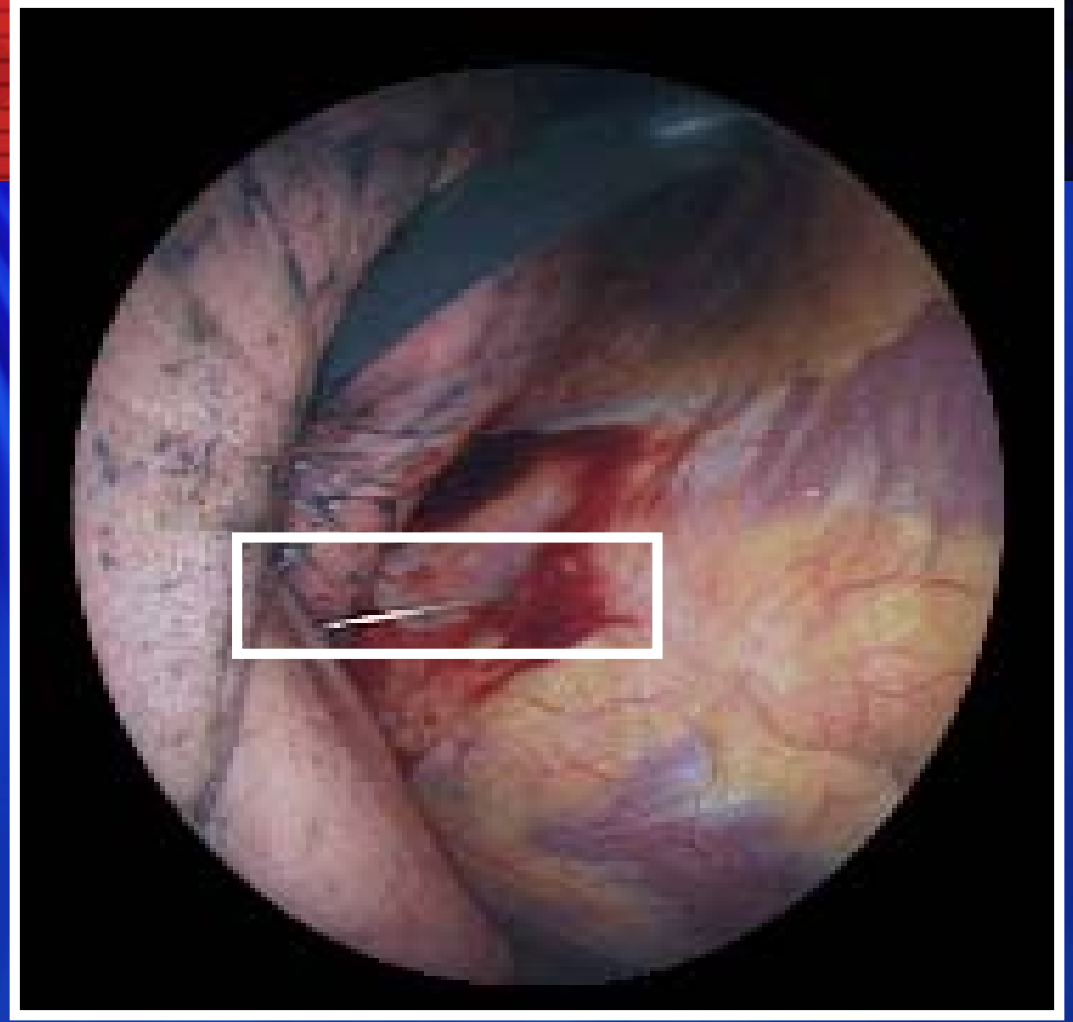


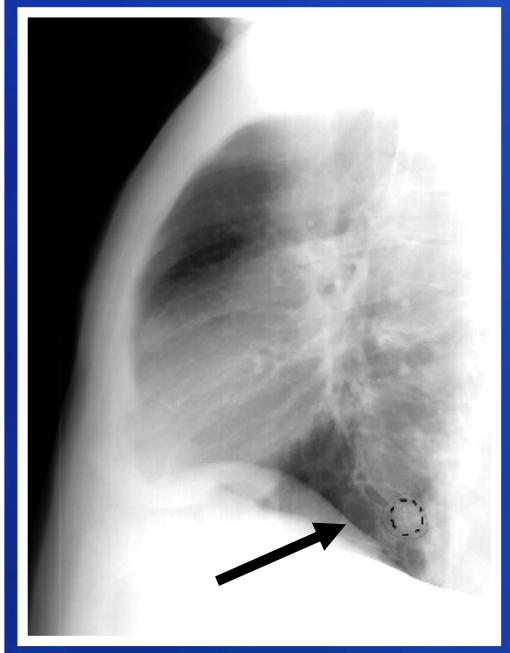
- LUL nodule 48sec

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Needle Localization

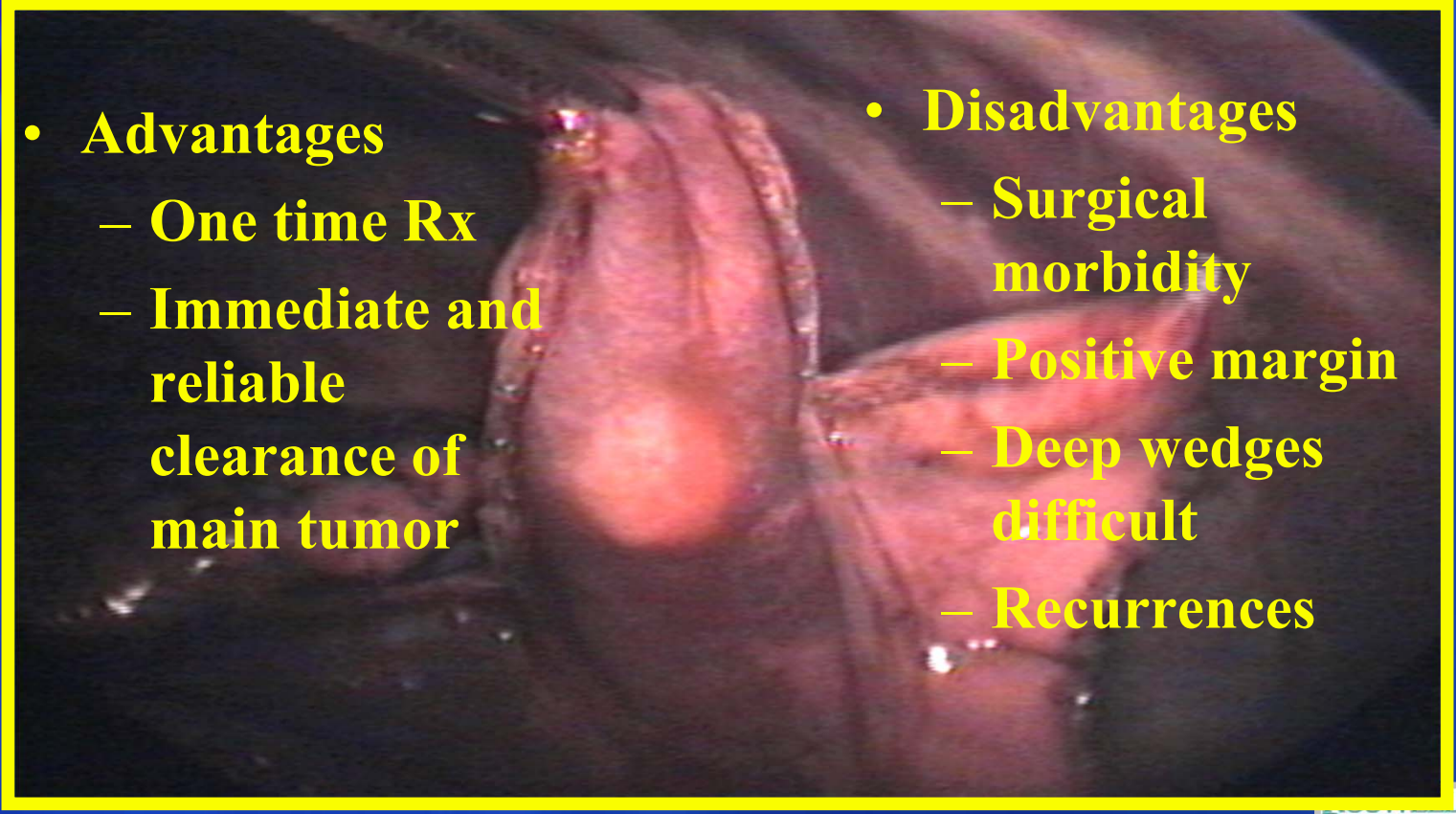




NCCN Webinar 2014

ROSWELL PARK CANCER INSTITUTE®

Thoracoscopic Wedge



- Advantages
  - One time Rx
  - Immediate and reliable clearance of main tumor
- Disadvantages
  - Surgical morbidity
  - Positive margin
  - Deep wedges difficult
  - Recurrences

PARK CANCER INSTITUTE®

NCCN Webinar 2014

National Comprehensive Cancer Network®

Slides Presented by Dr. Cheney

Tissue Acquisition in NSCLC: Pathology Perspective

Guidelines for Tissue Acquisition

- Multidisciplinary Approach
- Collaboration between surgeon, interventional radiologist/pulmonologist, medical oncologist and pathologist
- Everyone on the team needs to know why the patient is being biopsied!
- What is best technical approach for tissue acquisition?
- Who should acquire sample?
- What type of sample should be acquired? FNA, Core Bx, Wedge, ?

- If therapy is going to be determined by a test(s) result, then a high quality, representative biospecimen is required for testing
  - Not all tissue samples are equal!!
- Pre-analytical variables (ischemic time, fixation type/length of fixation, storage conditions, freeze/thaw, etc.) impact clinical suitability of biospecimen
- Tissue quality control documentation is essential for accurate molecular testing (CAP guidelines requirement)
  - % tumor (vs stroma/necrosis)
  - Fixation time

Goal

- **1⁰ concern** is to ensure that biospecimen(tissue sample) is adequate for;
  - Diagnosis (Adenocarcinoma vs SCC vs other)
    - Immunohistochemistry (limited panel)
  - Molecular testing

Immunohistochemistry

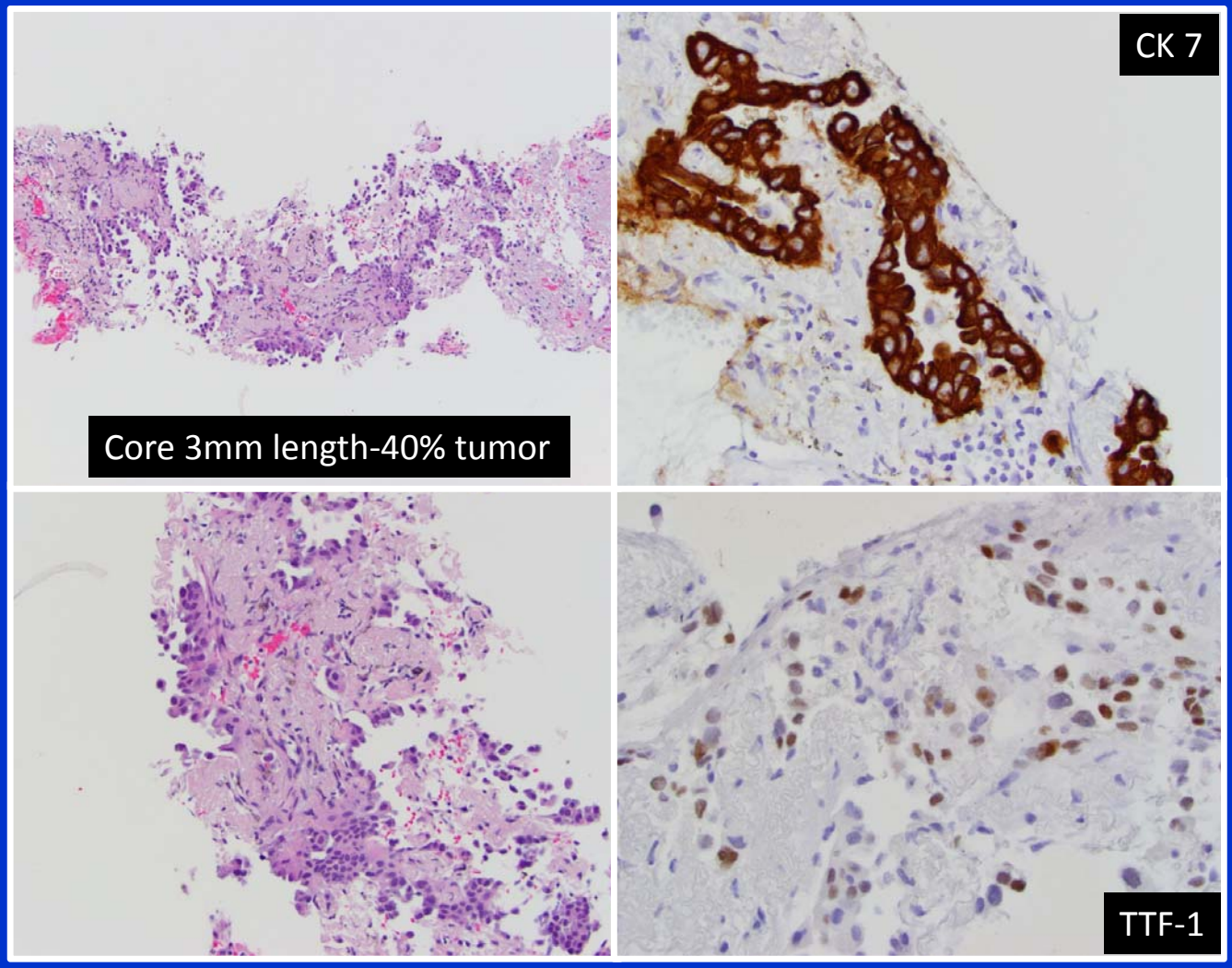
- Defines histologic type- Adenoca vs SCC vs other
- Distinguish 1^0 lung Ca from met/mesothelioma/other
- Use IHC judiciously, **minimalist*** approach(requires knowledge of clinical setting- eg., no hx of colon ca, probably no need to do CK20!)
- **IHC panel- TTF-1, p63/p40, CK5/6, +/-mucicarmine**
  - Adenoca- TTF-1 +; muci +/-; (Napsin +)
  - SCC- p63/p40, CK5/6 +
  - Neuroendocrine- CD56, Synaptophysin, Chromogranin, NSE

- ***NB- if your path report has 2 pages of IHC results there may be a problem!**

Case

- Hx- 52y/o smoker, pleural effusion, RUL nodule
- CT guided core needle bx RUL

Pathology (limited IHC panel)



Adenocarcinoma- CK7/TTF-1 +; **EGFR mutated**

Tissue Sample Acquisition

- Rapid On-Site Evaluation (ROSE)
  - OR, Endoscopy, Radiology suites with **on-site lab** or mobile cart
    - Requires cytotech/lab aide, cytopathologist/fellow
    - Lab- reagents, microscope, PC, etc
  - Remote ROSE (where, how)
- Intraoperative- standard approach
  - Frozen section/touch preps
  - Turn Around Time-15-20 min/specimen

ROSE

- Advantage(s)-real time assessment of tissue sample;
  - Determine specimen adequacy for Dx and ancillary studies
  - Increases sensitivity/specificity over blind approach-⬇ # of passes
    - Type of lesion sampled, size, and **operator skill/experience**
  - Triage sample as needed if not Ca
    - Flow cytometry (lympoproliferative), microbiology(infectious)
  - Rapid Dx (ie., immediate Tx for SVC syndrome)
  - **Education component-** enhances dialogue between endoscopist and pathologist increasing endoscopist understanding/correlation between what they see/feel and histologic reality
    - Endoscopist " I am **absolutely certain** I am in the mass !"
    - Pathologist "You are, but it is just fibrous stroma & inflammation-no tumor cells are present"

ROSE (cont.)

- Disadvantage(s)
  - Cost - requires personnel-
    - lab aide/cytotech/cytopathologist (Fellow)
  - Time commitment- can be lengthy process, interferes with other pathology duties
  - Fixed location of off site lab- additional expense for reagents, equipment, etc.
    - Mobile carts with microscope, reagents, etc.- may be suboptimal
  - Reimbursement- not truly reflective of effort!
    - First pass, immediate assessment of each unique site- (CPT 88172 $43)
    - Additional passes, same site with immediate eval of each pass (CPT 88177 $22)

ROSE

Does rapid on-site really have to be on-site?

- **Options**
  - **Non-pathology** personnel prepare smears on-site with real time transport to Pathology for staining/interpretation
    - Proper smear prep requires education, experience, and feedback to develop consistency and quality (generally **not an optimal solution)**
    - May be successful if limited # of personnel involved
      - ie., Same person preparing smear all the time

ROSE-Telecytopathology Option

- ❖ Static (still image),dynamic (real time viewing), whole slide imaging

- Process
  - On-site cytotech/lab aide prepares/stains smears, employ dynamic imaging system on-site to transmit image over network to cytopathologist office for review/preliminary Dx

- Advantages
  - Difficult cases can quickly be reviewed by several cytopathologists
  - Multiple cases from different locations can be viewed by 1 pathologist rapidly
  - Decrease work flow interruption for cytopathologist; no off site work or travel time

- Disadvantages
  - Requires skilled tech on-site
  - Cannot remotely control field viewed or magnification easily
  - Cost- depending on system maybe up to $25-50K
  - May not have optimal interaction between endoscopist & cytopathologist

- Concordance (Telecyto vs traditional on-site cytopath) Final Dx >97%
- Diagnostic accuracy vs traditional on-site- (1-3 % non-Dx by either method)
- No increase in # of passes to obtain diagnostic tissue with Telecytopath approach
- Cytopathologist Evaluation time- Telepath 7.5-12 min/case; may be up to 50 min for traditional on-site(includes travel, on-site waiting time)

Remote ROSE Option

- Rapid transport of on-site prepared smear (cytotech/path lab aide) to central lab for staining/interpretation
  - via Pneumatic tube (1-3 minutes) or dedicated “runner”
- Advantages
  - Control quality of smear(not thick/dried, etc)-prepared by path
  - Adjust staffing for volume (prep only and/or interpretation)
    - Eg- if more than 1 sample sent, can temporarily deploy additional techs/cytopathologist rather than sending additional personnel to remote endoscopy site if done on-site
  - Consistent turn around time (approx. 8-10 min/pass)
  - Difficult cases can be reviewed by other cytopathologists
- Disadvantages
  - Requires mechanism for rapid transport of smear (tube, runner?)
  - Still need on-site prep personnel to prepare smear
  - Does not enhance communication with endoscopist

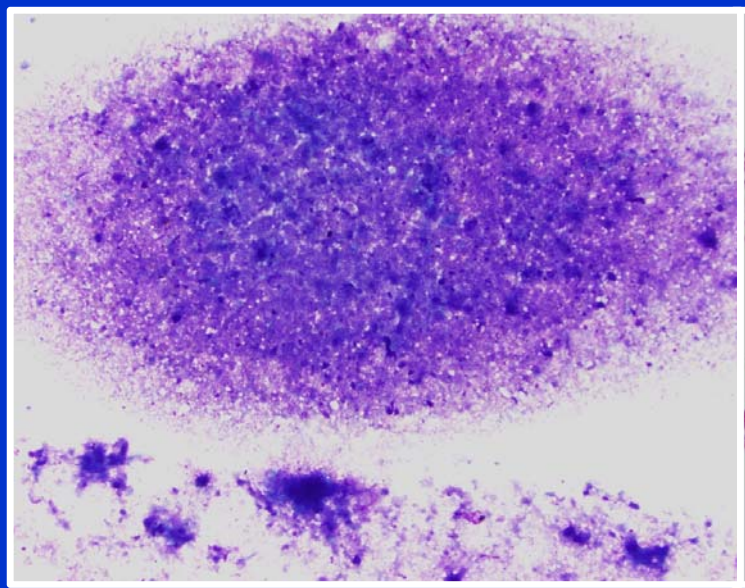
To ROSE or Not?

- Method selected depends on resources-need to individualize
  - Staffing- # of cytotechs/lab aides, cytopathologists
  - Endoscopy Volume
  - Physical space availability at site
    - Proper lab space vs re-designed closet?
  - Cost fully allocated -personnel, equipment, reagents, imaging systems, **Endoscopy/OR suite operating cost/min**
  - **Clinician preference** ****

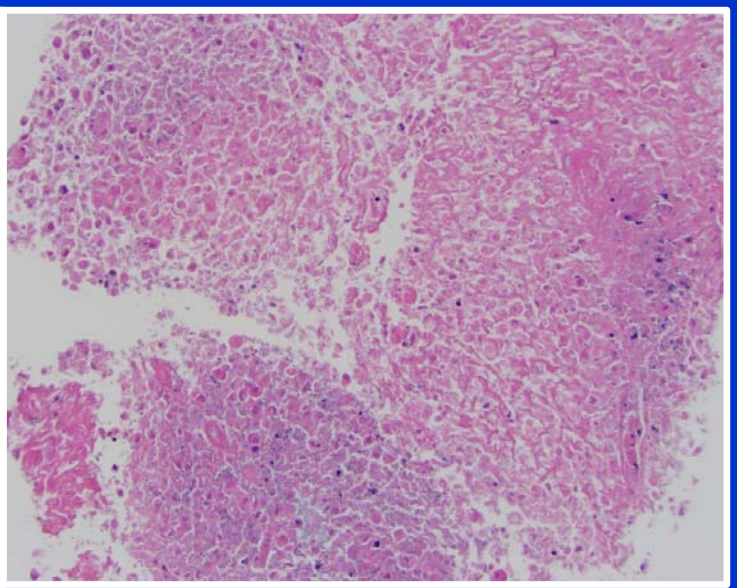
Tissue requirements for Molecular testing

- Depends on
  - tumor composition (prefer >50% tumor)
    - % tumor nuclei
    - % necrosis
    - % stroma/inflammation
  - Sensitivity of molecular test
    - PCR based assay, sequencing (NGS)
    - FISH (as few as 50 cells)
- Sampling size-problematic, not entirely predictable
  - EBUS minimum of 4 passes
    - (ref. Optimizing Endobronchial Ultrasound for Molecular Analysis. How many passes are needed? Yarmus et al. Annals ATS 10:6; Dec 2013)
  - Cores (determined by diameter of needle)
    - 2-3 for 14 guage; 4 for 21 guage
- More to follow in subsequent webinar- Dr. Chireac, Brigham and Women's

RUL Mass- CT only



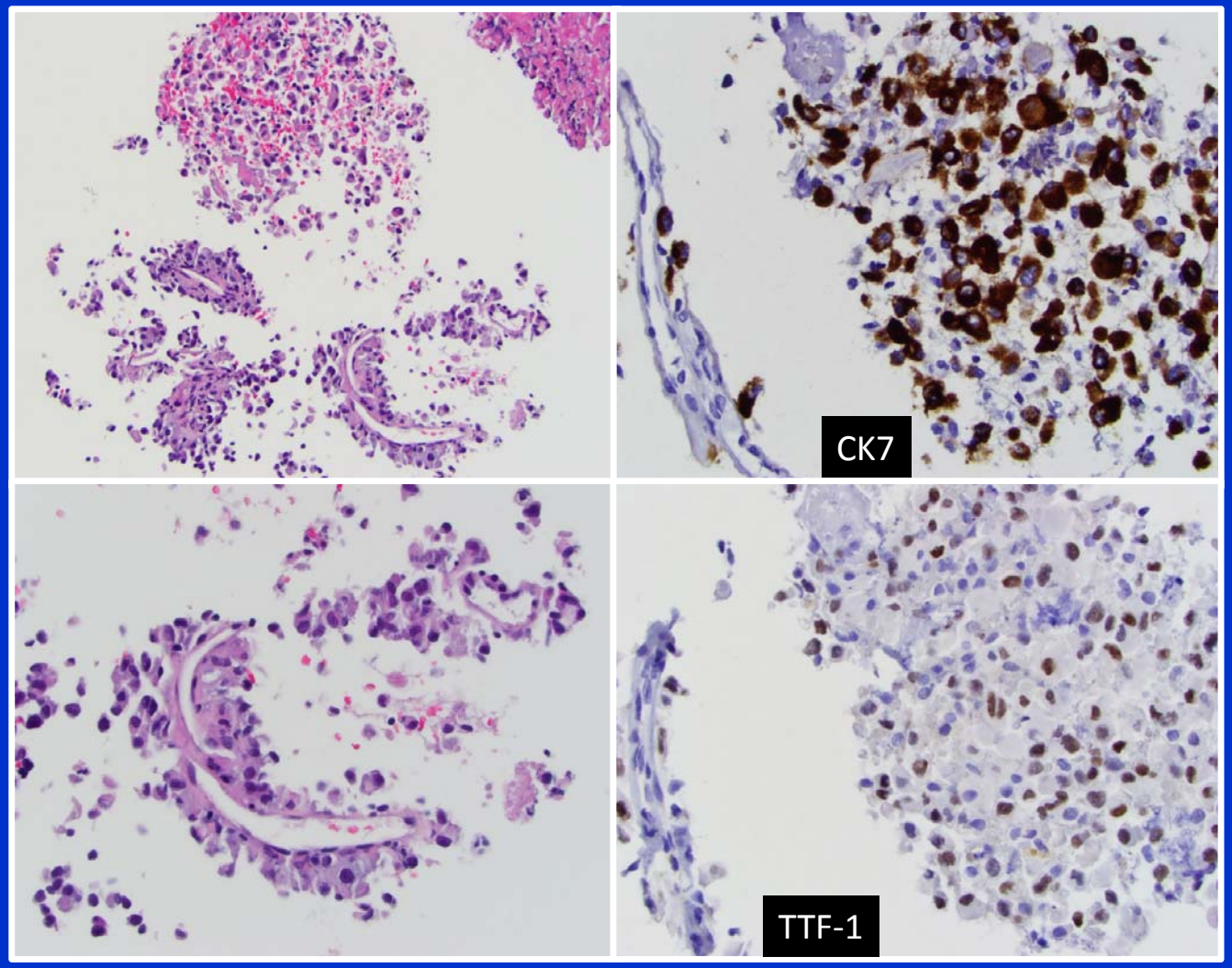
Touch Prep of Core Bx
Diff Quick Stain



Necrotic Tumor- non diagnostic

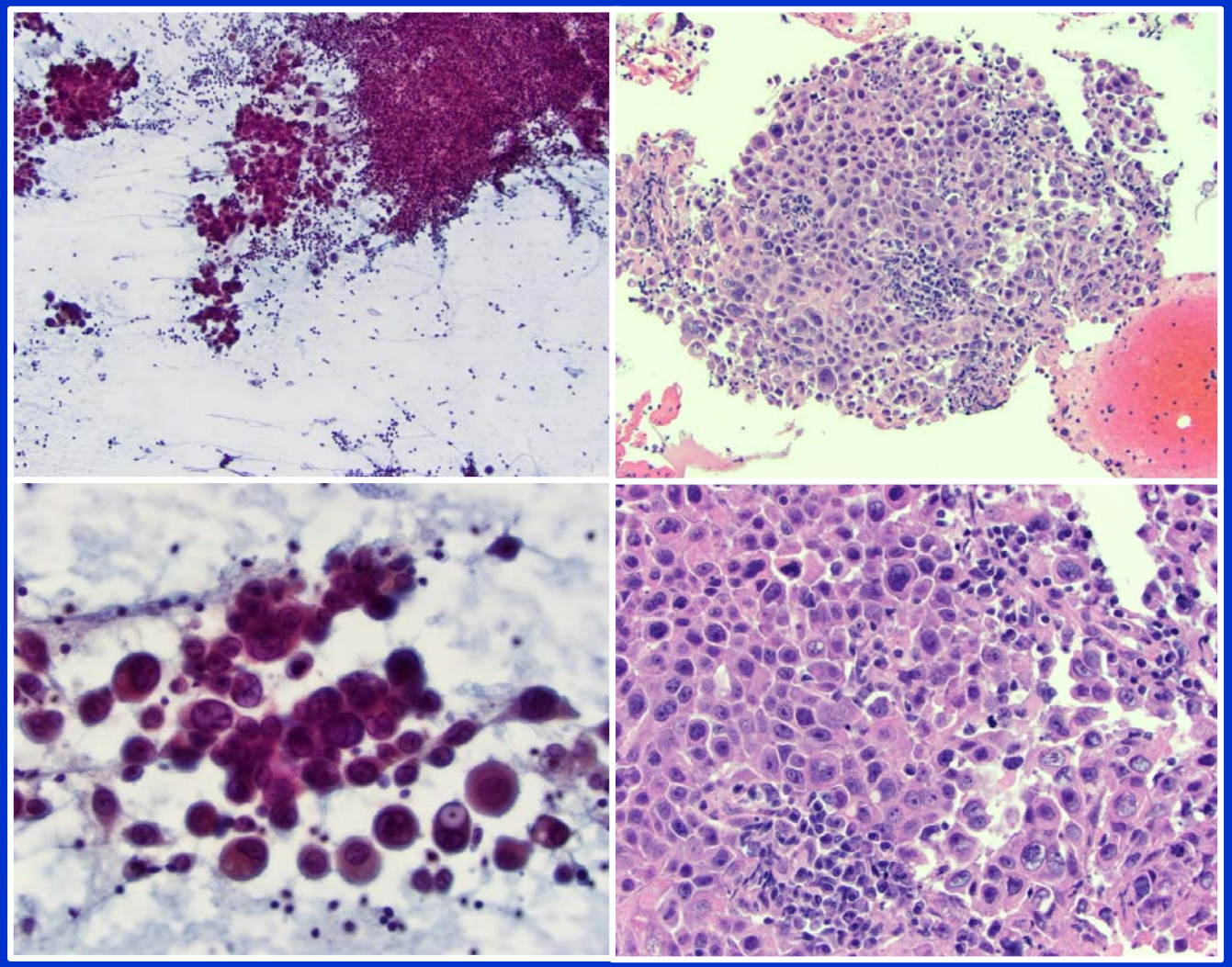
Unsatisfactory for Dx/Molecular

RUL CT-PET guided



Dx: Adenocarcinoma, Well Diff; EGFR wild type

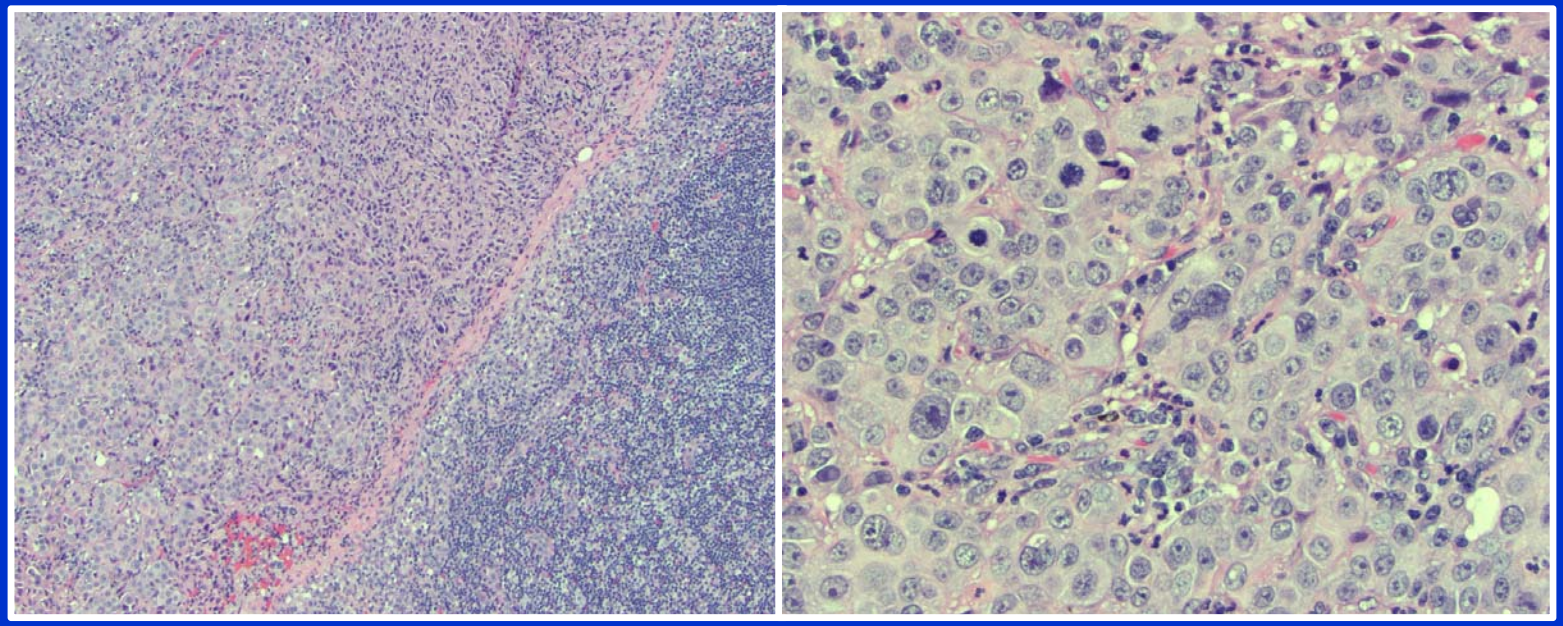
EBUS 4R LN



Smears

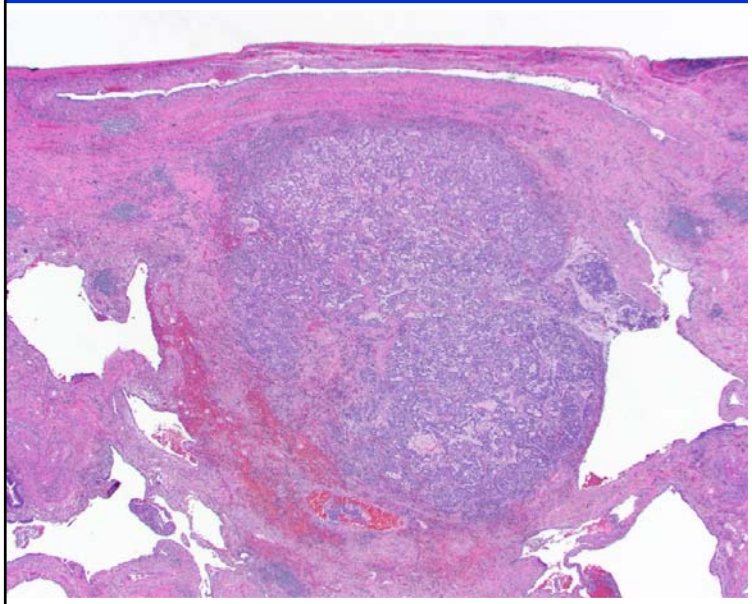
Cell Block -FFPE

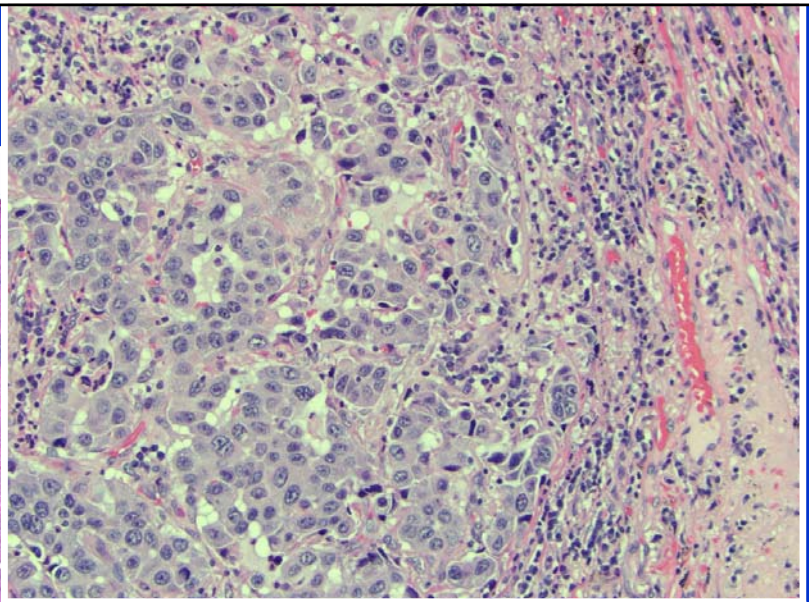
TEMLA

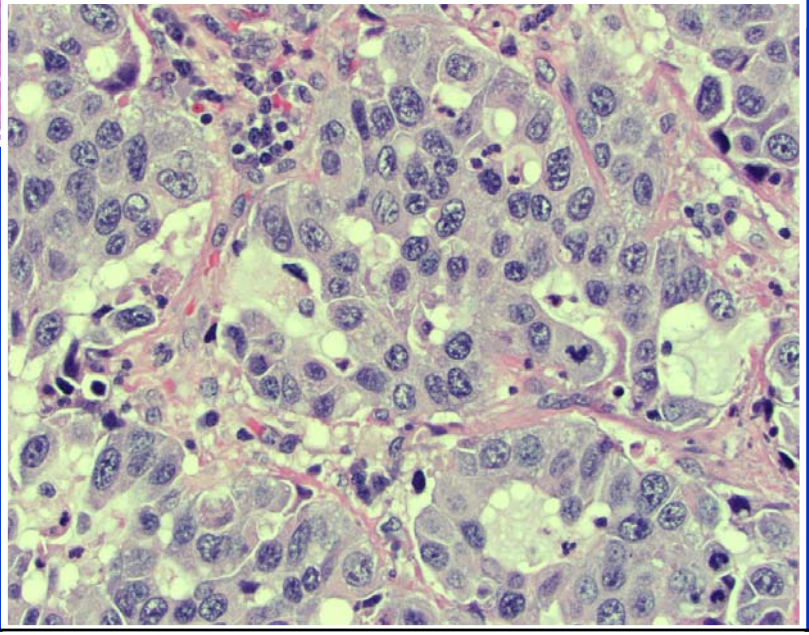


4R LN

Wedge Resection LUL



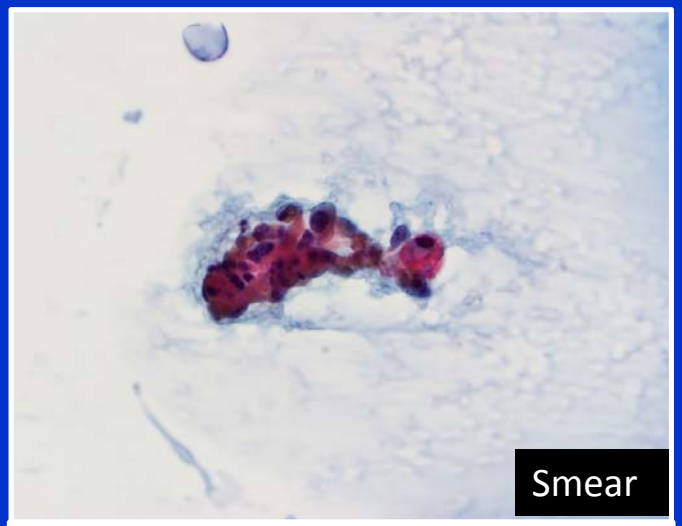


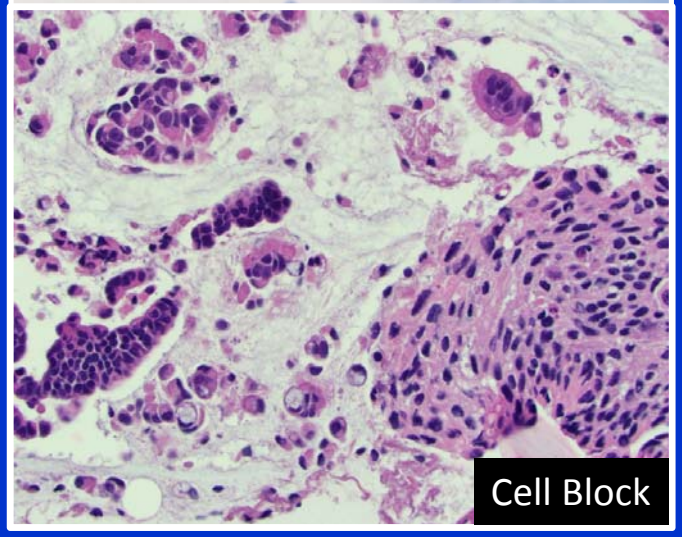


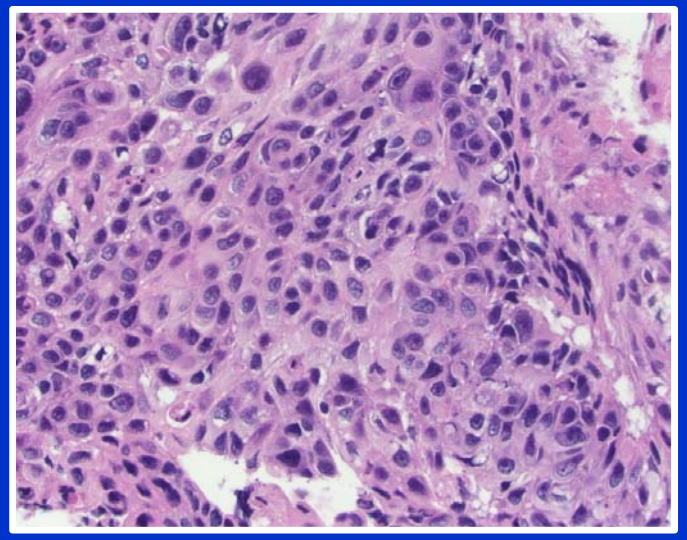
Dx: LUL, Wedge Resection:
Invasive Moderately Differentiated Adenocarcinoma, Predominantly Acinar Type,
Dimensions- 1.0x 0.9 x 0.9 cm

Stage- pT1a N3

Super D (Navigational Bronch)

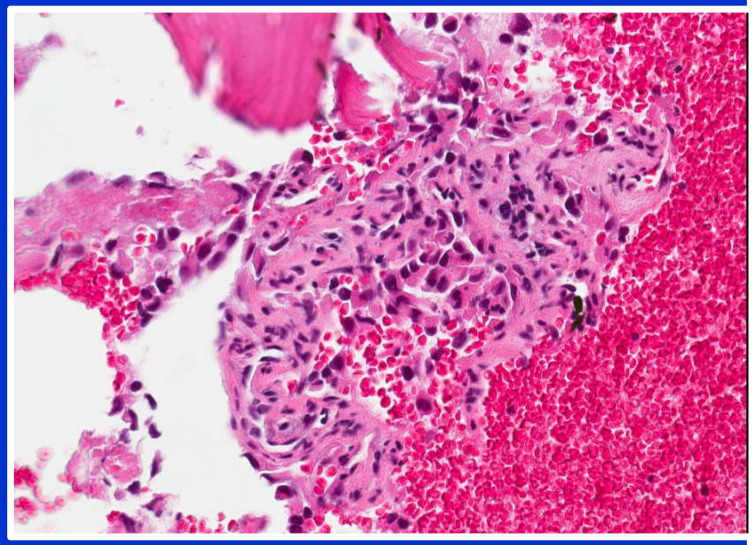


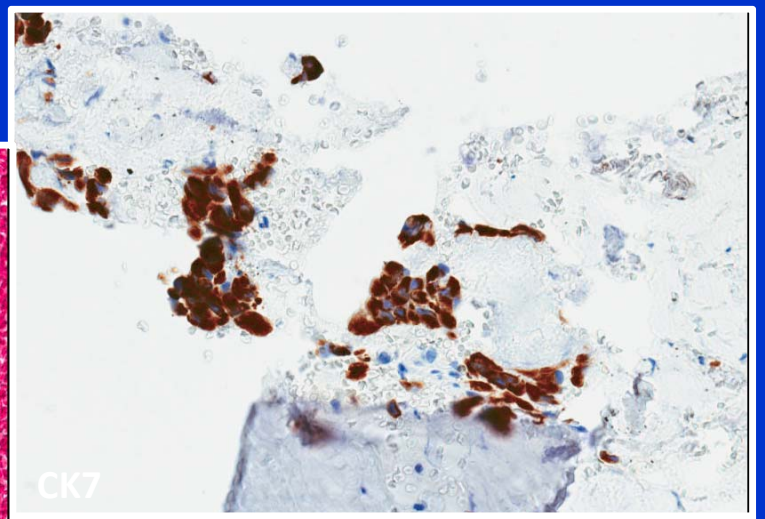


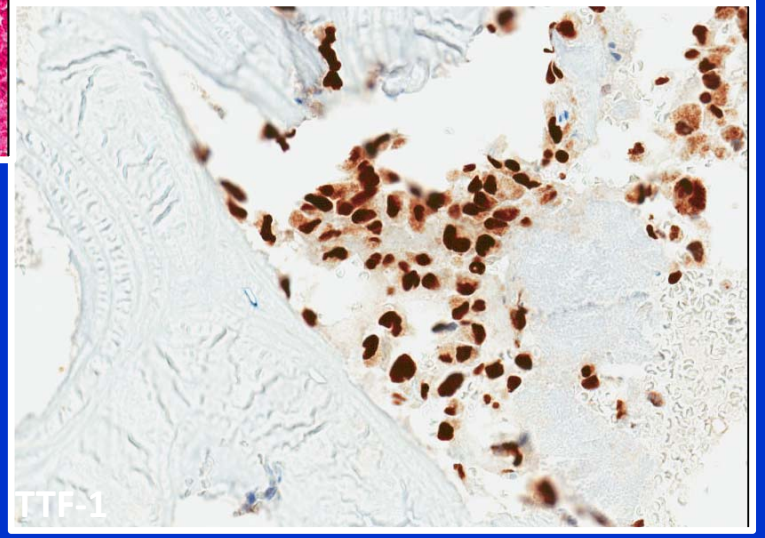


RLL, Navigational Bronchoscopy Biopsy: Squamous Cell Carcinoma, Moderately Differentiated

T2 Spine met



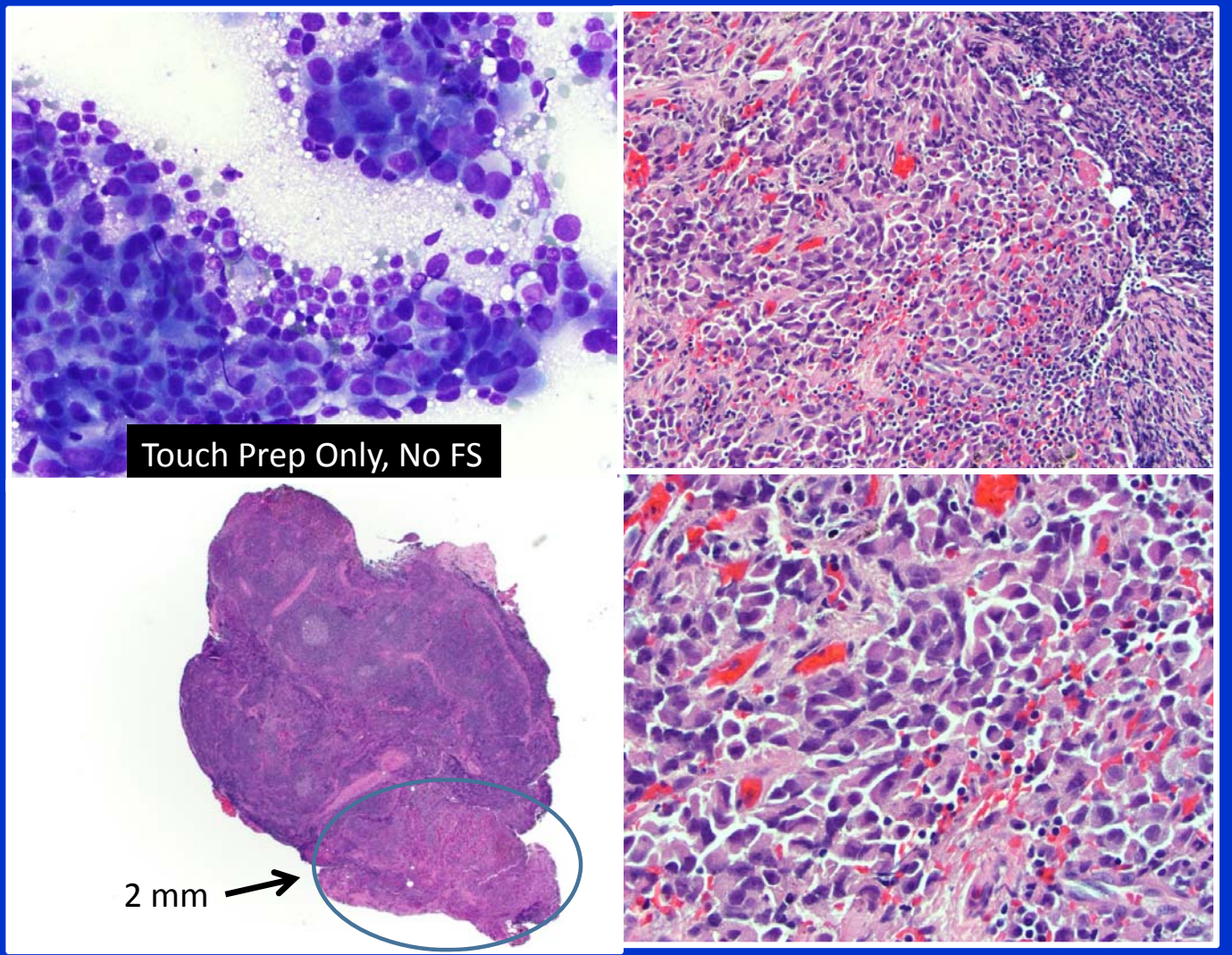




FNA Spine Met at T2
CK7/TTF-1 +

Diagnosis: Metastatic Adenocarcinoma c/w Lung Origin

Mediastinoscopy



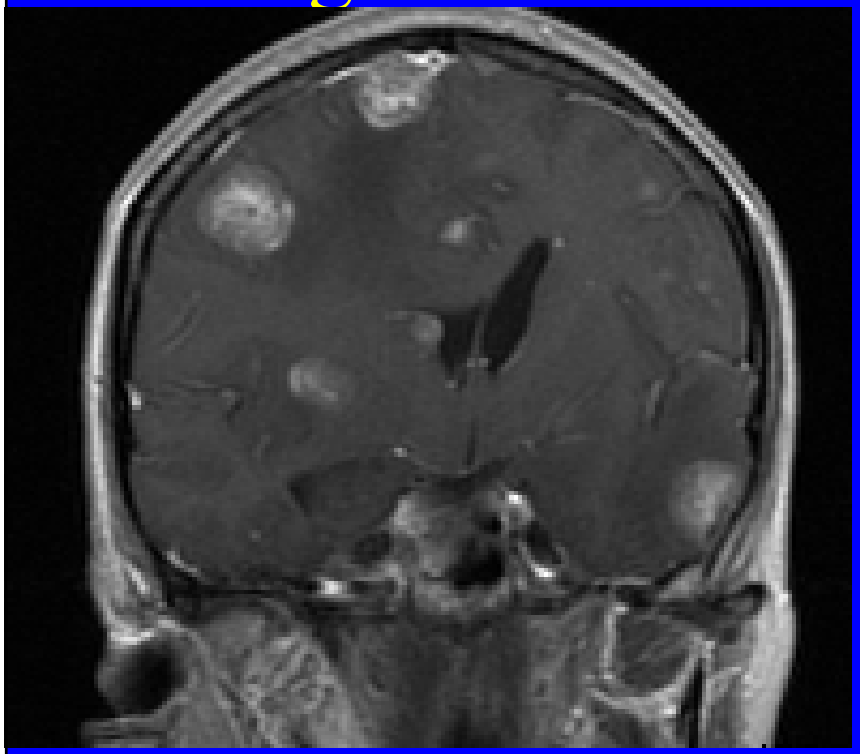
Dx: Metastatic Adenoca c/w lung primary; ALK neg

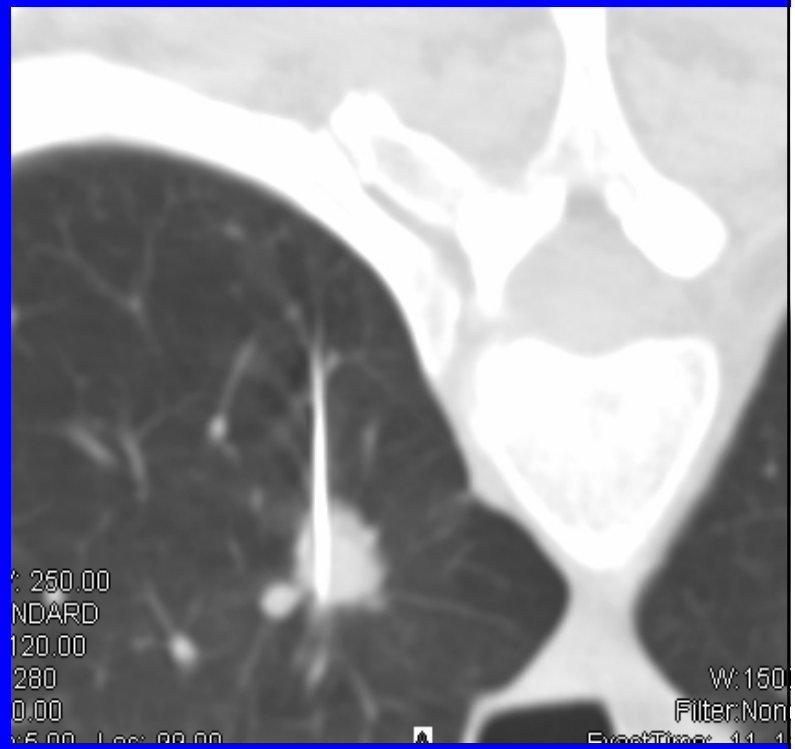
National Comprehensive Cancer Network®

Slides Presented by Dr. Loud

Image-Guided Percutaneous Tissue Acquisition in Lung Cancer

Female with multiple brain metastases and 10 mm lung nodule CT-guided Bx: small cell carcinoma





Roswell Park Radiology

- 5-6K interventional radiology procedures/yr.
- 250-300 image-guided lung biopsies/yr.
- Most CT-guided. Peripheral lesions can be U/S-guided

Indications for lung biopsy

- Benign vs. malignant (lung Ca vs. metastasis)
- Primary lung Ca – tissue type, aggressiveness
- Selection criteria: Size, appearance, growth, PET positivity, clinical scenario/risk-benefit balance

Contraindications to lung biopsy

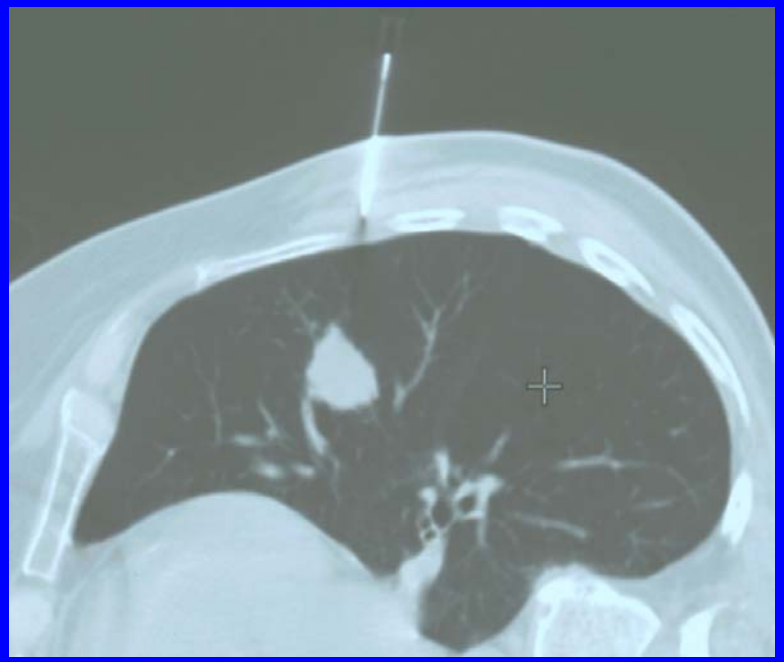
- Uncorrectable coagulopathy
- Inability to cooperate
- Risks outweigh benefits
- "Don't touch" lesions (hamartoma, AVM, suspected infection, infarct, granuloma)
- Is there a metastatic site to biopsy? To allow simultaneous dx and staging

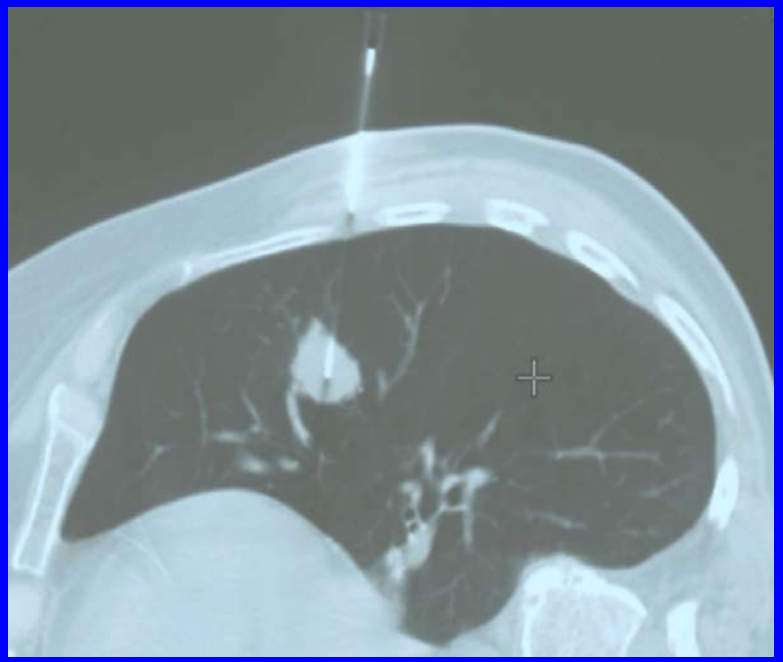
Molecular Studies

- Routinely performed for > 1 year
- Adequate tissue volume vital – core biopsies preferred
- On-site cytologic evaluation!

CT-guided lung biopsy

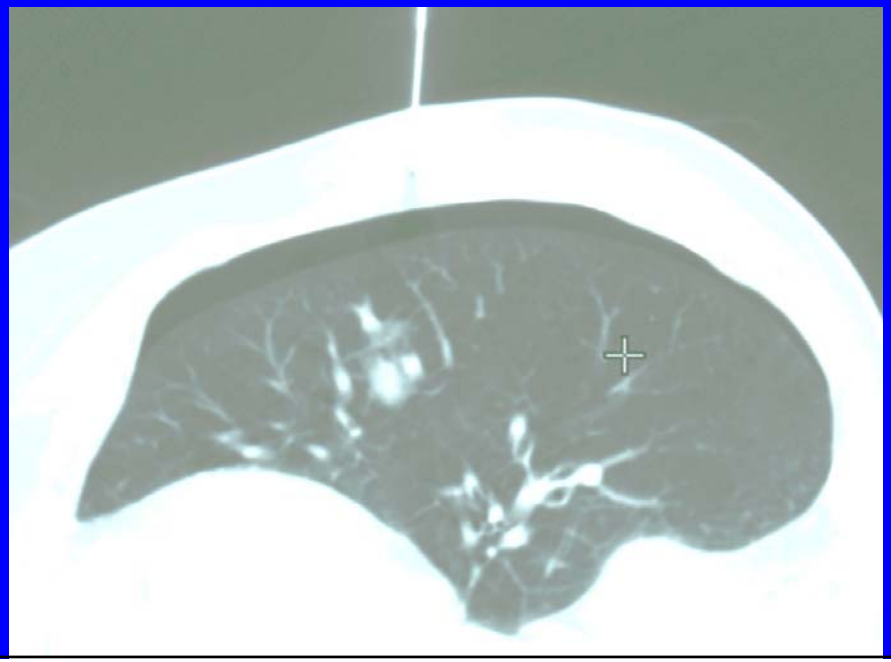
- Position patient. Conscious sedation
- Prep, anesthetize, and place coaxial needle
- Confirm position - advance biopsy needle





CT-guided lung biopsy

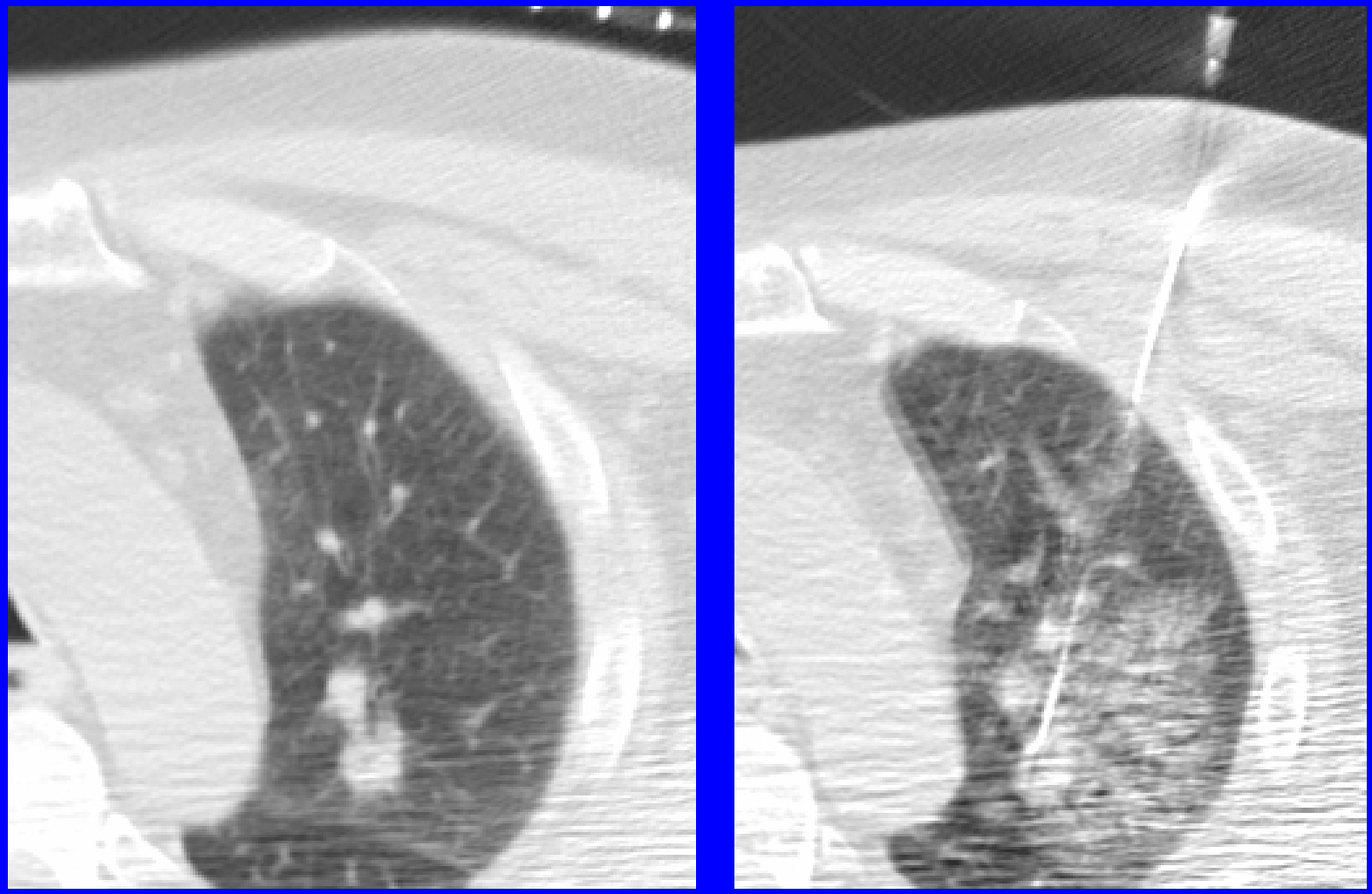
- Confirm adequacy of pathologic sample at the time
- Check for complications (post-bx scan, CXR, monitoring)



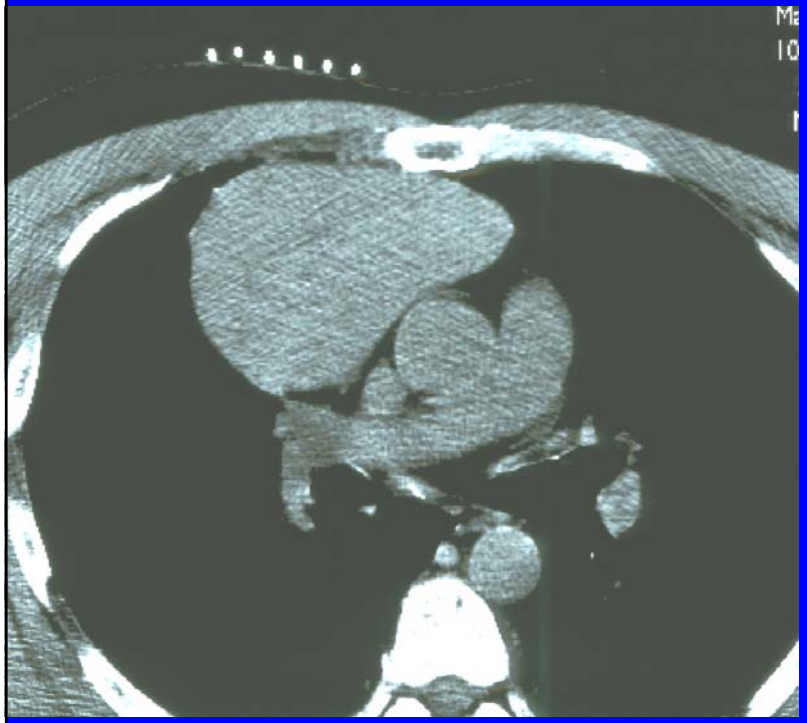
Complications of lung biopsy

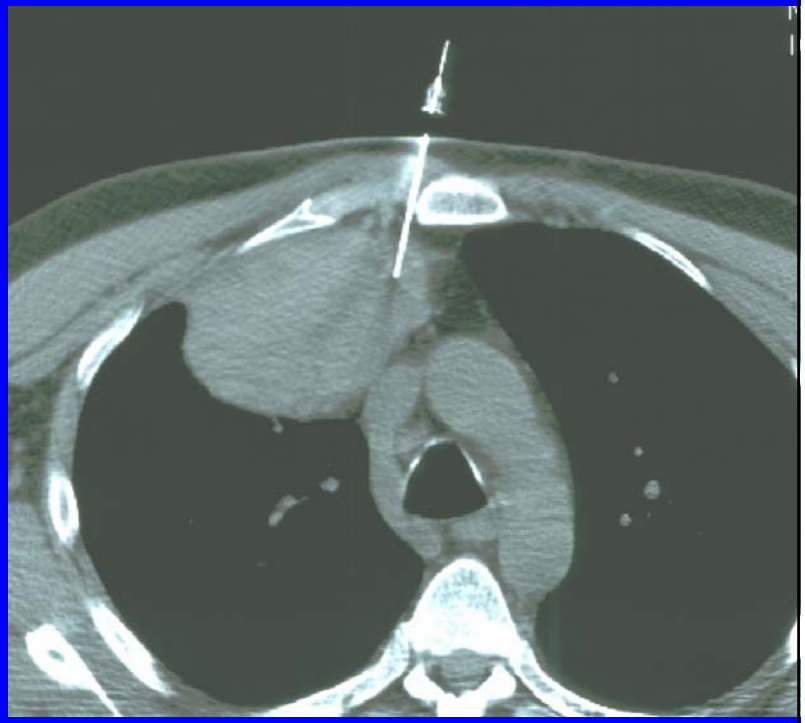
- Pneumothorax 20-25%. If large or symptomatic may require small caliber chest tube placement for management
- Pulmonary hemorrhage or hemothorax
- Air embolism or infection – rare

Pulmonary Hemorrhage

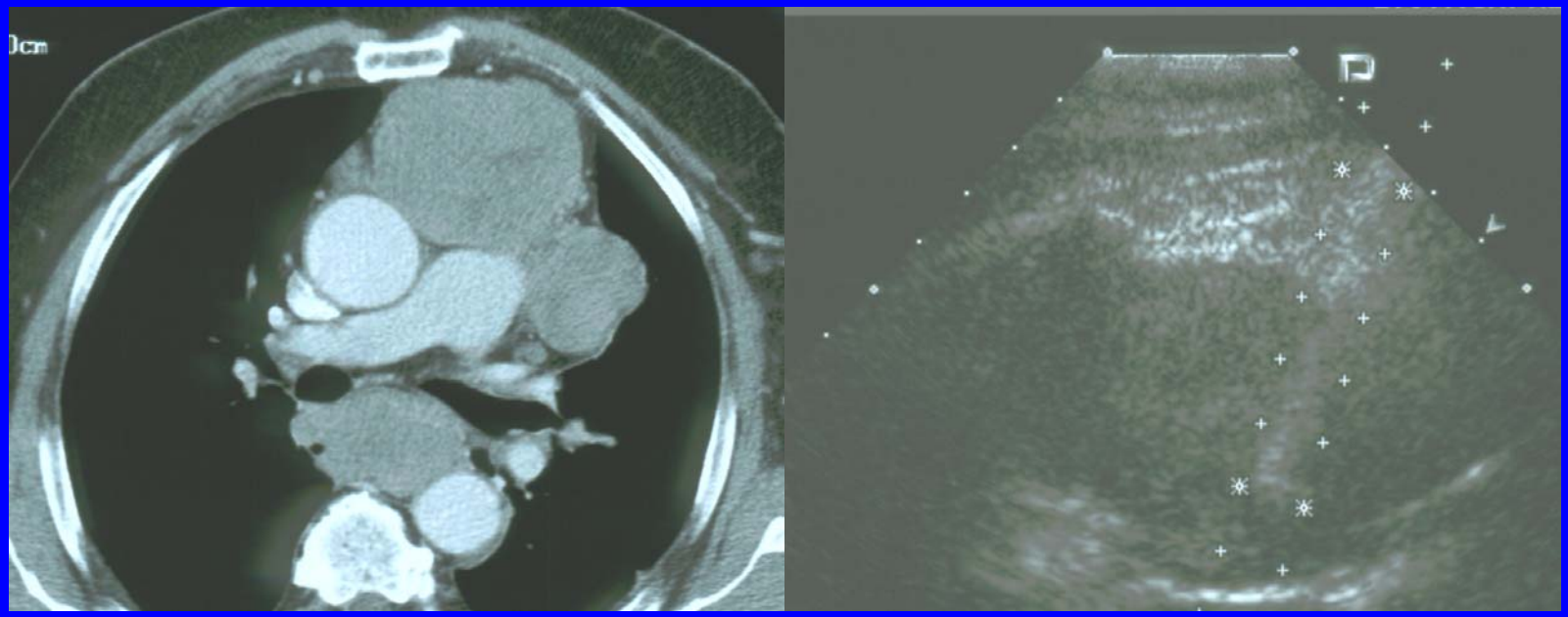


Mediastinal Biopsy

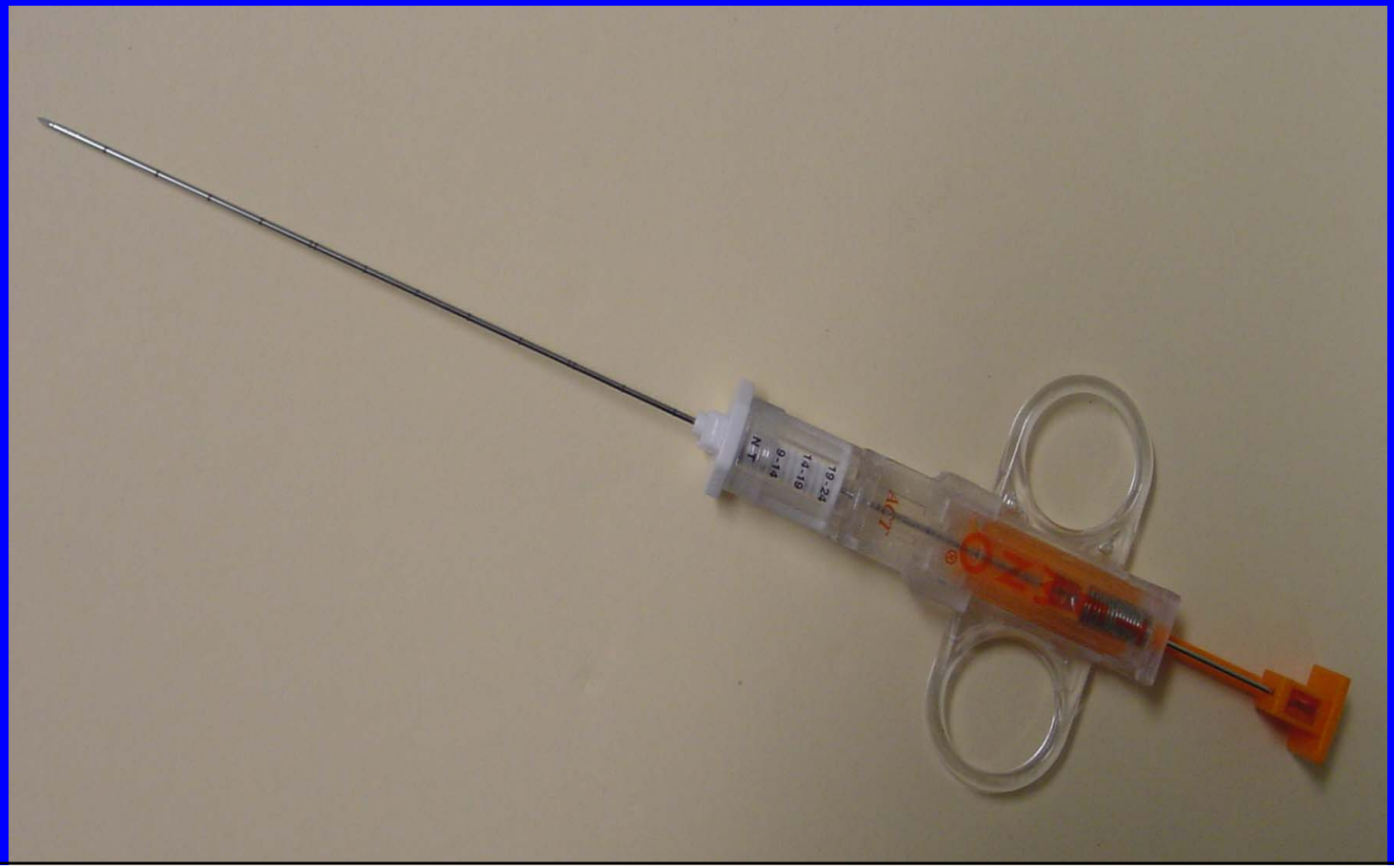




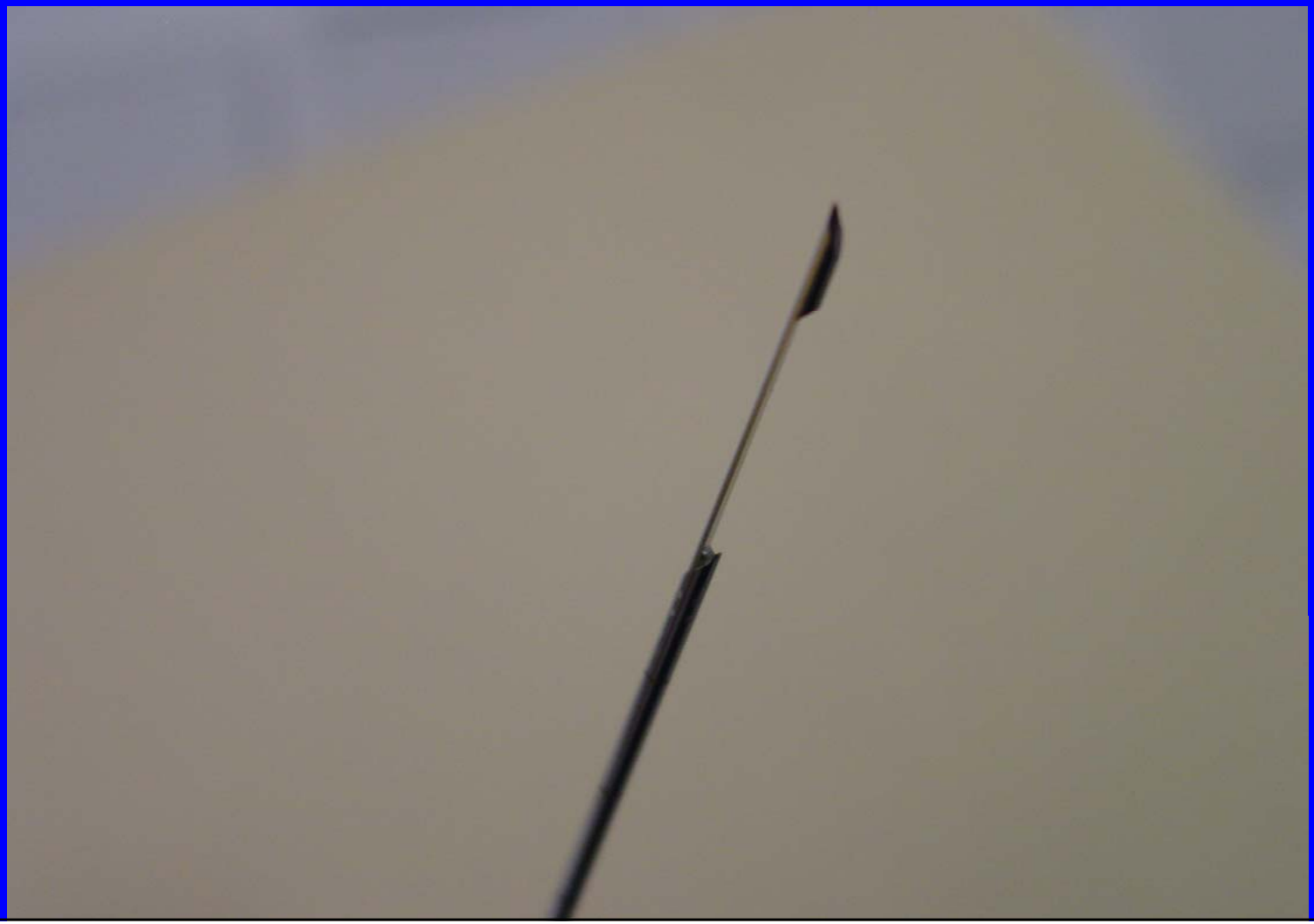
Ultrasound-guided mediastinal biopsy



Core biopsy gun

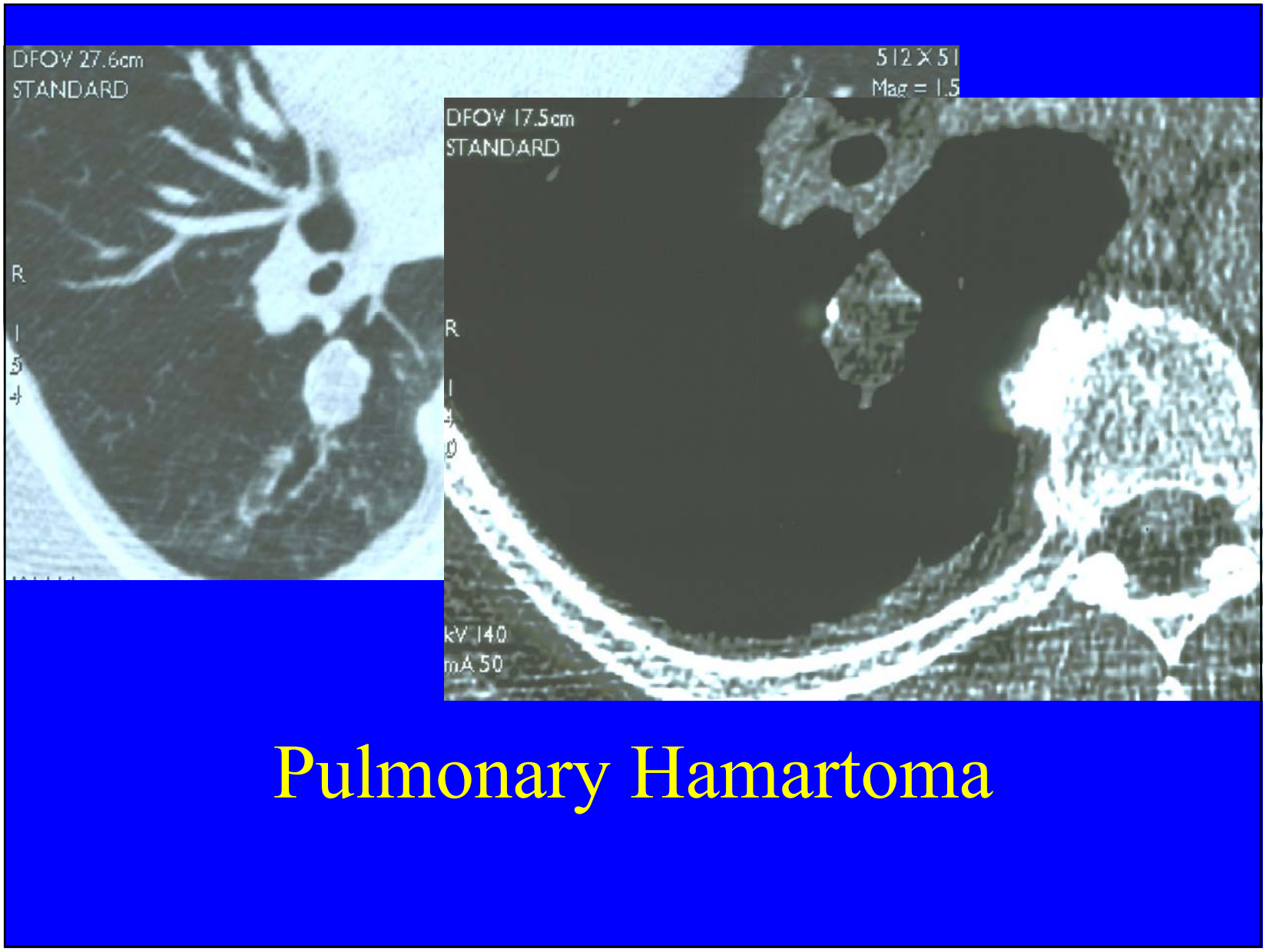


Core biopsy

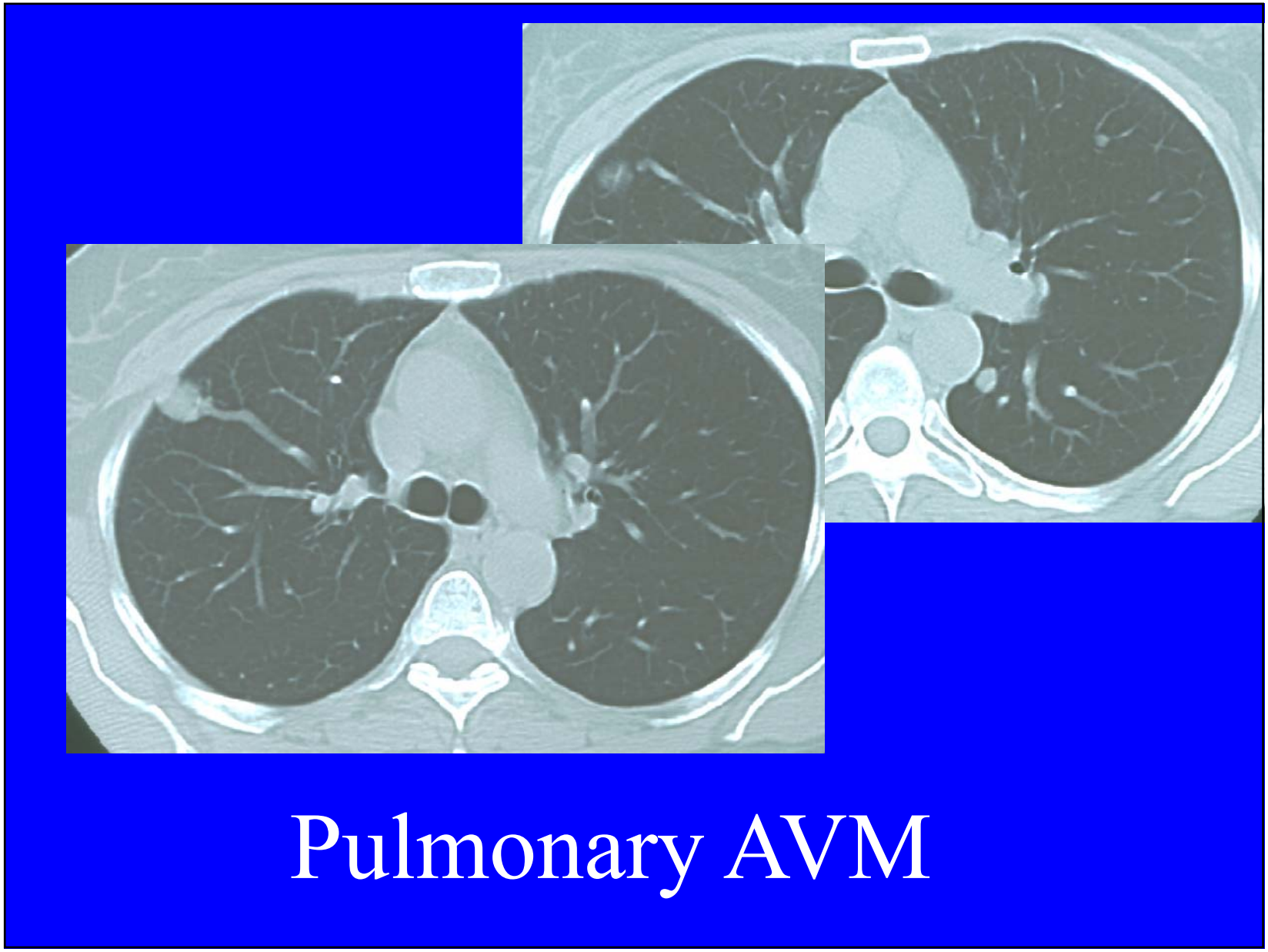


Alternatives to percutaneous biopsy

- VATS or open resection
- Various bronchoscopic biopsy techniques
- **Observation** – Small nodules or low suspicion. Important for low-dose CT lung cancer screening: 40-60% will have nodules but 95-98% of these will prove to be benign on long term F/U.

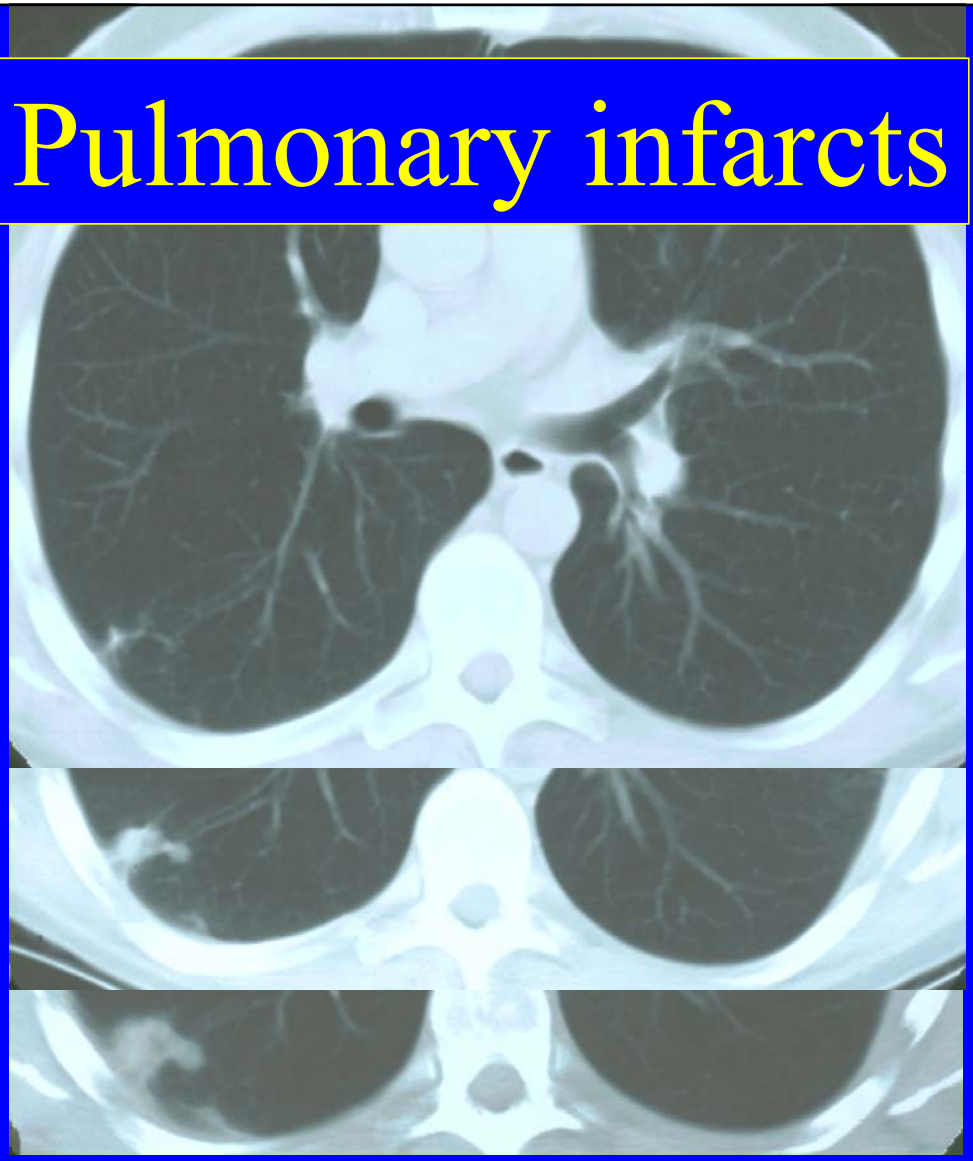


Pulmonary Hamartoma

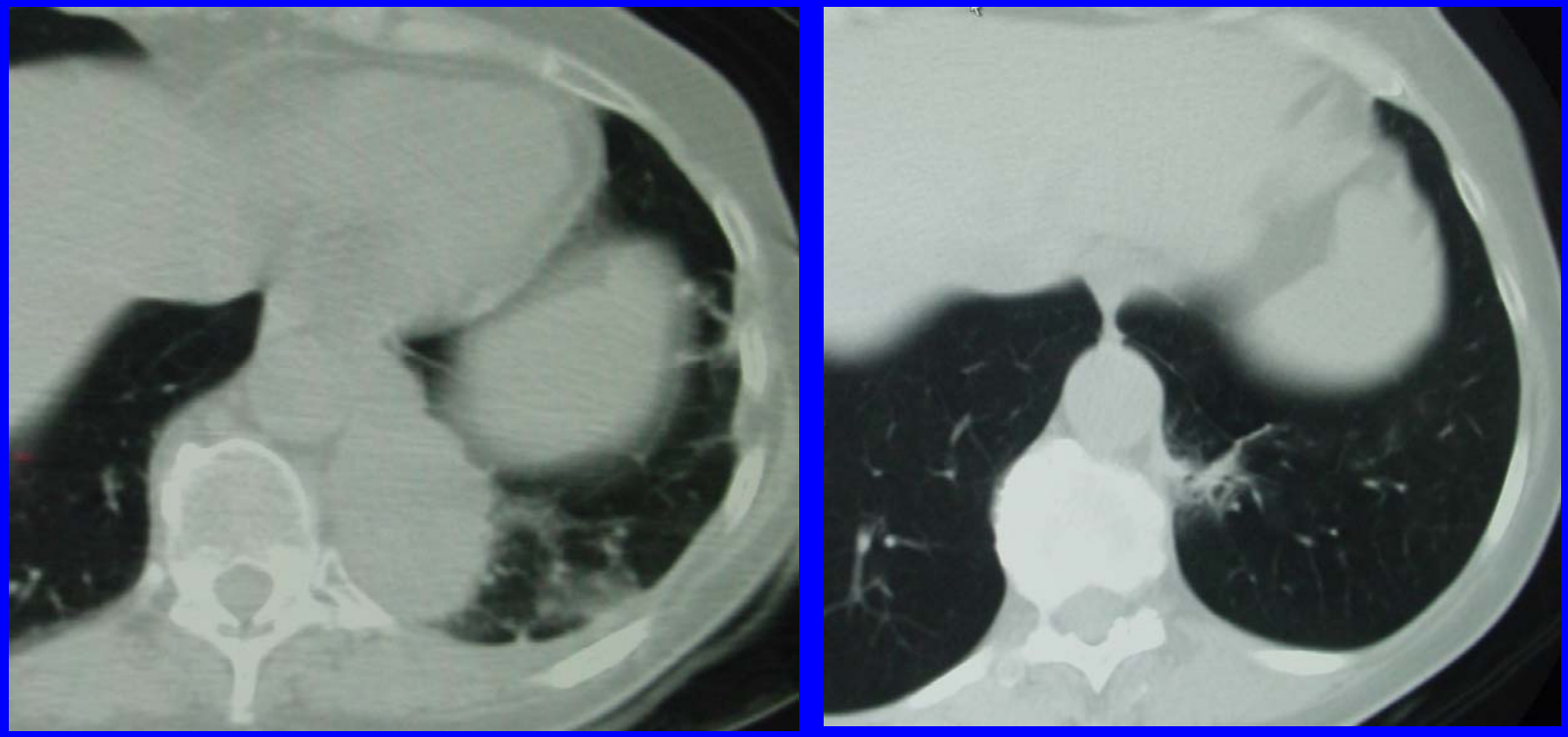


Pulmonary AVM

Pulmonary infarcts

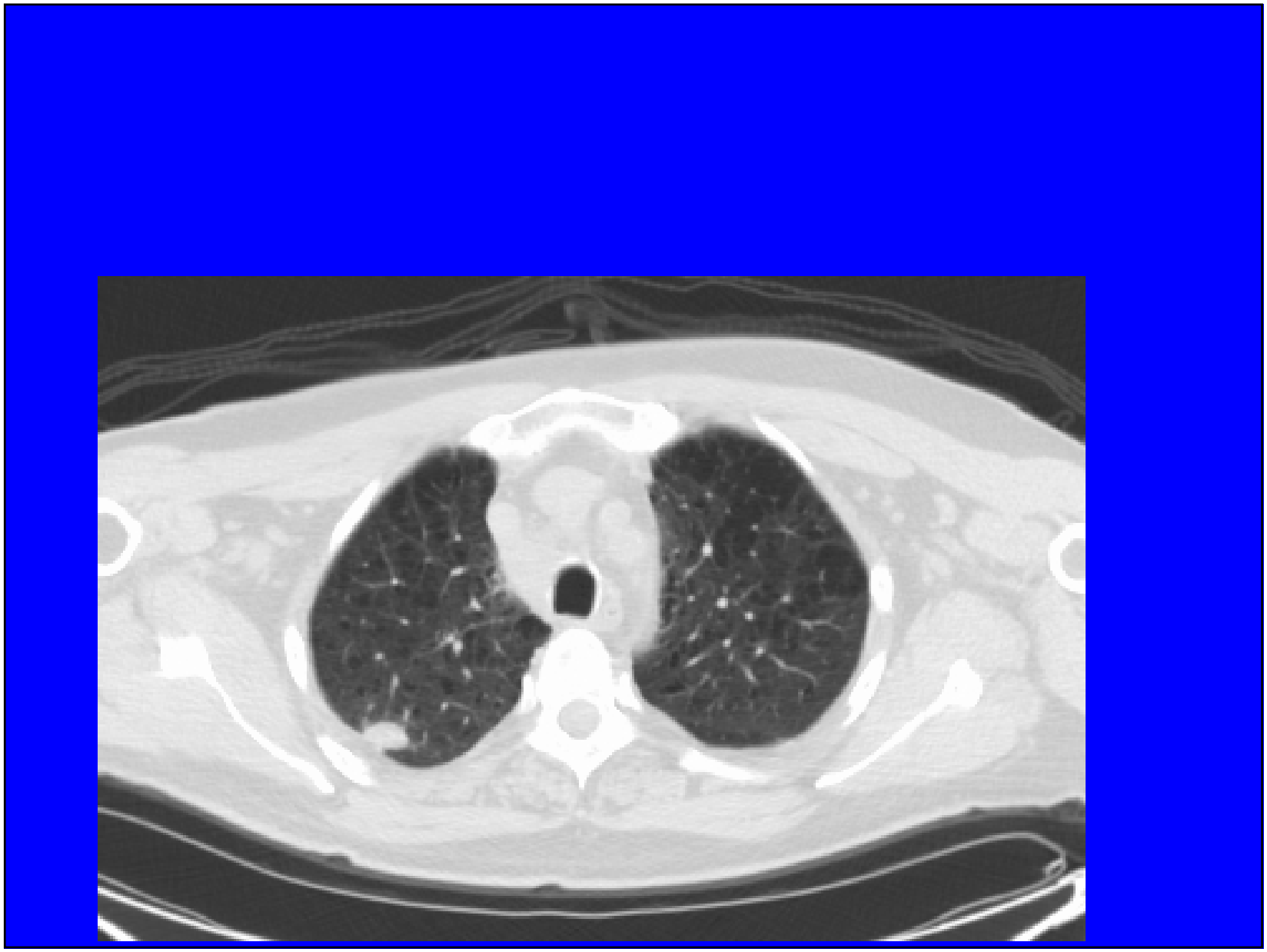


Pneumonia mimicking a mass

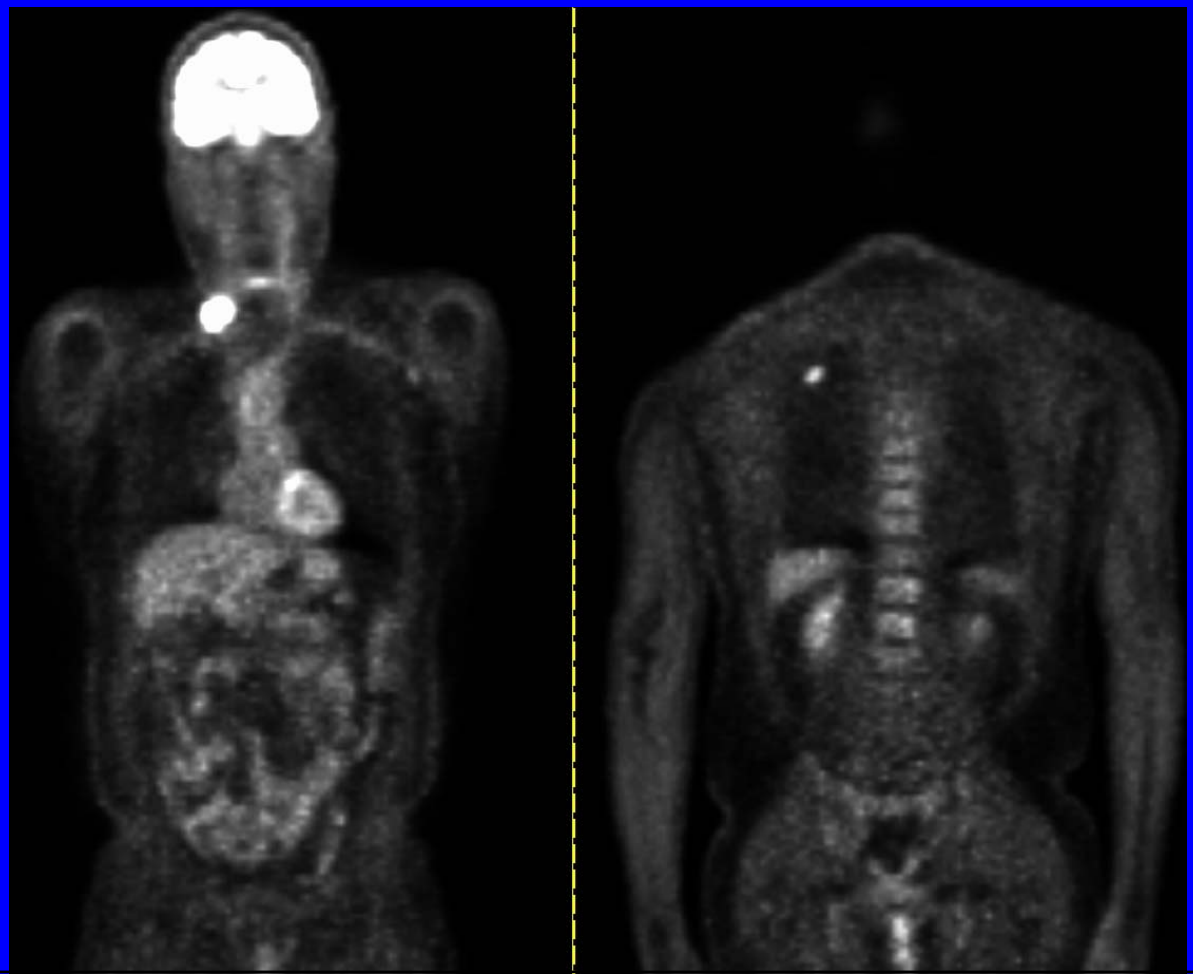


Positron Emission Tomography (PET)

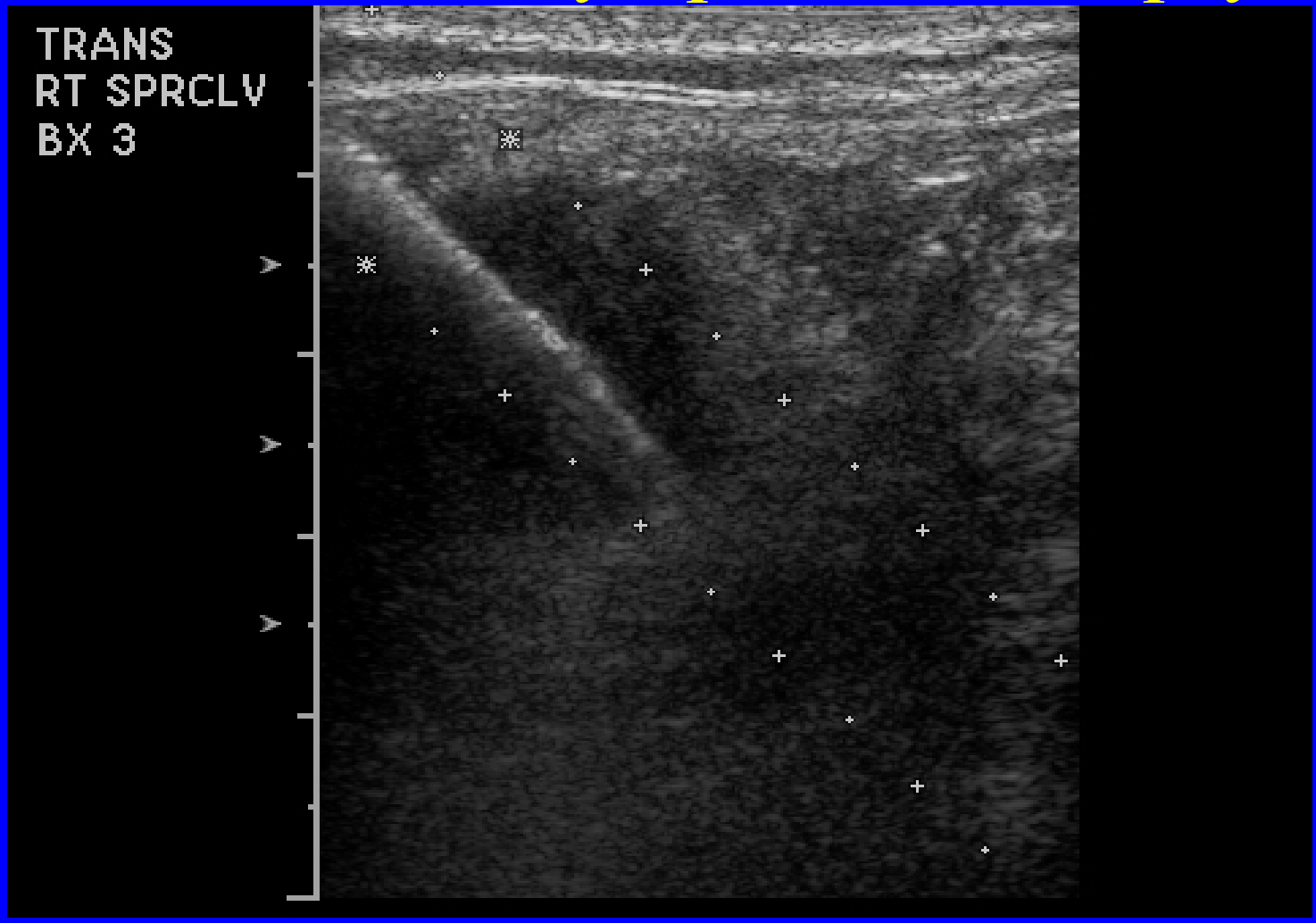
- Commonly performed for disease staging and evaluation of solitary nodules.
- Pre-biopsy evaluation: Important for lesion evaluation and detection of metastases so biopsies may be safer, more accurate, and allow for improved disease staging.



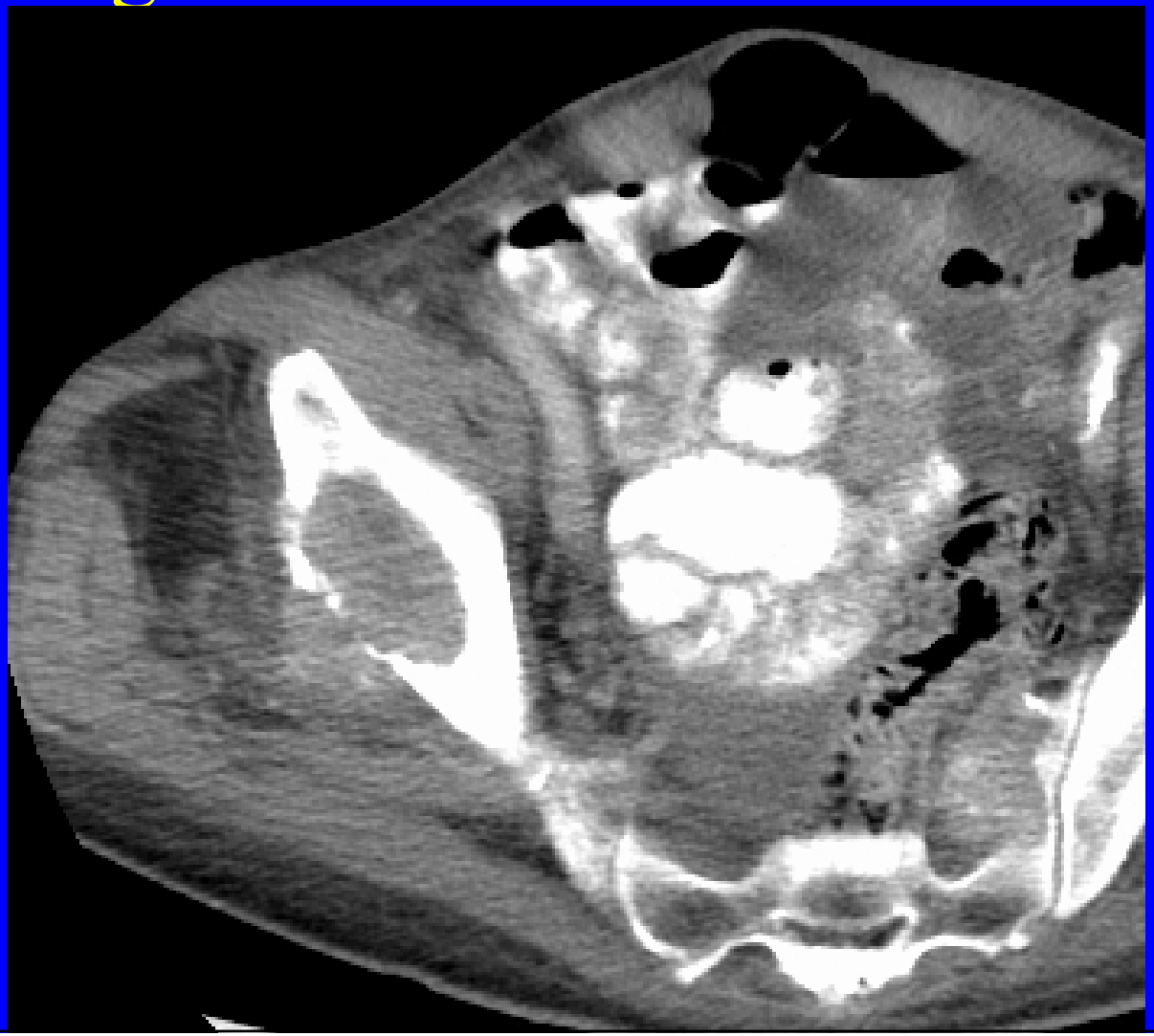
PET-CT



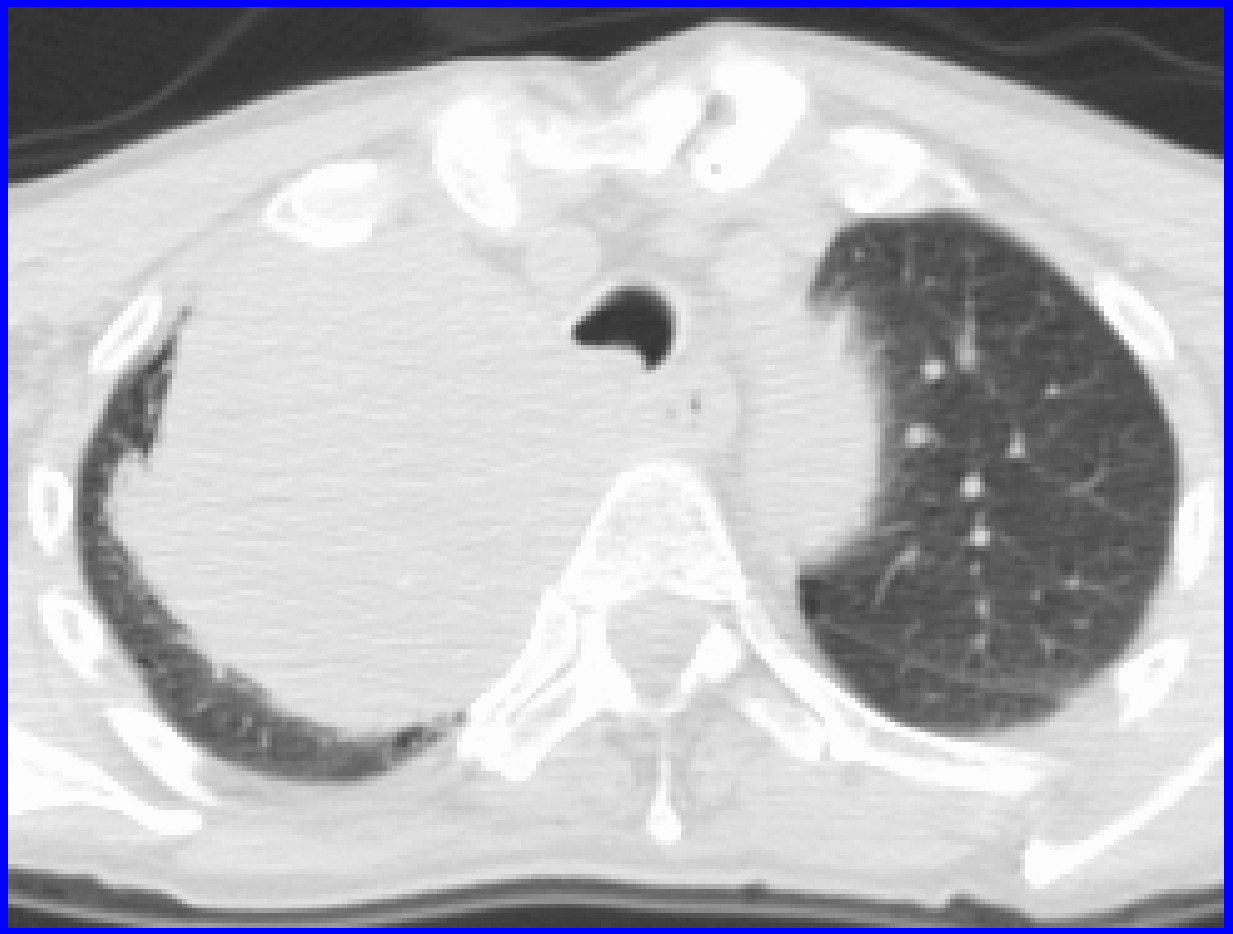
U/S-Guided Lymph Node Biopsy



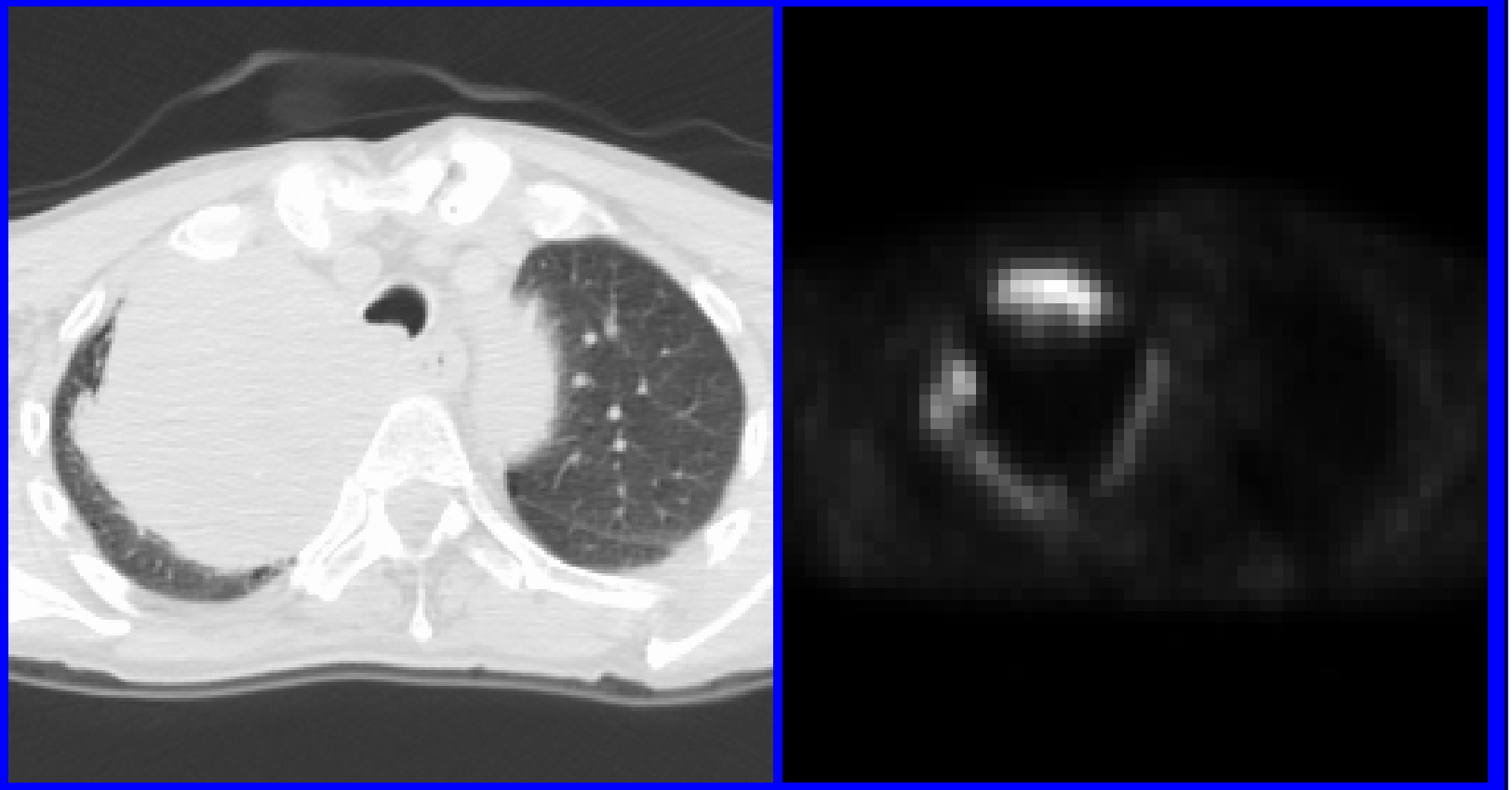
Lung Cancer-Metastatic to Bone



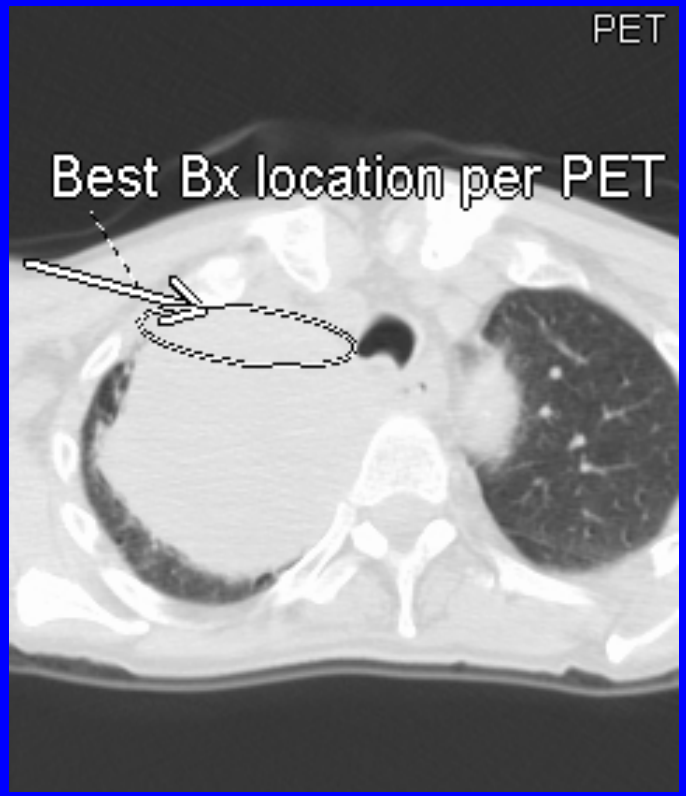
Smoker with right upper lung mass. Initial biopsy shows only necrosis

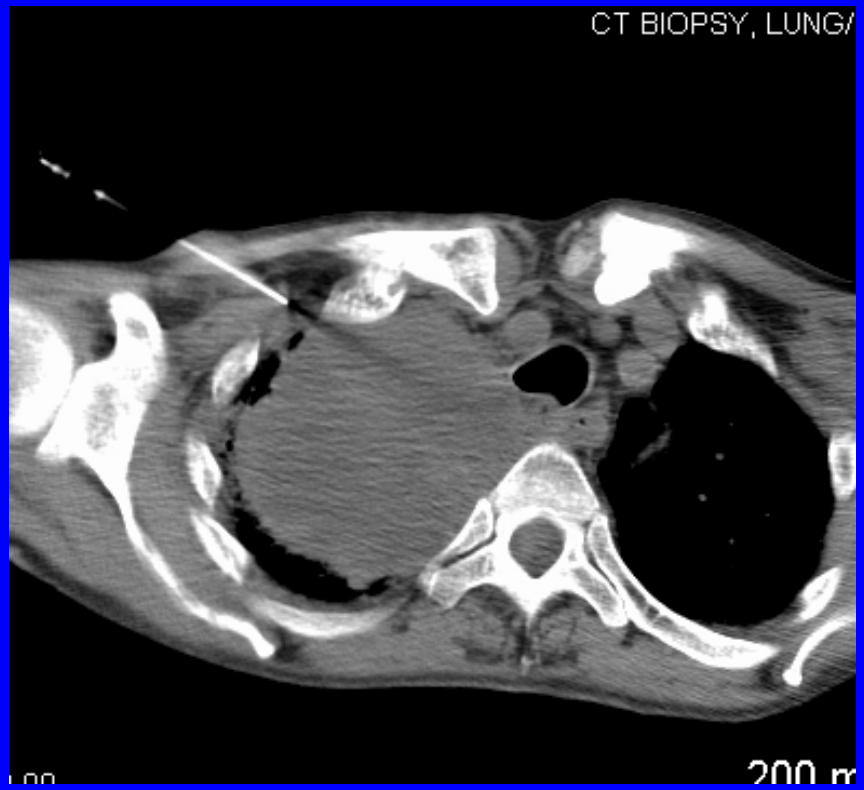


RUL lung mass PET-CT



PET-guided CT biopsy: Squamous cell Carcinoma





Summary

- Image-guided biopsy is safe, cost-effective, and generally preferred when the lesion is accessible and immediate surgical resection or continued observation is not indicated
- Early PET-CT can improve biopsy results, and potentially detect other sites of disease so tissue acquisition can be optimized and safety, accuracy, and staging improved

National Comprehensive Cancer Network®

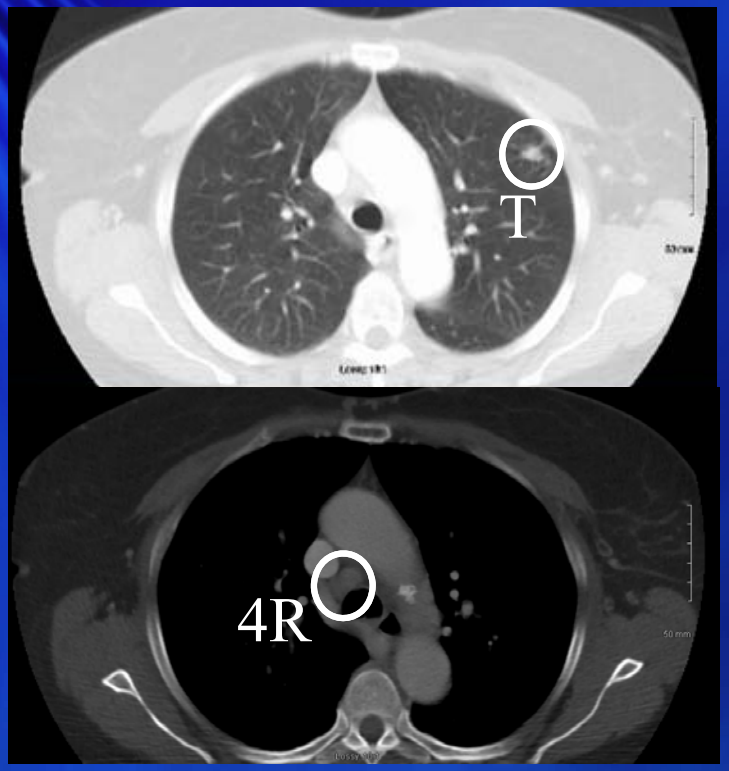
Case Presentations

Methods of Tissue Acquisition Lung Cancer

CASE PRESENTATIONS

NCCN Webinar 2014

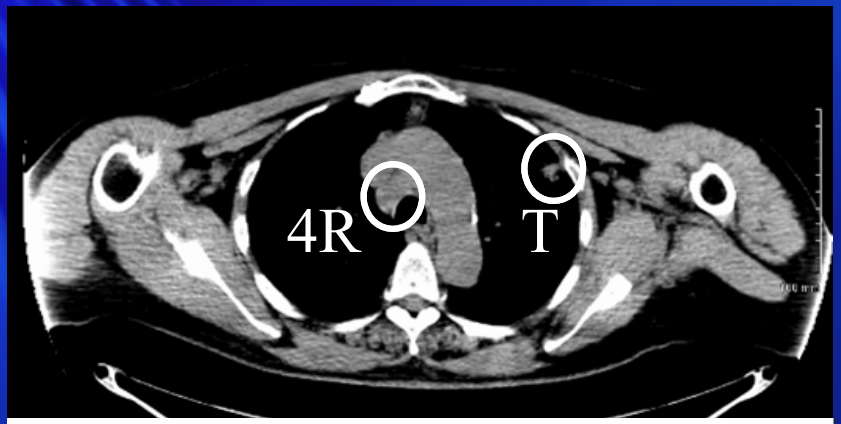
Case CB



- 65 y.o. Female
- cT1bN3M0
- HTN, DM, Poor Dentition
- LUL SUV 21.9
- Good PFTs

ROSWELL PARK CANCER INSTITUTE®

Case CB

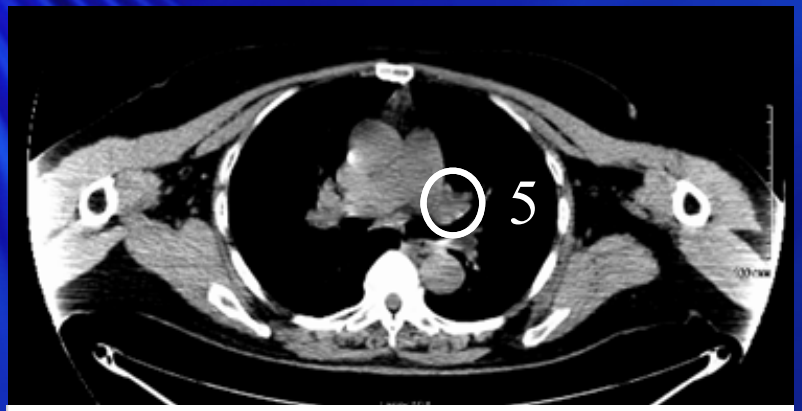


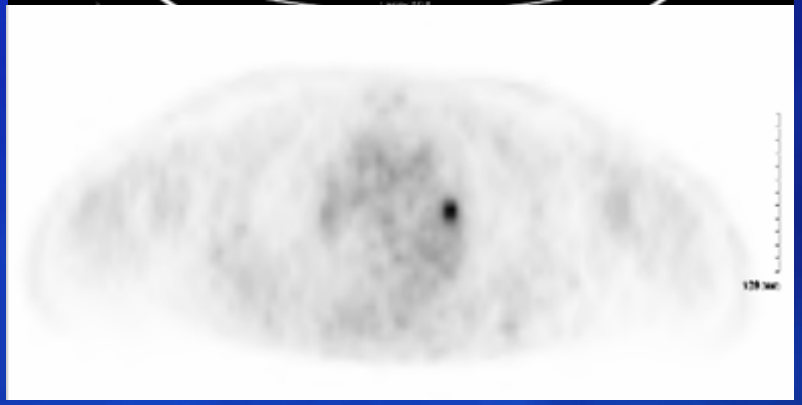
- 65 y.o. Female
- cT1bN3M0
- HTN, DM, Poor Dentition
- LUL SUV 21.9
- Good PFTs

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case CB





- 65 y.o. Female
- cT1bN3M0
- HTN, DM, Poor Dentition
- LUL SUV 21.9
- Good PFTs

ROSWELL PARK CANCER INSTITUTE®

Case CB

- **What's next for tissue?**

•65 y.o. Female

•cT1bN3M0

•HTN, DM, Poor Dentition

•LUL SUV 21.9

•Good PFTs

ROSWELL PARK CANCER INSTITUTE®

Case CB

- **EBUS of 4R Node**
- **Protocol Rx**
  - **Dental Extraction**
  - **TEMLA**
  - **WEDGE**
  - **VATS LN Dissection**

•65 y.o. Female

•cT1bN3M0

•HTN, DM, Poor Dentition

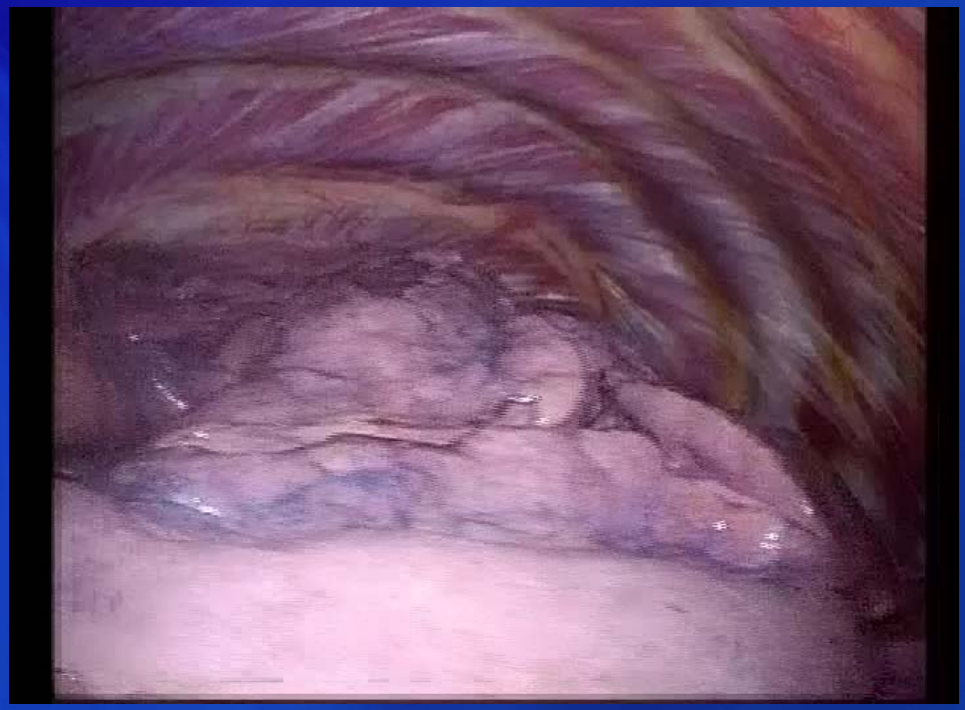
•LUL SUV 21.9

•Good PFTs

ROSWELL PARK CANCER INSTITUTE®

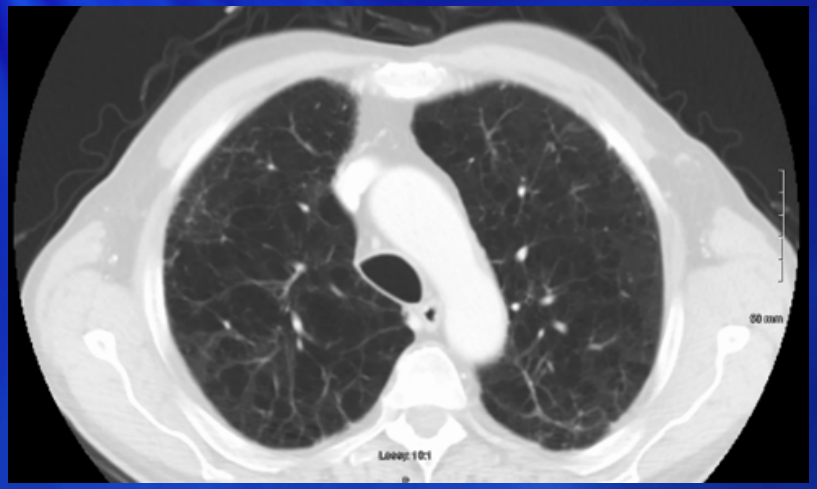
NCCN Webinar 2014

Case CB



NCCN Webinar 2014

Case LC

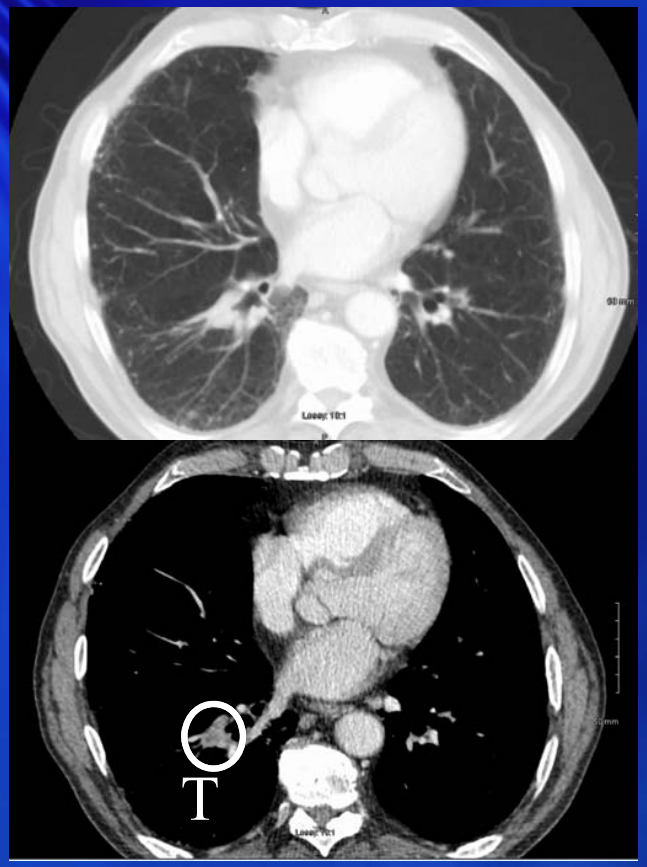


- 80 y.o. Male
- cT1aN0M0
- COPD, GERD
- RLL SUV 3.2
- PFTs 50% predicted
- Nigh time O2

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case LC



- 80 y.o. Male
- cT1aN0M0
- COPD, GERD
- RLL SUV 3.2
- PFTs 50% predicted
- Night time O2

NCCN Webinar 2014

Case LC

- **What's next for tissue?**

•80 y.o. Male
•cT1aN0M0
•COPD, GERD
•RLL SUV 3.2
•PFTs 50% predicted
•Night time O2

ROSWELL PARK CANCER INSTITUTE®

Case LC

- **Navigation Bronchoscopy**

- **SBRT for treatment**

•80 y.o. Male

•cT1aN0M0

•COPD, GERD

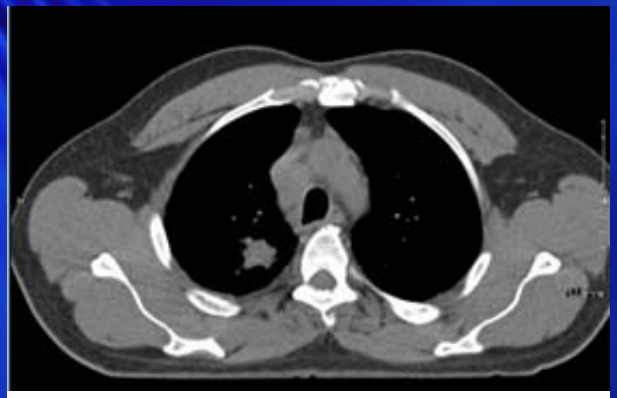
•RLL SUV 3.2

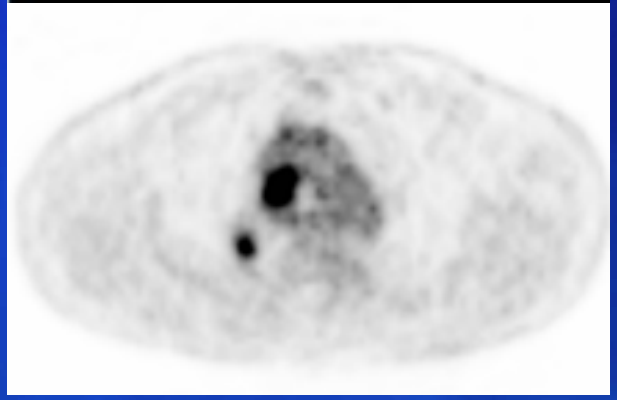
•PFTs 50% predicted

•Night time O2

ROSWELL PARK CANCER INSTITUTE®

Case EG





- 63 y.o. Male
- cT2N2M1
  (+bone bx)
- Coronary/Valve Heart Disease
- Tissue needed for genomic testing

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case EG

- **What's next for tissue?**

•63 y.o. Male

•cT2N2M1

(+bone bx)

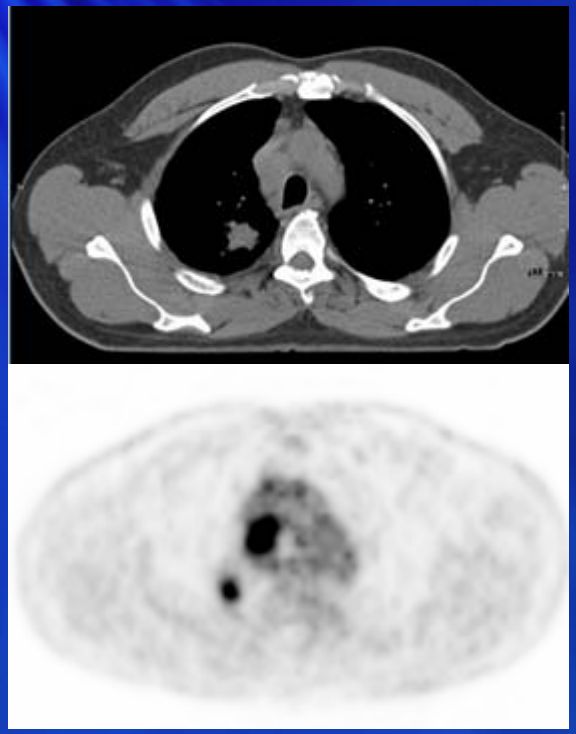
•Coronary/Valve Heart Disease

•Tissue needed for genomic testing

ROSWELL PARK CANCER INSTITUTE®

Case EG

- **Mediastinoscopy**

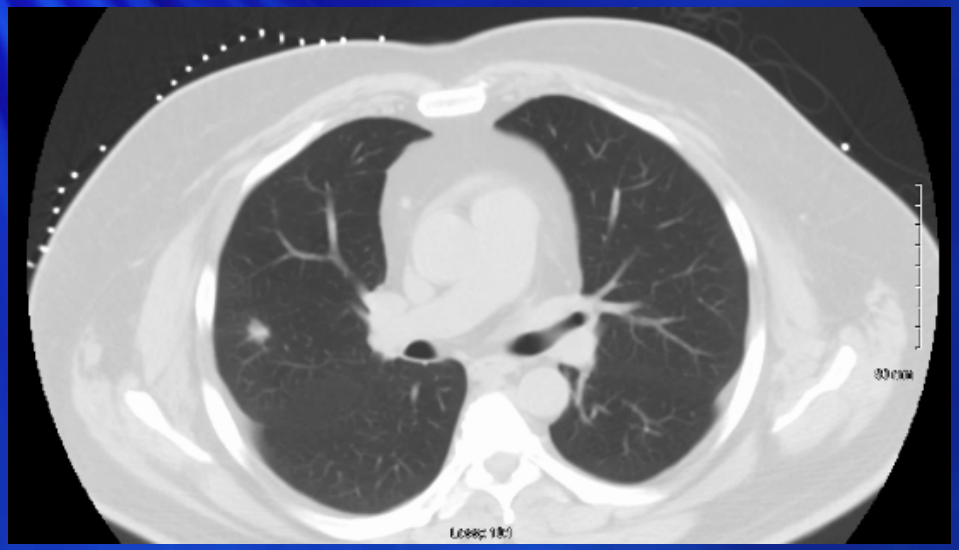


- 63 y.o. Male
- cT2N2M1
  (+bone bx)
- Coronary/Valve Heart Disease
- Tissue needed for genomic testing

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case WW



- 58 y.o. Male
- cT1aN0M0
- HTN, Asthma
- NonPET Avid but growing
- PFTs Good

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case WW

- **What's next for tissue?**

•58 y.o. Male

•cT1aN0M0

•HTN, Asthma

•NonPET Avid but growing

•PFTs Good

ROSWELL PARK CANCER INSTITUTE®

Case WW

- **CT Biopsy**

•58 y.o. Male

•cT1aN0M0

•HTN, Asthma

•NonPET Avid but growing

•PFTs Good

- **Wedge for treatment**

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case EZ

- 65 y.o. Female
- pT3N2bM0 Rectal
- Hx Chemo
- Former smoker

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case EZ

- **What's next for tissue?**

•65 y.o. Female

•pT3N2bM0 Rectal

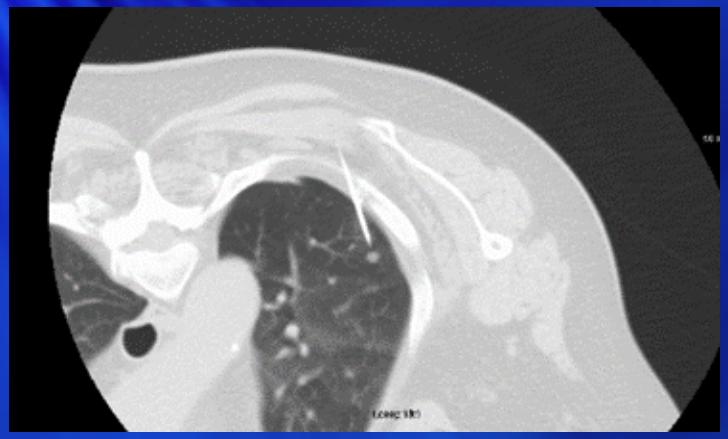
•Hx Chemo

•Former smoker

ROSWELL PARK CANCER INSTITUTE®

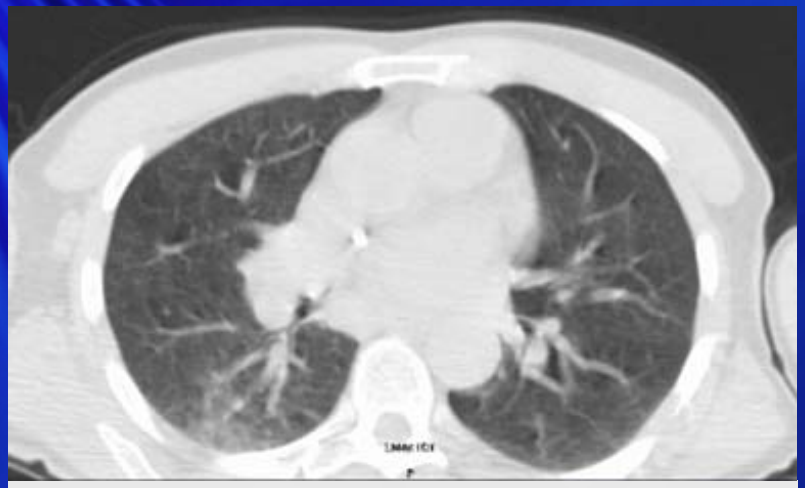
Case EZ

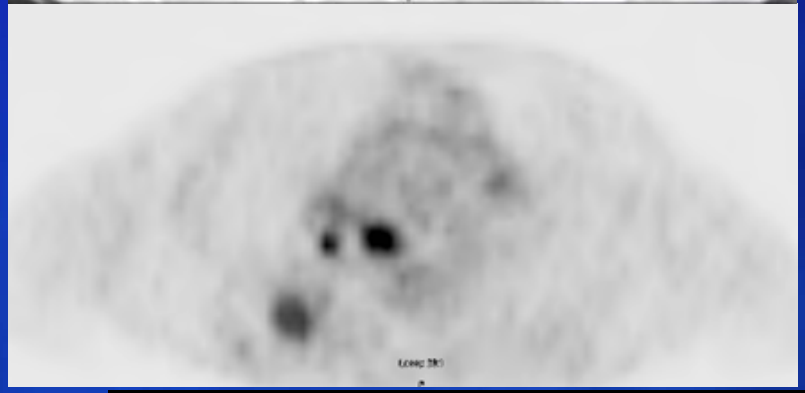
- **Pre-wedge CT localization**



- 65 y.o. Female
- pT3N2bM0 Rectal
- Hx Chemo
- Former smoker

Case DM



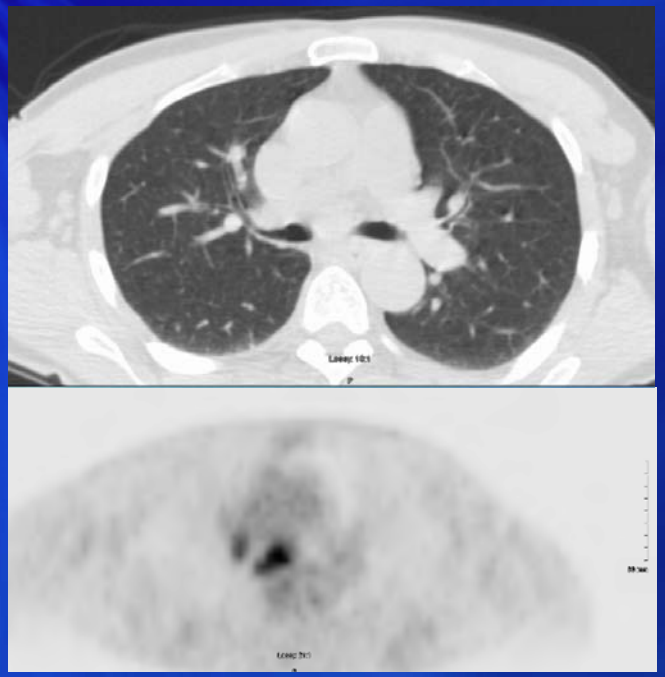


- 66 y.o. Male
  Merchant Marine
- cT2N2M0
- Former smoker

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

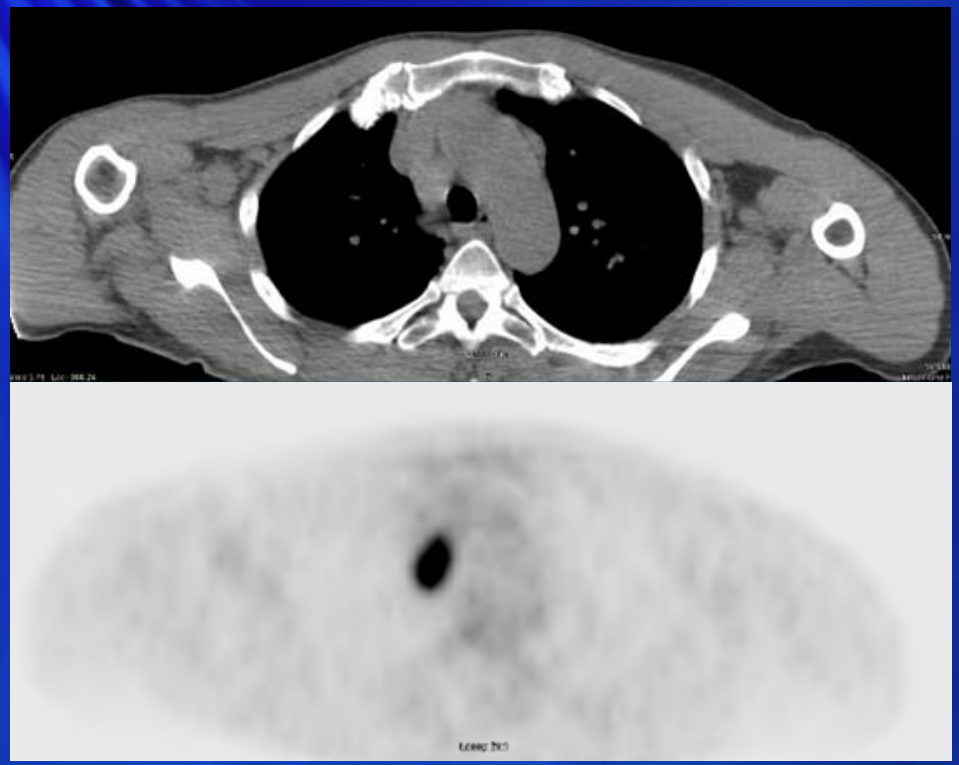
Case DM



- 66 y.o. Male Merchant Marine
- cT2N2M0
- Former smoker

ROSWELL PARK CANCER INSTITUTE®

Case DM



- 66 y.o. Male Merchant Marine
- cT2N2M0
- Former smoker

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014

Case DM

- **What's next for tissue?**

•66 y.o. Male Merchant Marine

•cT2N2M0

•Former smoker

ROSWELL PARK CANCER INSTITUTE®

Case DM

- **EBUS**

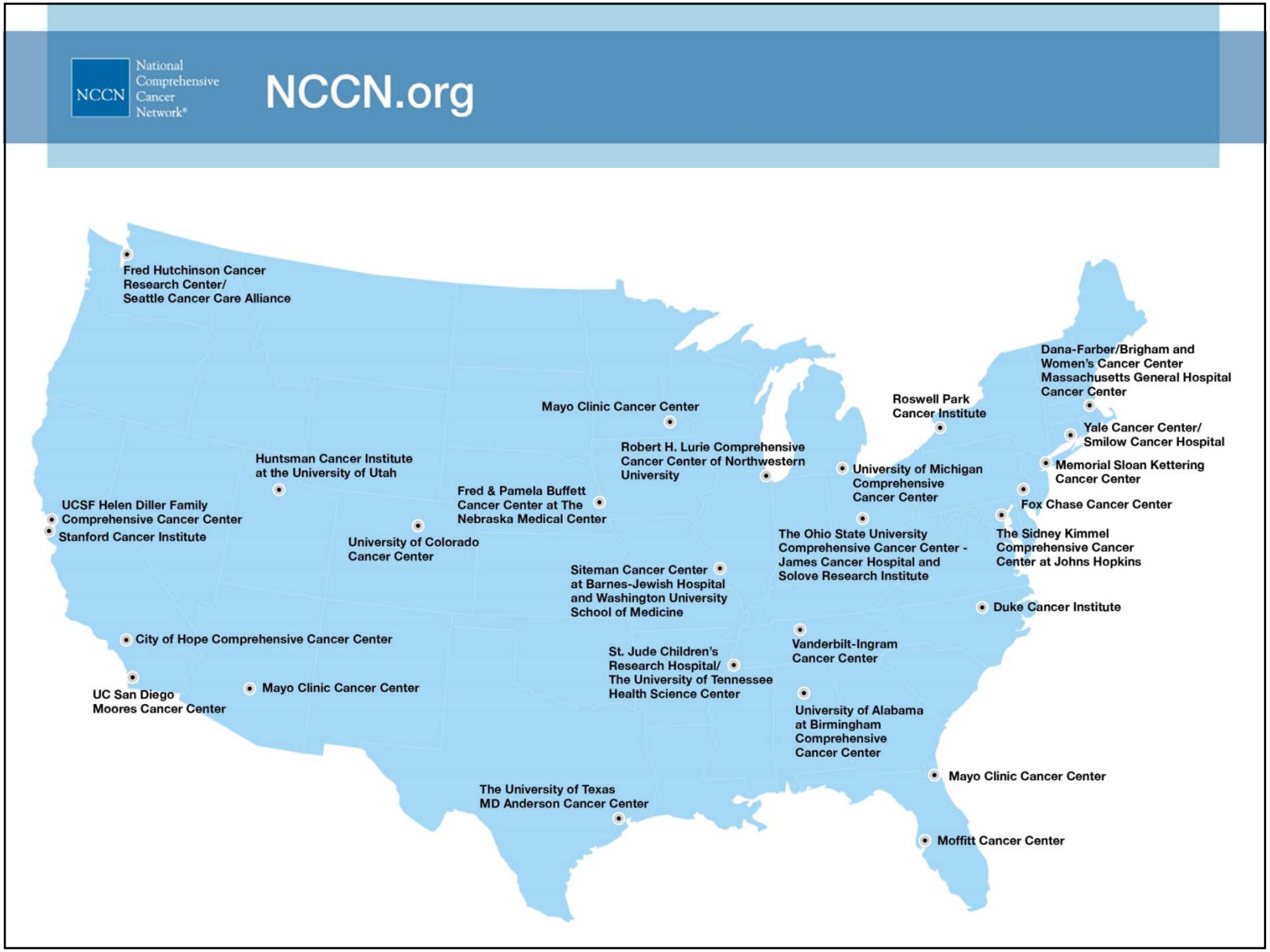
•66 y.o. Male
Merchant Marine

•cT2N2M0

•Former smoker

ROSWELL PARK CANCER INSTITUTE®

NCCN Webinar 2014



NCCN Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer
Best Practices in Molecular Testing in NSCLC

Presented live on August 15, 2014

By

Lucian R. Chirieac, MD
Dana-Farber/Brigham and Women's Cancer Center

A recording of this live webinar is available at http://education.nccn.org/node/52901 until June 17, 2015.

Intended Audience and Learning Objectives

Intended Audience:

This slide deck is designed to meet the educational needs of medical oncologists, radiation oncologists, surgical oncologists, pathologists, nurses, pharmacists, and other healthcare professionals who manage patients with non-small cell lung cancer.

Learning Objectives:

Following this session, participants should be able to:

- Discuss the molecular testing considerations for patients with ALK rearrangements and EGFR mutations

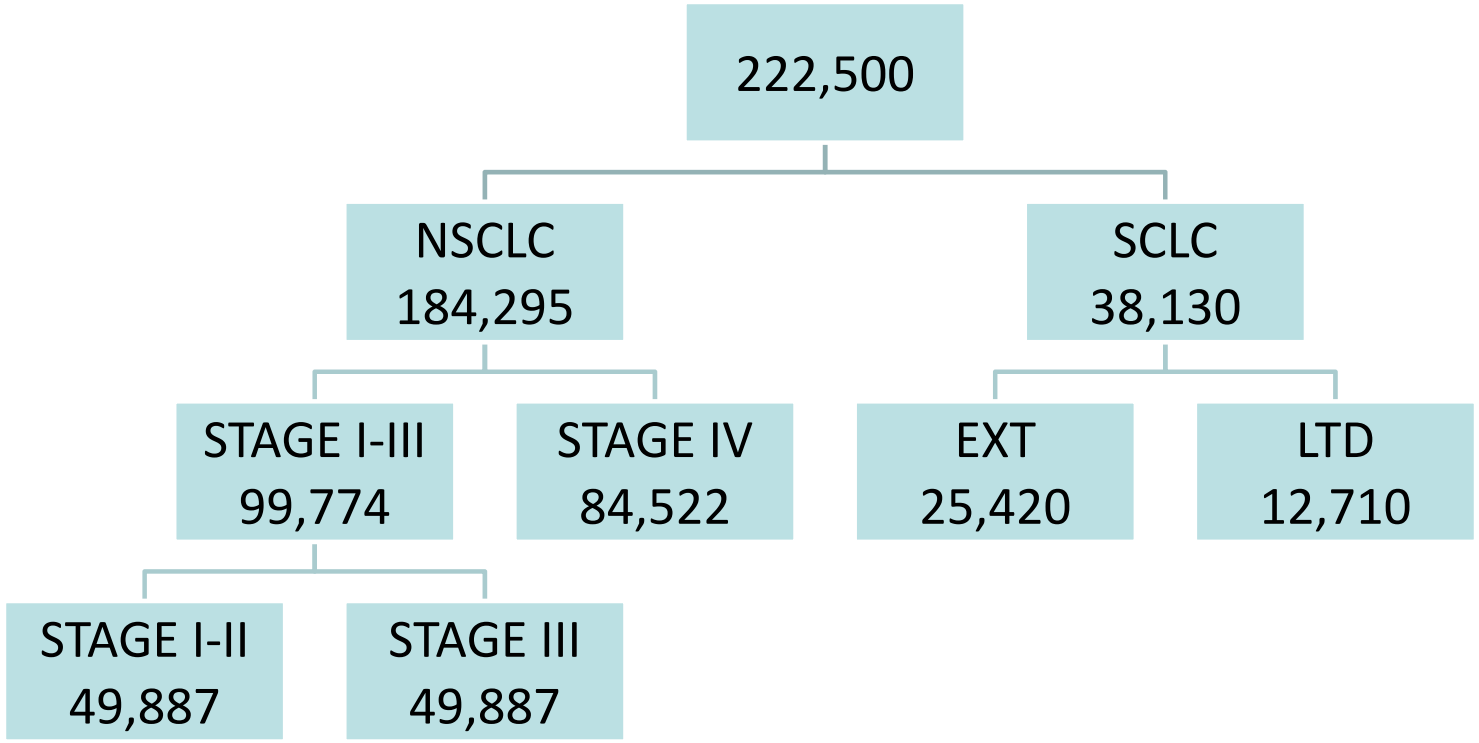
OVERVIEW

1. In the United States, lung cancer remains the leading cause of cancer mortality in both men and women, with more than 50% of patients presenting with locally advanced, inoperable, or metastatic disease.

2. Approximately 33% of patients with non–small-cell lung cancer (NSCLC) present with advanced-stage disease while most patients with early stage NSCLC will eventually develop metastatic lung cancer.

3. Despite the numerous therapeutic options available, only 17% of patients with lung cancer survive beyond 5 years from diagnosis.

Estimated Incidence of Lung Cancer in US in 2014



OVERVIEW

1. Recent advances in genetic and histological markers, coupled with emerging targeted agents for NSCLC, have the potential to improve patient outcomes.

2. There also has been much progress in the treatment of advanced NSCLC in the last several years as clinical trials have demonstrated improved outcomes with novel therapeutic agents directed against a wide array of molecular targets.

3. Pathologists function in several broad areas, including as diagnosticians and investigators, and are uniquely positioned to assist oncologists with the development of a comprehensive treatment plan.

OVERVIEW

- The following educational activity will present a case scenario, using the latest treatment options and diagnostic markers to help pathologists improve patient outcomes.

LEARNING OBJECTIVES

After completing this activity, the participant should be able to:

- **Describe** the prognostic and predictive role of histologic and immunohistochemical markers in NSCLC therapy
- Based on tumor biology, **evaluate** current and emerging therapeutic strategies that incorporate targeted agents with chemotherapy for patients with advanced NSCLC
- **Recognize** how gene expression profiling and mutation analysis may help to customize therapy for patients with NSCLC.

Case Presentation

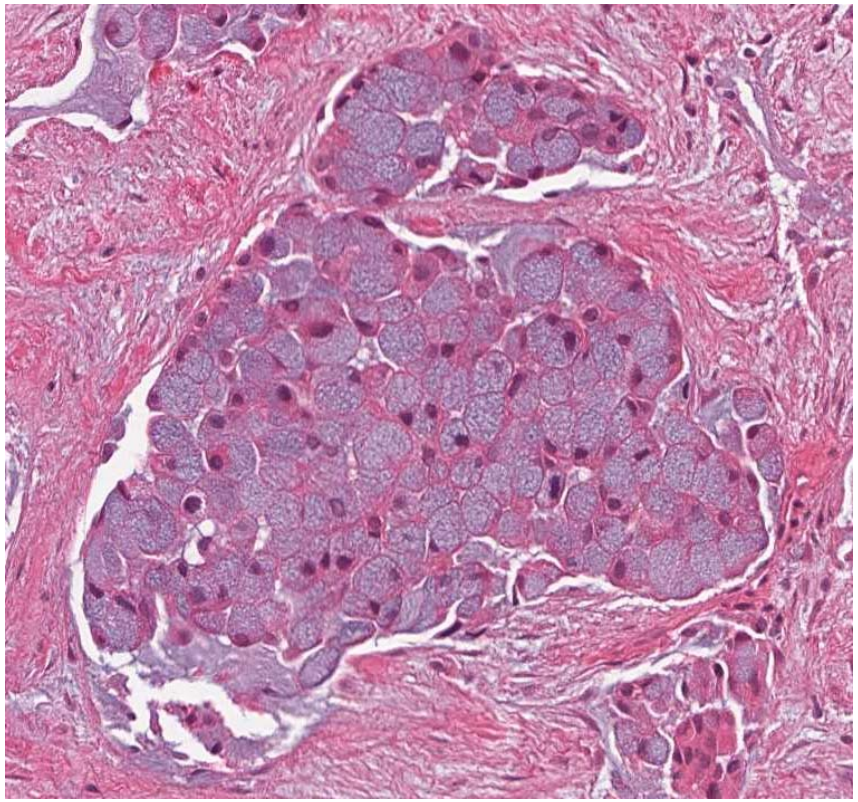
- The patient is a 51-year-old nonsmoking woman, who was in her usual state of health until March. At that point, she developed a cough. She was treated with macrolide antibiotics without benefit.

- A computed tomography (CT) scan was performed and the results showed a 1-cm nodule in her right lung. She was referred to the thoracic surgery service who noted that she had extensive pleural disease after an exploration in June.

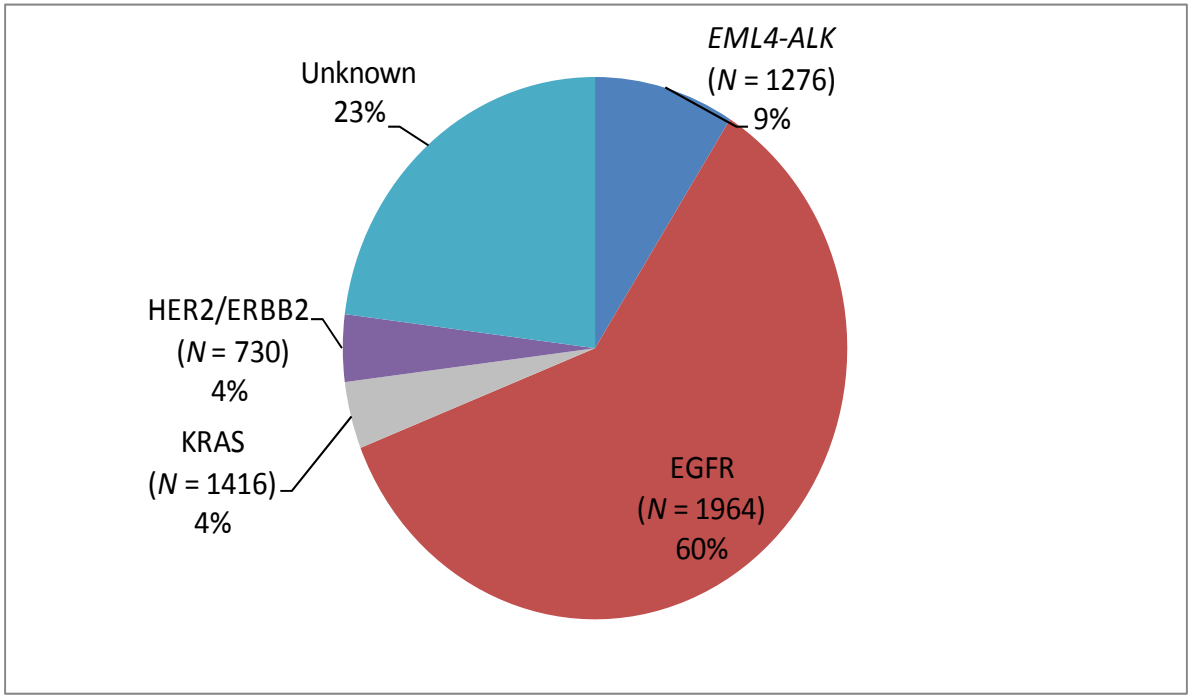
- The final pathology from biopsies of the right pleura as well as the pleura immediately overlying the pericardium reveals adenocarcinoma with signet-ring cell features. The immunohistochemistry is positive for cytokeratin 7 and thyroid transcription factor-1 (TTF-1).

- All of these findings are consistent with a stage IIIB lung primary tumor.

Case Presentation



Prevalence of Mutations in Non-Smoking Women



Sasaki T, Rodig SJ, Chirieac LR, Jänne PA.. Euro J Cancer. 2010;46:1773-1780

Case Presentation

- She received chemotherapy, but a routine 3-month surveillance CT showed slight worsening of her pleural disease. She has an unusual story and suspicion was raised that the tumor might harbor abnormalities in the *ALK* gene.

Question 1

Which of the following statements regarding ALK gene is accurate?

A. ALK is involved in a characteristic translocation of a subset of anaplastic large-cell lymphomas.

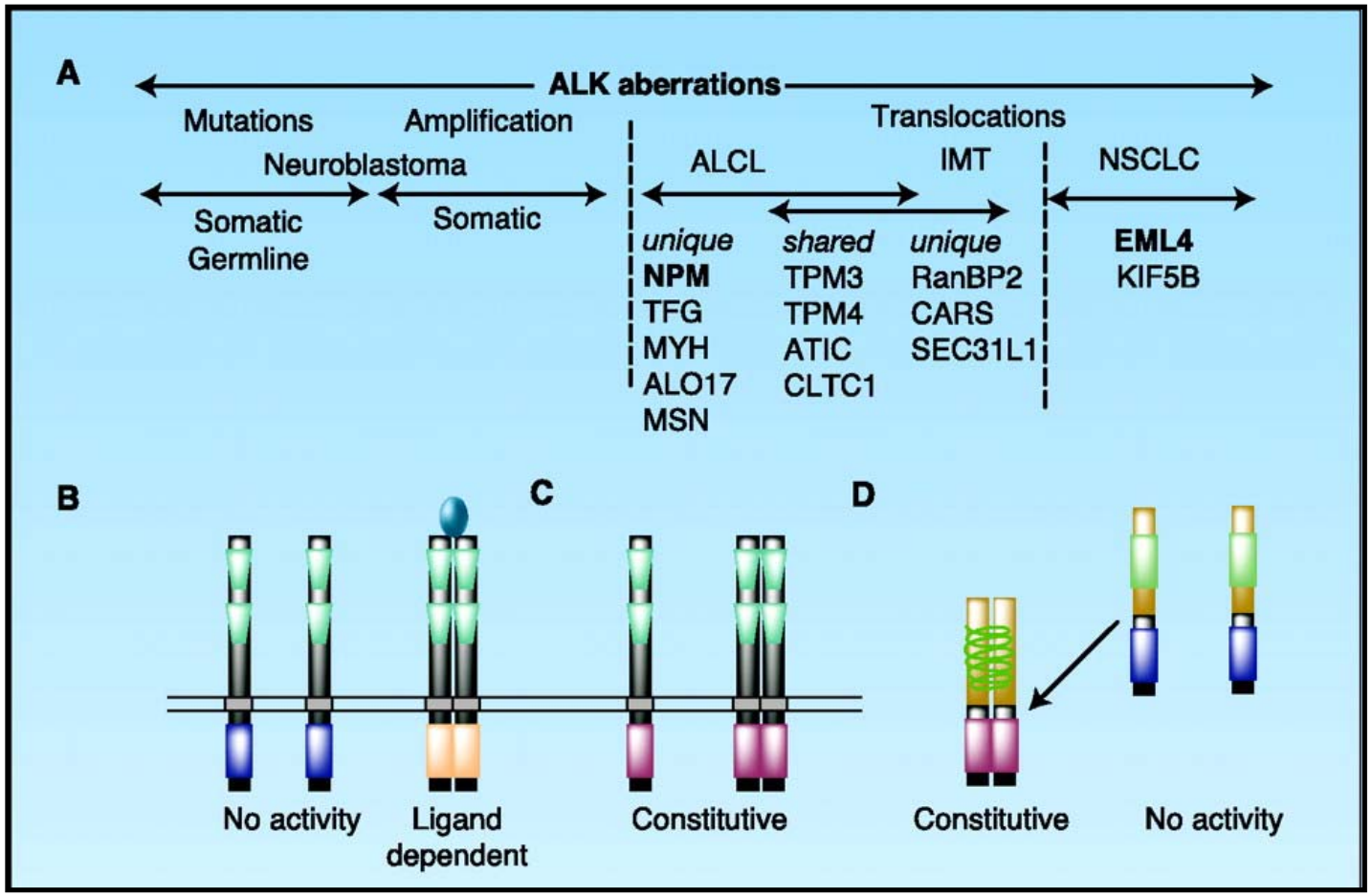
B. ALK is normally expressed in all the human tissues.

C. ALK is not altered in inflammatory myofibroblastic tumors.

D. Neuroblastomas have only germline point mutations in the ALK kinase domain.

E. ALK is translocated in pseudosarcomatous myofibroblastic proliferations of the genitourinary tract.

ALK Aberrations for Different Cancers



Mosse et al. Clin Cancer Res. 2009;15:5609-5614

Question 2

In which of the following types of patients are EML4-ALK translocations most likely ***NOT*** to occur?

A. Younger patients

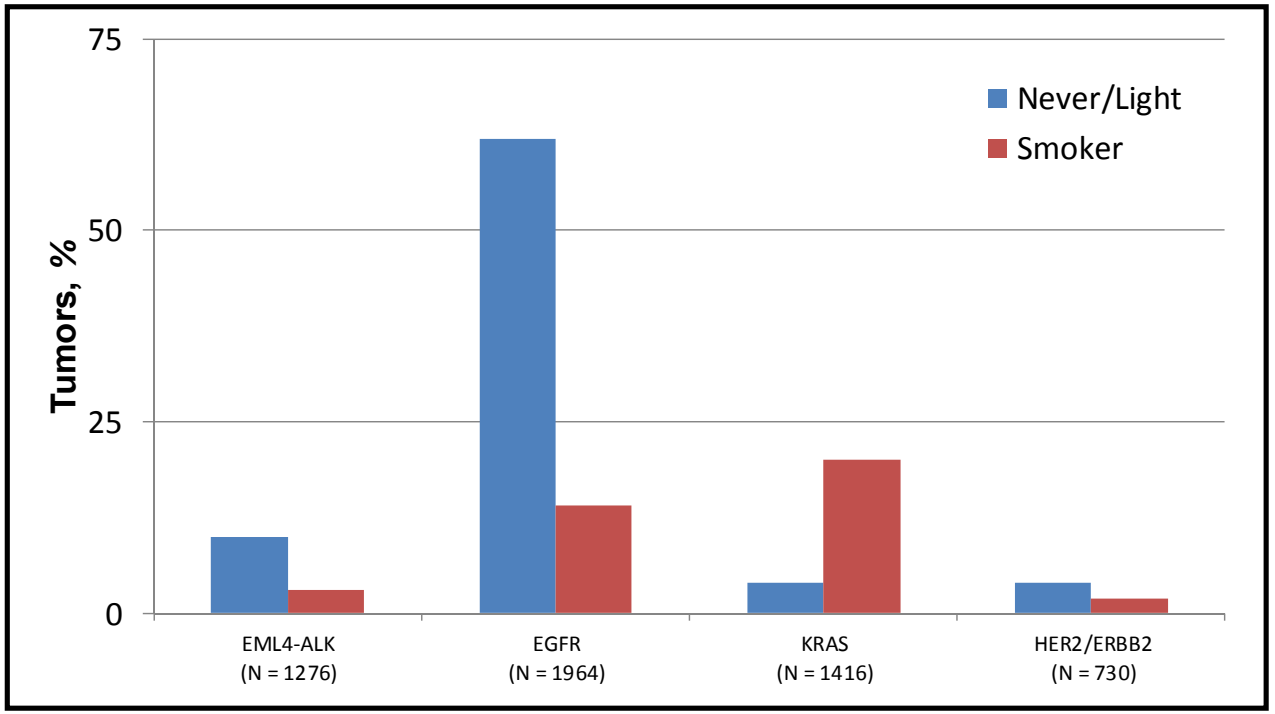
B. Patients with advanced non–small-cell lung cancer (NSCLC)

C. Patients with lung cancer and EGFR mutations

D. Never or former/light smokers

E. Asian patients

Percent of Tumors with Various Genetic Alterations



Sasaki T, Rodig SJ, Chirieac LR, Jänne PA.. Euro J Cancer. 2010;46:1773-1780

Case Presentation

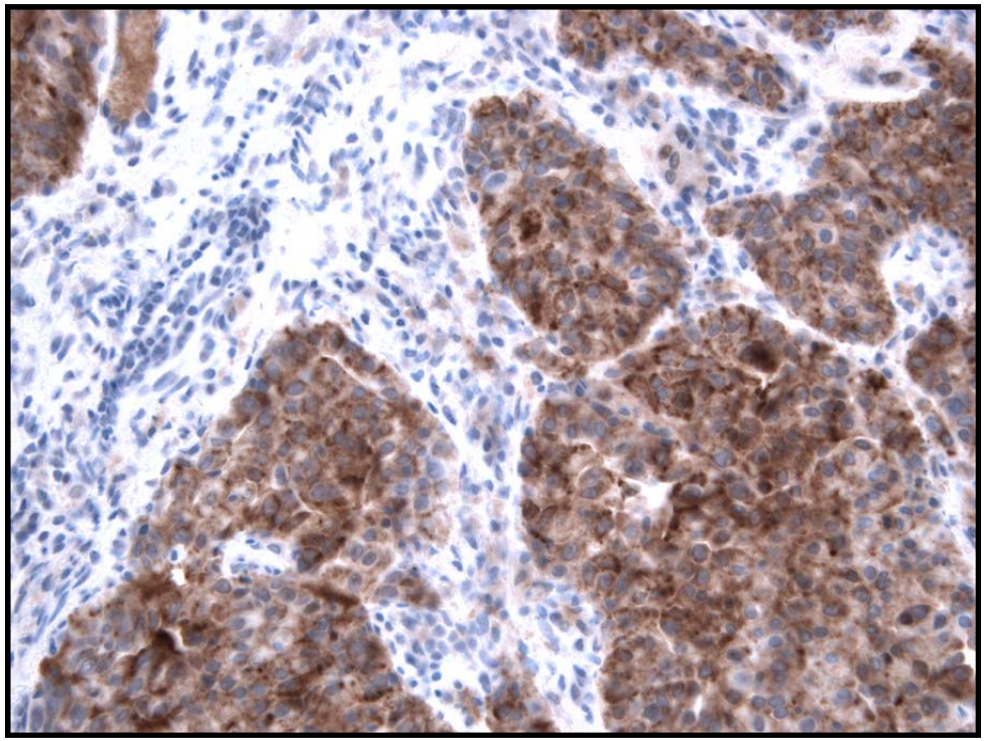
- Despite these general differences, the clinical characteristics alone are not sufficient to predict the *ALK* genetic aberration with absolute certainty. Therefore, genetic testing of her lung cancer is necessary.

Question 3

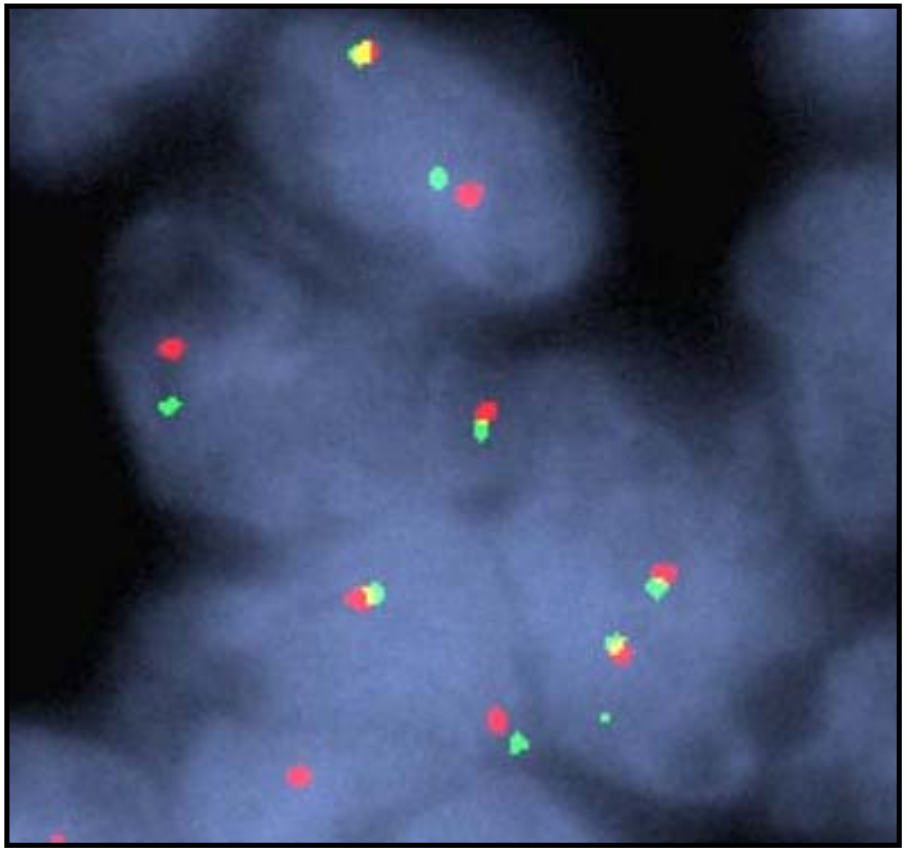
Which of the following tests is preferred for identifying lung adenocarcinomas with ALK gene rearrangements?

A. Immunohistochemistry
B. Distinct histology on H&E
C. Fluorescence in situ hybridization (FISH)
D. Chromogenic in situ hybridization (CISH)
E. Reverse transcription-polymerase chain reaction (RT-PCR)

ALK Immunohistochemistry



ALK Fluorescence In Situ Hybridization

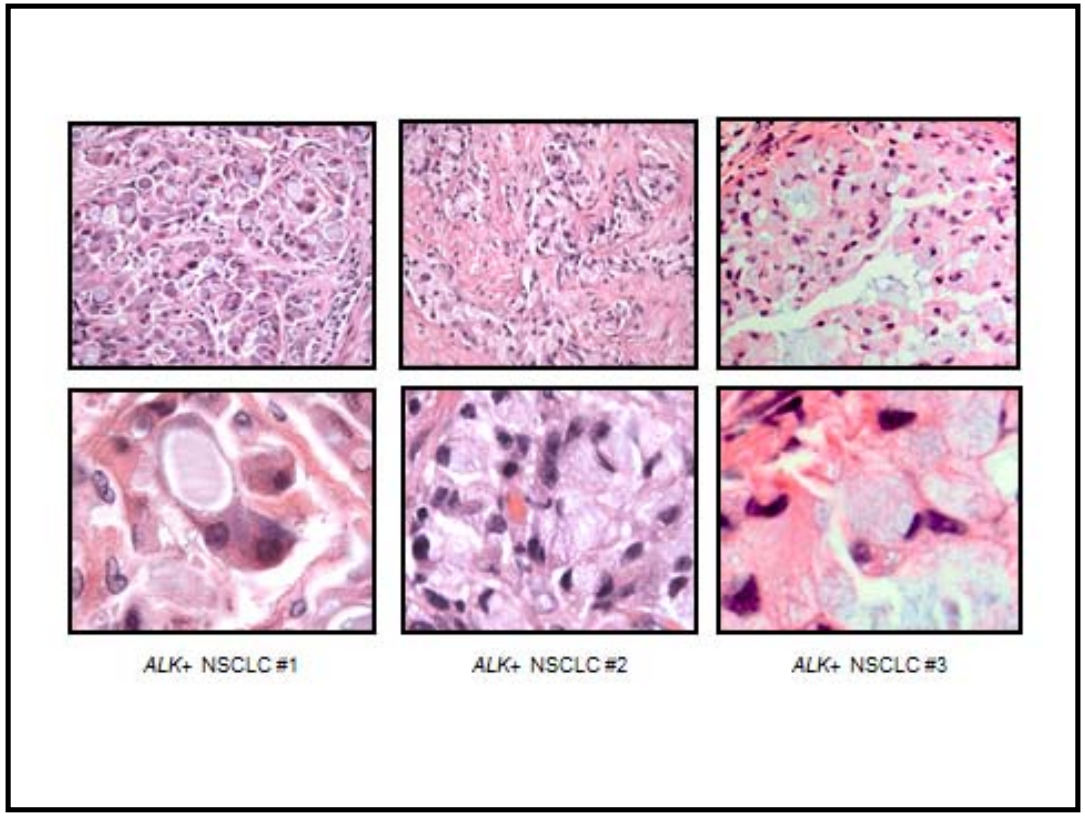


Question 4

The morphologic profile of ALK-rearranged lung cancers is unique and consists of which of the following?

A. Adenocarcinoma with an acinar pattern
B. Adenocarcinoma with a solid pattern and signet-ring cells
C. Squamous cell carcinomas
D. Papillary carcinomas
E. Mucinous carcinomas

Morphologic Profile of ALK-Rearranged Lung Cancers



Clin Cancer Res. 2009;15:5216-5223

Question 5

Why is it important to identify the *ALK*-rearranged tumor?

A. It predicts response to chemotherapy.
B. It predicts response to EGFR tyrosine-kinase–based therapy.
C. It predicts a better prognosis.
D. It predicts for a better response with ALK inhibitor therapy.
E. It shows a high sensitivity for radiation therapy.