# Lung cancer

# Surgery for Lung Cancer in the Era of Personalized Medicine

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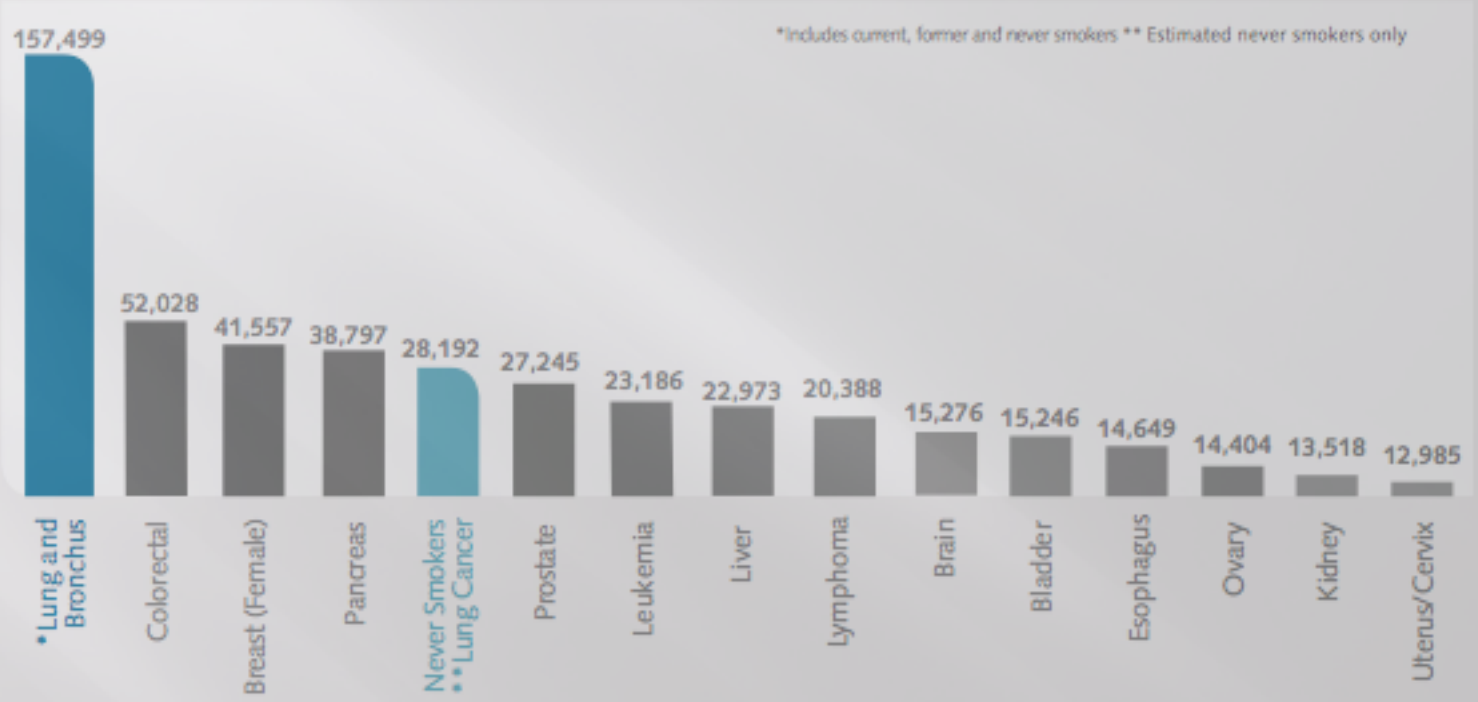
# Surgery for Lung Cancer in the Era of Personalized Medicine

# LUNG CANCER IS THE LEADING CAUSE OF CANCER DEATH (i)




## SNAPSHOT OF PEOPLE WITH LUNG CANCER (ii)

432

70

72

16.8

432 americans die of lung cancer every day!

70

72

16.8

432 americans die of lung cancer every day!

70 mean age at diagnosis!

72

16.8

432 americans die of lung cancer every day!

70 mean age at diagnosis!

72 mean age at death!

16.8

432 americans die of lung cancer every day!

70 mean age at diagnosis!

72 mean age at death!

16.8 percent surviving 5 years!

- Lung cancer takes more lives than breast, prostate and colon cancers combined

- 15% are diagnosed before spread (81% prostate and 60% breast)

- Lung cancer kills more women than any other cancer

- Lung cancer overtook breast cancer as leading cause of death among women in 1987 and now claims more lives of more women than breast, ovarian and cervical cancer combined.

- Lung cancer kills more women than any other cancer

- Incidence has been rising since the 1930s

- Lung cancer overtook breast cancer as leading cause of death among women in 1987 and now claims more lives of more women than breast, ovarian and cervical cancer combined.

- 20% of women with lung cancer never smoked (10% in men)

- Majority of second hand smokers who die from lung cancer are women

## Non Smokers

- Lung cancer in non smokers is twice as common in women vs men
- Mutations associated with NSCLC (EGFR) more common than in men

NSCLC Molecular Mutations

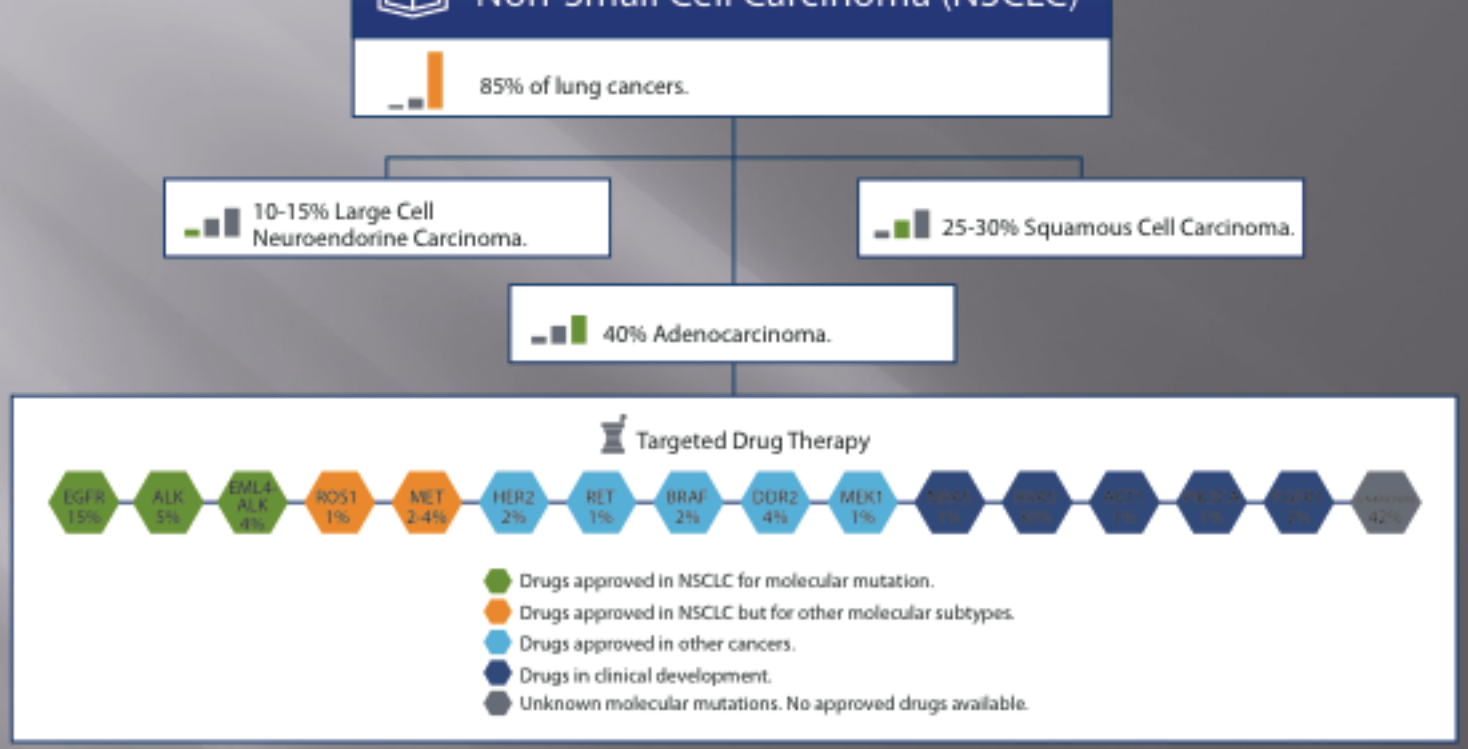
EGFR Epidermal Growth Factor Receptor

ALK Anaplastic lymphoma receptor tyrosine kinase

KRAS Kirsten rat sarcoma viral oncogene

NSCLC Molecular Mutations

Non-Small Cell Carcinoma (NSCLC)




## EGFR Epidermal Growth Factor Receptor

- Found on the surface of epithelial cells
- Over expressed in certain malignancies

- Over expressed in certain malignancies
- Exon 19 del
- Exon 21 (L858R, L861)
- Predictive of treatment benefit
- Sensitizing mutations
- Primary resistance associated to KRAS mutation and ALK rearrangement
- EGFR T790M associated with secondary resistance
- Resistance after 8 to 16 mo

## EGFR

*EGFR* Mutation Prevalence in Different Lung Adenocarcinoma Patient Populations[a]

| | EGFR Mutation Prevalence, % | EGFR Mutation Positive | EGFR Mutation Negative | n (N) |
|---|---|---|---|---|
| Asian/Pacific[b] | 45 | 1547 | 1905 | 31 (3452) |
| White[c] | 24 | 853 | 2681 | 10 (3534) |
| African American[d] | 20 | 19 | 78 | 3 (97) |
| Hispanic[e] | 17 | 65 | 307 | 4 (372) |
| Asian/Indian[f] | 52 | 114 | 106 | 1 (220) |

Abbreviations: n, number of studies; N, number of patients.

*J Thorac Oncol*. 2013 July ; 8(7): 823–859.

EGFR

Randomized Clinical Trial Data on Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Therapy Versus Chemotherapy as First-Line Therapy for Patients With *EGFR*-Lung Cancers

(TKI) Therapy Versus Chemotherapy as First-Line Therapy for Patients With *EGFR*-Lung Cancers

| Study | No. of Patients With EGFR-Mutated Lung Cancers | Response Rate (EGFR TKI Versus Chemotherapy), % | Progression-Free Survival (EGFR TKI Versus Chemotherapy), mo |
|---|---|---|---|
| EURTAC[280] | 173 (86 erlotinib and 87 chemo) | 58 versus 15 | 9.7 versus 5.2 (HR 0.37) |
| OPTIMAL[281] | 154 (82 erlotinib and 72 chemo) | 83 versus 36 | 13.1 versus 4.6 (HR 0.16) |
| NEJ 002[91] | 228 (114 gefitinib and 114 chemo) | 74 versus 31 | 10.8 versus 5.4 (HR 0.30) |
| WJTOG3405[26] | 117 (58 gefitinib and 59 chemo) | 62 versus 32 | 9.2 versus 6.3 (HR 0.49) |
| IPASS[790] | 261 (132 gefitinib and 129 chemo) | 71 versus 47 | 9.5 versus 6.3 (HR 0.48) |
| LUX LUNG3[282] | 345 (230 afatinib and 115 chemo) | 56 versus 23 | 11.1 versus 6.9 (HR 0.58) |

Abbreviations: Chemo, chemotherapy; HR, hazard ratio.

*J Thorac Oncol*. 2013 July ; 8(7): 823–859.

ALK (anaplastic lymphoma kinase)

- Alk gene rearrangement: fusion with other genes such as echynoderm microtubule associated protein like 4 or EML4
- 2-7% patients with NSCLC
- Resistance to TKI's
- More likely in men, younger age group
- Mixed squamous histology (none in squamous histology)

ALK (anaplastic lymphoma kinase)

Studies Specifically Reporting Outcome of *ALK* Rearrangement Studies in Squamous Cell Carcinomas

Studies Specifically Reporting Outcome of ALK Rearrangement Studies in Squamous Cell Carcinomas

| Source, y | n | ALK Rearrangement Positive, % |
|---|---|---|
| Takeuchi et al,[299] 2008 | 71 | 0 |
| Takahashi et al,[39] 2010 | 75 | 0 |
| Inamura et al,[10] 2008 | 48 | 0 |

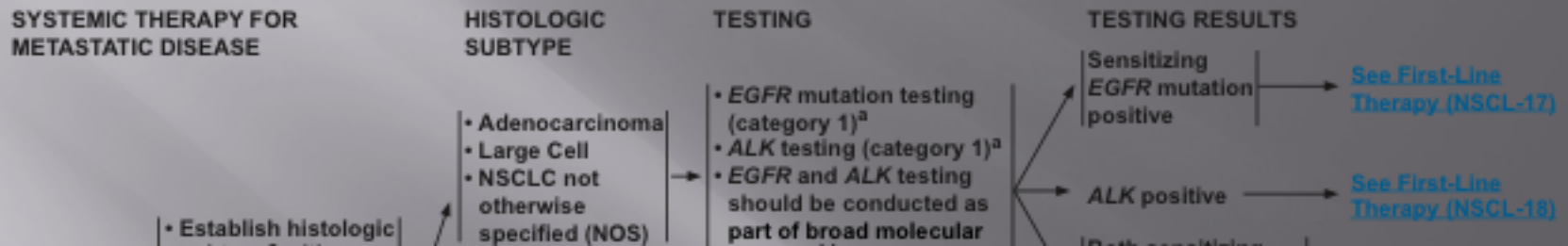
Abbreviation: n, number of squamous cell carcinoma samples tested.

## KRAS

- 25% patients with adenocarcinoma
- associated with smoking

- associated with smoking
- prognostic biomarker for shorter survival
- overlapping with EGFR <1%

## NCCN Guidelines Metastatic Disease Treatment



Metastatic Disease

- Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy if appropriate)
- Smoking cessation counseling
- Integrate palliative care[c] (See NCCN Guidelines for Palliative Care)

Squamous cell carcinoma

- Consider *EGFR* mutation and *ALK* testing[ii] especially in never smokers or small biopsy specimens, or mixed histology[jj]
- *EGFR* and *ALK* testing should be conducted as part of broad molecular profiling[hh]

Sensitizing *EGFR* mutation positive → See First-Line Therapy (NSCL-17)

*ALK* positive → See First-Line Therapy (NSCL-18)

Both sensitizing *EGFR* mutation and *ALK* are negative or unknown[kk] → See First-Line Therapy (NSCL-20)

# NCCN Guidelines Metastatic Disease Treatment

**SENSITIZING EGFR MUTATION POSITIVE[a]**

**FIRST-LINE THERAPY[ee]**

*EGFR* mutation discovered prior to first-line chemotherapy → Erlotinib[ii] (category 1) or Afatinib[ii] (category 1) or Gefitinib[ii] (category 1)

Sensitizing[l]

Progression[mm,nn]

Asymptomatic → **SUBSEQUENT THERAPY[ee]** Osimertinib[pp] or Continue Erlotinib or Afatinib or Gefitinib

Brain[oo] → Consider local therapy and Continue Erlotinib or Afatinib or

Progression,[qq] Osimertinib[pp] or See First-line therapy options




# Molecular testing recommendations

American Society of Clinical Oncology
College of American Pathologists
International Society for the Study of Lung Cancer

International Society for the Study of Lung Cancer
Association of Molecular Pathologists Guideline

Published Ahead of Print on October 13, 2014 as 10.1200/JCO.2014.57.3055

## Molecular testing recommendations

- Testing in all patients with advanced stage adenocarcinoma or adenocarcinoma component
- Small tumor samples of other histologies where adenocarcinoma can not be excluded
- Both primary tumors and metastatic lesions suitable for testing

for testing

- Testing in early stage lung cancer: rapid initiation of therapy if early recurrence cost?

Published Ahead of Print on October 13, 2014 as 10.1200/JCO.2014.57.3055

## Cost effectiveness?

# Cost-Effectiveness of Multiplexed Predictive Biomarker Screening in Non-Small-Cell Lung Cancer

*Dorothy Romanus, PhD,* Stephanie Cardarella, MD,† David Cutler, PhD,‡ Mary Beth Landrum, PhD,§ Neal I. Lindeman, MD,‖ and G. Scott Gazelle, MD, PhD¶*

(*J Thorac Oncol.* 2015;10: 586–594)

# Cost effectiveness?

**TABLE 1** Strategies

| Strategy | Test | Treatment |
|---|---|---|
| No test | None | CisPem[a] ► Pem ► DTX ► Erlot ►BSC |
| Empiric therapy[b] | EGFR/ALK IHC ► ALK FISH for ALK IHC 1–3+ | Empiric CisPem × 4 cycles ► test result conditional treatment:<br>EGFR +: Erlot ► DTX ► BSC<br>ALK +: Criz ► DTX ► BSC<br>Other: CisPem[a] ► Pem ► DTX ► Erlot ►BSC |
| Empiric- switch therapy[c] | EGFR/ALK IHC ► ALK FISH for ALK IHC 1–3+ | Empiric CisPem × 1 cycle ► test result ► test result conditional treatment:<br>EGFR +: Erlot ► CisPem[a] ► DTX ► BSC<br>ALK +: Criz ► CisPem[a] ► DTX ► BSC<br>Other: CisPem[a] ► Pem ► DTX ► Erlot ►BSC |

| | | |
|---|---|---|
| | | Other: CisPem[a] ► Pem ► DTX ► Erlot ►BSC |
| Test-treat | EGFR/ALK IHC ► ALK FISH for ALK IHC 1–3+ | EGFR +: Erlot ► CisPem[a] ► DTX ►BSC<br>ALK +: Criz ► CisPem[a] ► DTX ►BSC<br>Other: CisPem[a] ► Pem ► DTX ►Erlot ► BSC |

(*J Thorac Oncol.* 2015;10: 586–594)

## Cost effectiveness?

**TABLE 3.** Cost-Effectiveness Results[a]

| Strategy | LYs | Incremental LYs[b] | QALYs | Incremental QALYs[b] | Cost[c] | Incremental Cost[b] | ICER ($/LY) | ICER ($/QALY) |
|---|---|---|---|---|---|---|---|---|
| Standard care: No test, CisPem | 0.93 | — | 0.53 | — | $79,331 | — | — | — |
| Empiric therapy | 0.95 | 0.02 | 0.55 | 0.02 | $82,762 | $3431 | Extended dominance | Extended dominance |
| Test-treat | 0.97 | 0.02 | 0.56 | 0.01 | $83,413 | $651 | 102,000 | 136,000 |
| Empiric switch therapy | 0.97 | 0.00 | 0.56 | 0.00 | $86,645 | $3232 | Dominated | Dominated |

[a]Costs and life expectancy outcomes were discounted at a 3% annual rate. The "Empiric therapy" approach composed of CisPem continuation for four cycles before start of molecularly guided therapy. In the "Test-treat" approach, molecularly guided therapy was initiated after ascertainment of test results. In the "Empiric switch therapy," concurrent initiation of CisPem and testing was modeled followed by an immediate switch to test-result conditional treatment after one cycle of CisPem.

[b]Compared with the next best strategy in terms of effectiveness.

initiation of CisPem and testing was modeled followed by an immediate switch to test-result conditional treatment after one cycle of CisPem.

[b]Compared with the next-best strategy in terms of effectiveness.

[c]2013 $US.

LYs, life-years; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; CisPem, cisplatin and pemetrexed doublet.

(*J Thorac Oncol.* 2015;10: 586–594)

National Comprehensive Cancer Network®

# NCCN Guidelines Version 4.2016
# Non-Small Cell Lung Cancer

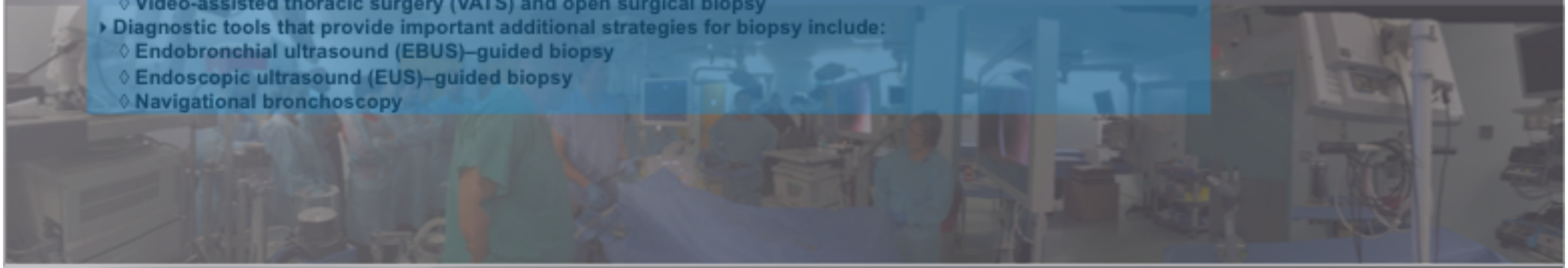
NCCN Guidelines Index
NSCLC Table of Contents
Discussion

## 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 core biopsy or fine-needle aspiration (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, 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.**

- 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.

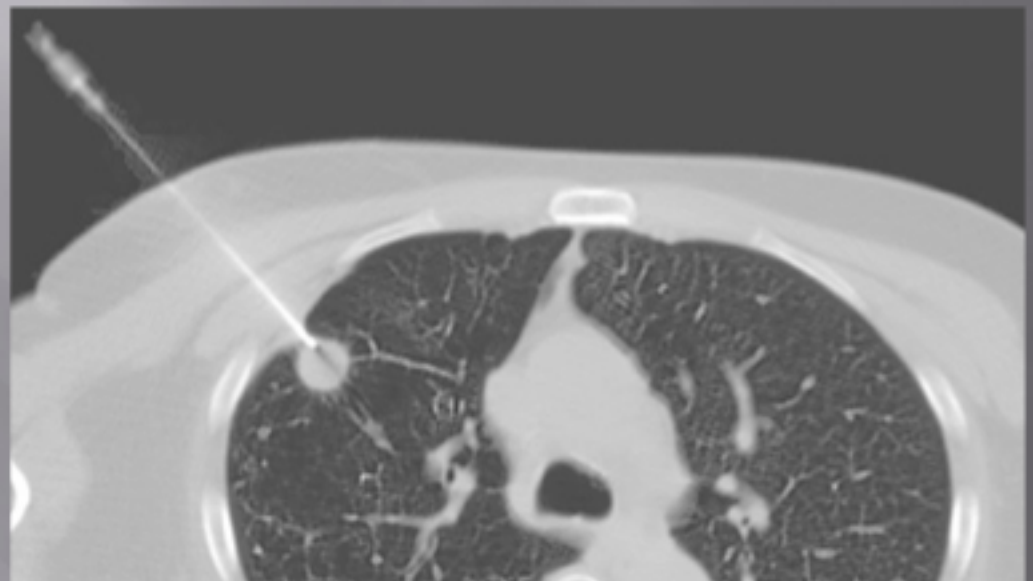
- In patients with suspected non-small cell lung cancer (NSCLC), many techniques are available for tissue diagnosis.
  - Diagnostic tools that should be routinely available include:
    - Sputum cytology
    - Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)
    - Image-guided transthoracic needle core biopsy (preferred) or FNA
    - 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
    - Endoscopic ultrasound (EUS)–guided biopsy
    - Navigational bronchoscopy



# Lung Cancer, Personalized Medicine

**3.6.2.1. In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fluid) is reliable. However, it is recommended that adequate tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable** (Grade 1B).

# CT guided needle/core biopsy



## TTNA or CT guided biopsy

- Needle or core
- Outpatient
- Interventional Radiolgy
- Pooled sensitivity 92%
- FNA vs. Core similar sensitivity: Core better to determine dx when non malignant

- FNA vs. Core similar sensitivity. Core better to determine dx when non malignant
- FP rate 1-2%
- Core yields more tissue for mutation analysis

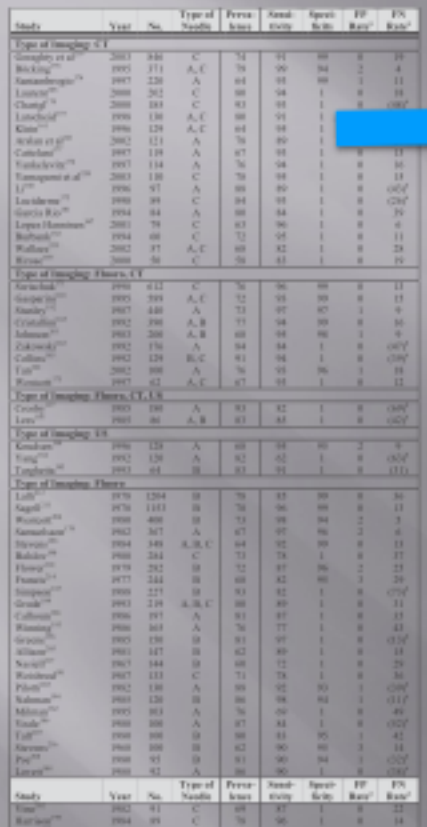
## TTNA or CT guided biopsy

Complications

- Bleeding 1% (18% required transfusion)
- PTX 15% (7% chest tube)
- Age 60-69, smokers, COPD increased risk complications

# CT guided needle/core biopy

PLATE 7. [Section 3.5.1] Test performance characteristics of transthoracic needle aspiration and/or biopsy for diagnosis of peripheral bronchogenic carcinomas.



| Study | Year | No. | Type of Needle | Prevalence | Sensitivity | Specificity | FP Rate[a] | FN Rate[a] |
|---|---|---|---|---|---|---|---|---|
| **Type of Imaging: CT** | | | | | | | | |
| Geraghty et al[219] | 2003 | 846 | C | 74 | 91 | 99 | 0 | 19 |
| Böcking[178] | 1995 | 371 | A, C | 79 | 99 | 94 | 2 | 4 |
| Santambrogio[136] | 1997 | 220 | A | 64 | 93 | 99 | 1 | 11 |
| Laurent[185] | 2000 | 202 | C | 80 | 94 | 1 | 0 | 18 |
| Charigl[170] | 2000 | 185 | C | 93 | 93 | 1 | 0 | (48)[b] |
| Larscheid[173] | 1998 | 130 | A, C | 80 | 91 | 1 | 0 | 26 |
| Klein[161] | 1996 | 129 | A, C | 64 | 95 | 1 | 0 | 8 |
| Arslan et al[221] | 2002 | 121 | A | 78 | 89 | 1 | 0 | 27 |
| Cattelani[177] | 1997 | 119 | A | 67 | 93 | 1 | 0 | 13 |
| Yankelevitz[134] | 1997 | 114 | A | 76 | 94 | 1 | 0 | 16 |
| Yamagami et al[228] | 2003 | 110 | C | 78 | 95 | 1 | 0 | 15 |
| Li[160] | 1996 | 97 | A | 88 | 89 | 1 | 0 | (43)[b] |
| Lucidarme[172] | 1998 | 89 | C | 84 | 93 | 1 | 0 | (26)[b] |
| Garcia Rio[181] | 1994 | 84 | A | 80 | 84 | 1 | 0 | 39 |
| Lopez Hanninen[167] | 2001 | 79 | C | 63 | 96 | 1 | 0 | 6 |
| Burbank[182] | 1994 | 60 | C | 72 | 95 | 1 | 0 | 11 |
| Wallace[223] | 2002 | 57 | A, C | 68 | 82 | 1 | 0 | 28 |
| Hirose[169] | 2000 | 50 | C | 58 | 83 | 1 | 0 | 19 |
| [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| **Average[c]** | | | | | **90** | **97** | **1** | **22** |
| Confidence Interval | | | | | 88–91 | 96–98 | | |

# Mediastinoscopy

- Gold standard
- Operating room
- General endotracheal anesthesia
- Same day discharge
- Morbidity 2%
- Mortality 0.08%
- Sensitivity 66-93%
- Specificity 100%

- Specificity 100%
- NPV 88-93% PPV 100% Accuracy 90-95%

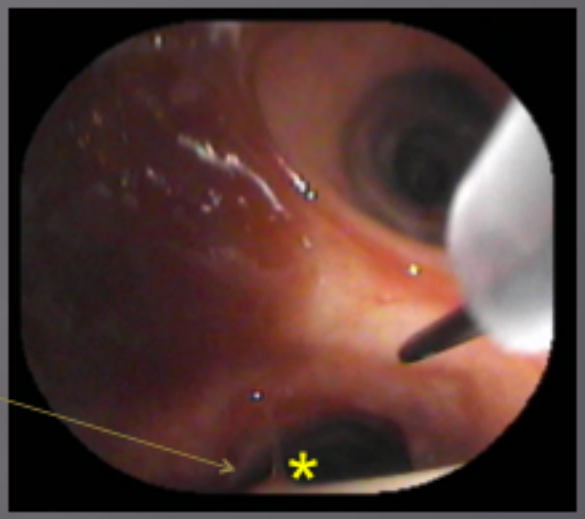
Whitson BA. Ann Thorac Surg 2007
Detterbeck FC. Chest 2003

# Video-mediastinoscopy

# Mediastinoscopy

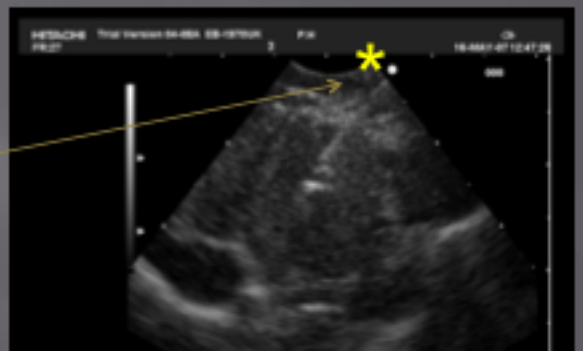
# EBUS-TBNA Technique - View

Endoscopic View
-
White Light Image

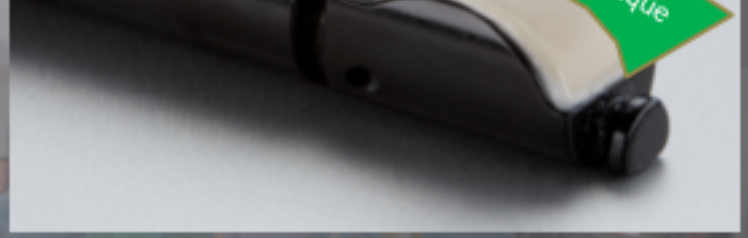



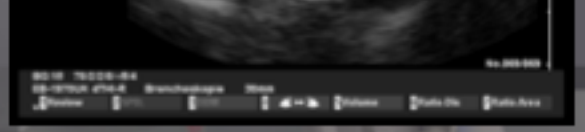
*Transducer seen at bottom of image

Echoendoscopic View
-
Ultrasound View

Ultrasound View





# EBUS TBNA

- Access to all nodal stations accesible via mediastinoscopy as well as N1 nodes
- Minimally invasive modality
- Outpatient
- Sedation or GETA (+/- confirmatory mediastinoscopy)
- Real time procedure
- Doppler mode to differentiate LN from vessels
- Wide spread of use
- STANDARD of care

# EBUS TBNA

Clinical Applications:

- Lymph node staging of lung cancer:
    - Pre-operative staging
    - Restaging after neo-adjuvant Tx
    - Evaluate for recurrence

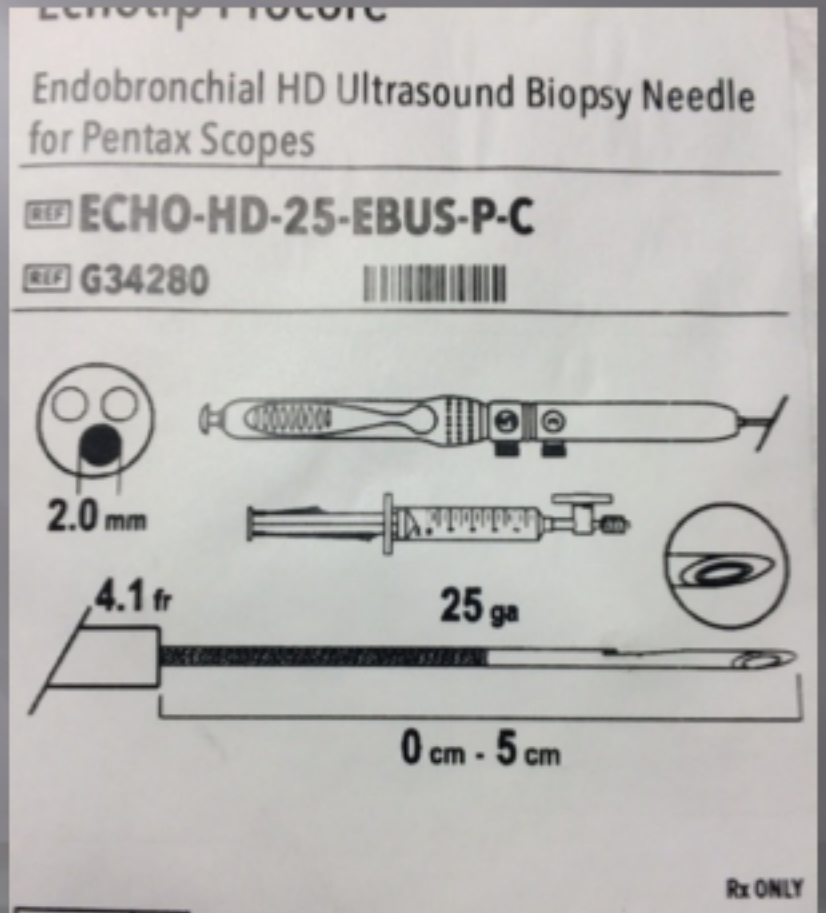
- Biopsy of centrally located lung or mediastinal tumors

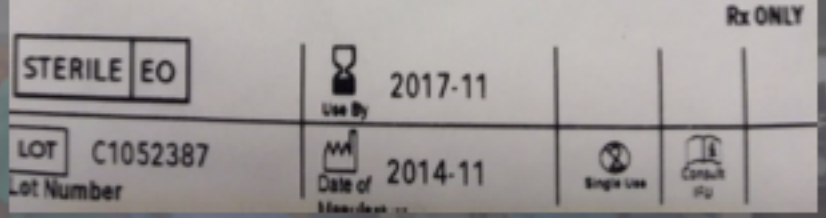
- Undiagnosed mediastinal adenopathy
    - Sarcoidosis (yield 90-96%), diagnostic accuracy 75%

- Sarcoidosis (yield 90-96%)  diagnostic accuracy 75%
- Lymphoma (sensitivity 57-91%)

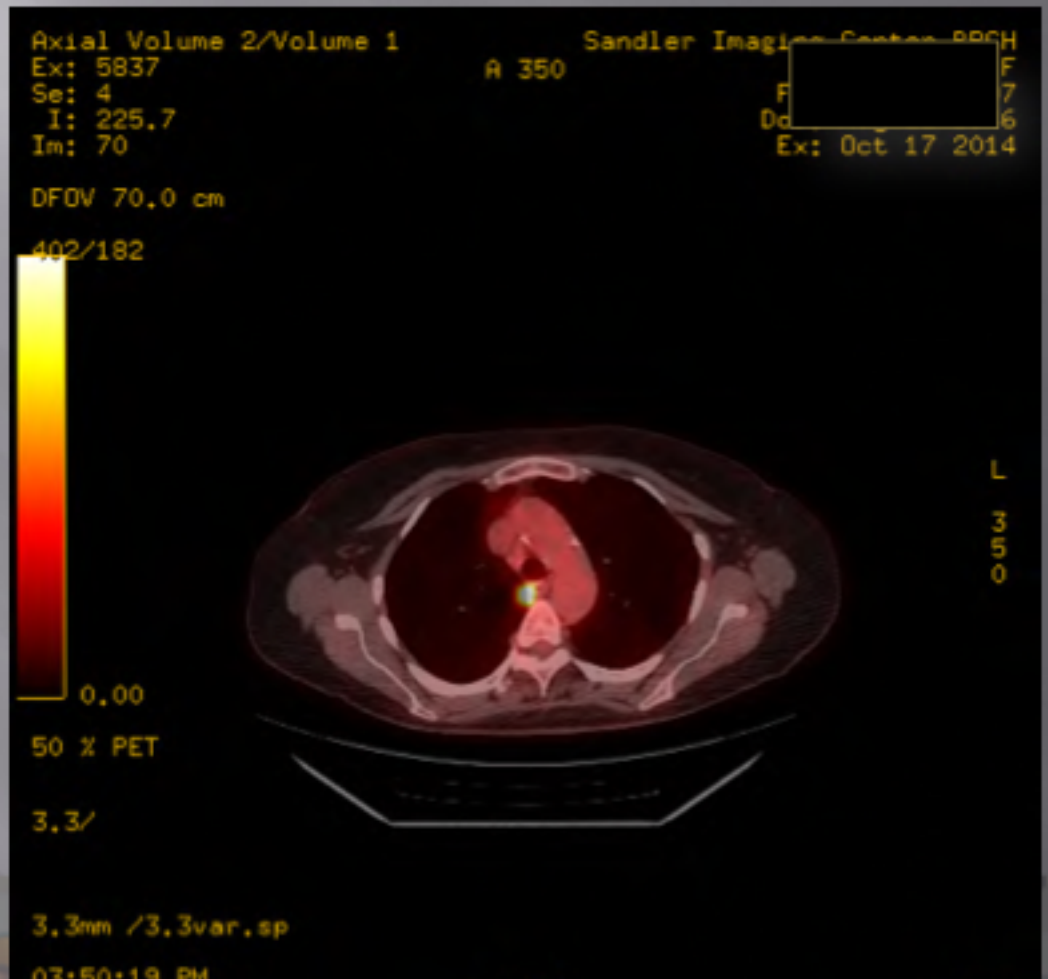
# EBUS TBNA

How I do it:

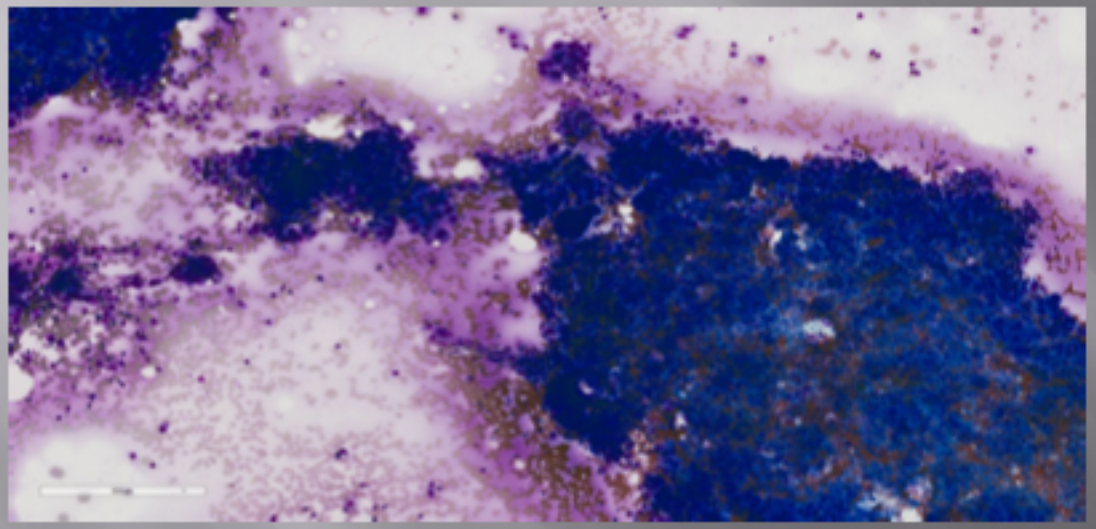



Rx ONLY
STERILE EO
2017-11
LOT C1052387
Lot Number
2014-11

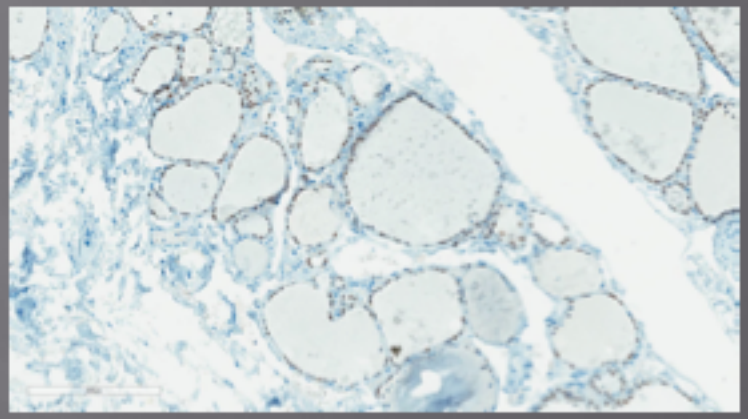
# EBUS TBNA


Axial Volume 2/Volume 1
Ex: 5837
Se: 4
I: 225.7
Im: 70
A 350
Ex: Oct 17 2014
DFOV 70.0 cm
402/182
0.00
50 % PET
3.3/
3.3mm /3.3var.sp
L 350

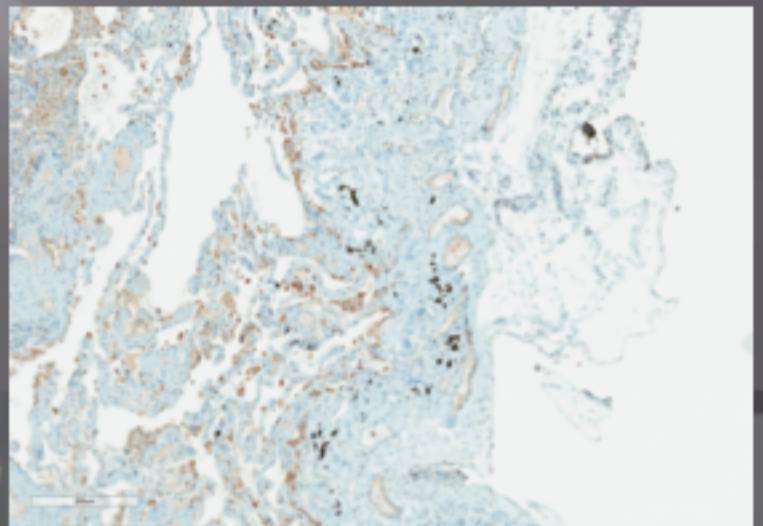

# EBUS TBNA



Diffquik

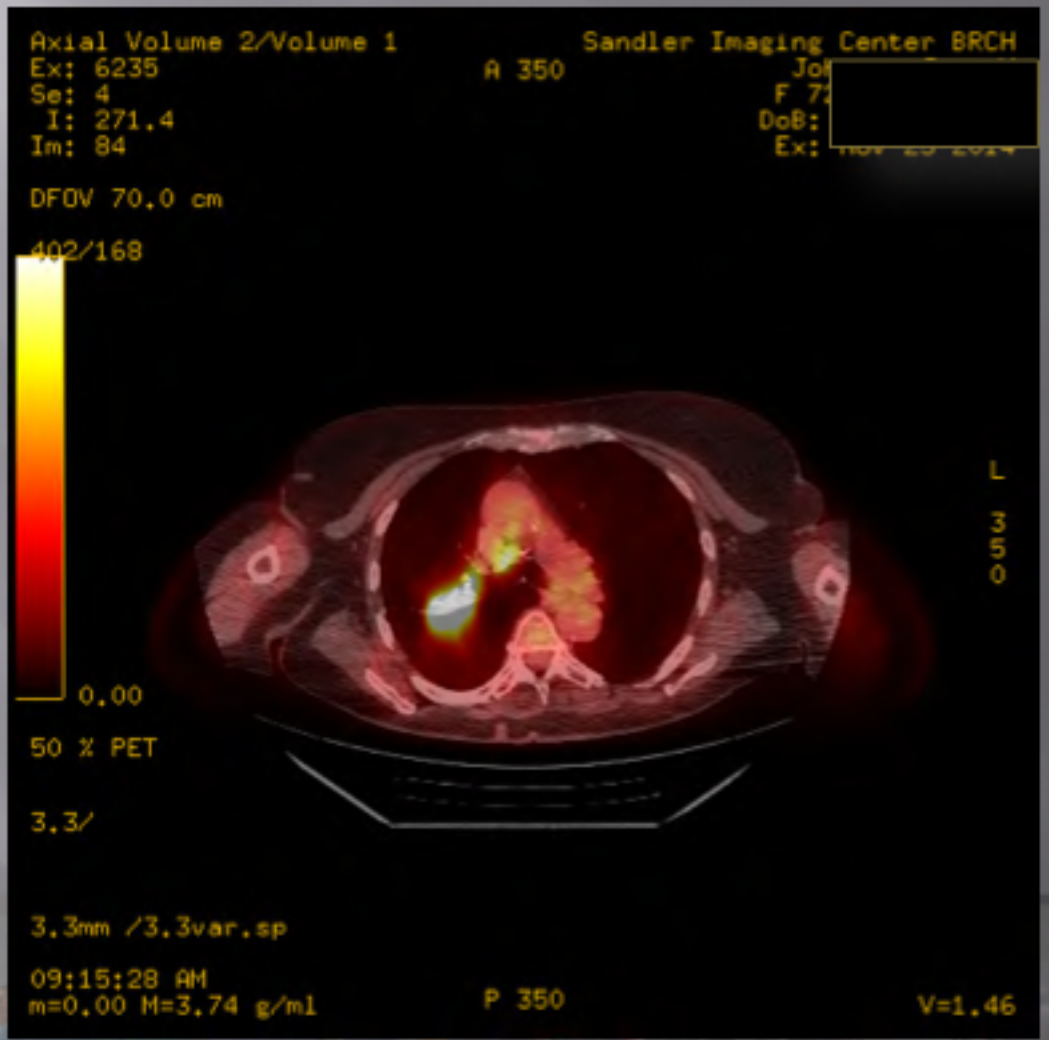


TTF1

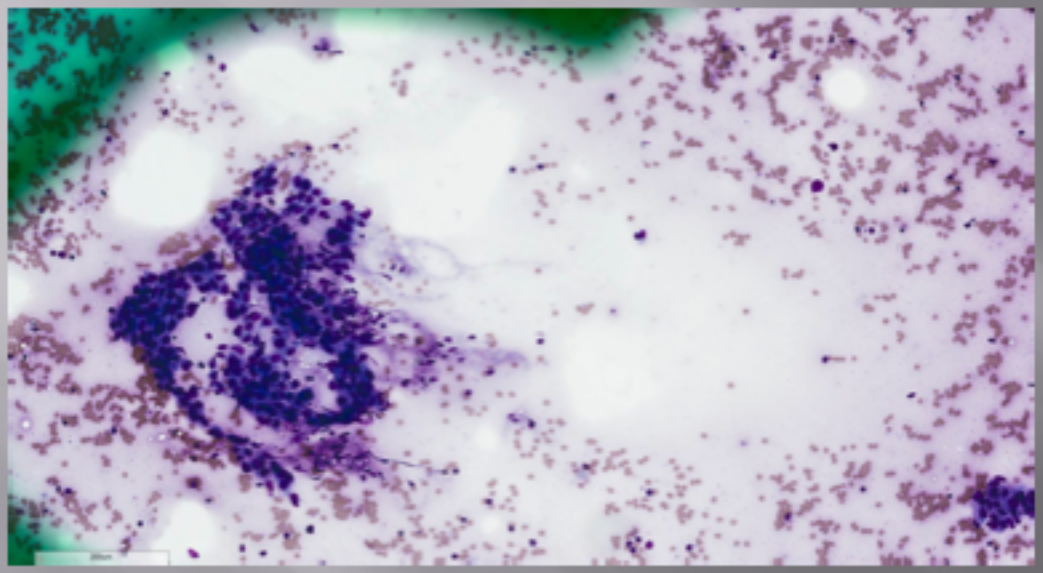


NapsinA

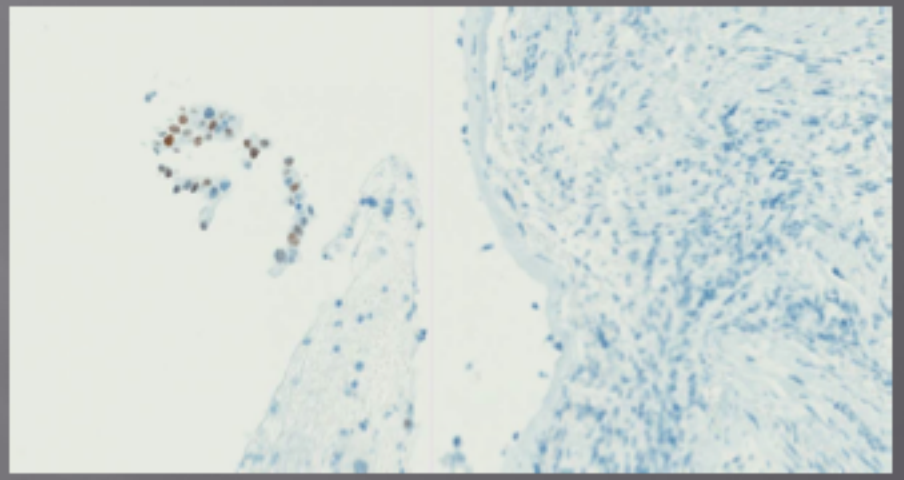
# EBUS TBNA



# EBUS TBNA



Diffquik



TTF1

**Addendum**

Date Reported: 12/30/2014

| Findings<br>Marker: | Value: | Result: |
|---|---|---|
| EML4-ALK rearrangement | None | No rearrangement |
| ALK break apart FISH | 4% | No rearrangement |
| FGFR1 FISH | 0.9 | No amplification |
| MET FISH | 1.1 | No amplification |
| EGFR expression | 15.04 | High expression |
| RRM1 expression | 3.39 | High expression |
| EGFR mutation | Wild type | No mutation |
| RET FISH | 4% | No rearrangement |
| ROS1 rearrangement FISH | 2% | No rearrangement |
| cMET expression | 11.10 | High expression |
| ERCC1 expression | 1.78 | High expression |
| TS expression | 31.83 | High expression |

Please see separate report from Response Genetics for additional information.

**Addendum**

Date Reported: 1/7/2015

# EBUS TBNA

| Study | Year | No. | Stage | Thoro | Prev | Sens | Spec[a] | PPV[a] | NPV |
|---|---|---|---|---|---|---|---|---|---|
| Fielding[341] | 2009 | 68 | cN1-3 | Sel | 87 | 95 | (100)[a] | (100)[a] | (67)[b] |
| Steinfort[334] | 2011 | 117 | cN1-3 | Sys | 80 | 97 | (100)[a] | (100)[a] | 87 |
| Cetinkaya[332] | 2011 | 52 | cN2-3 | Sys | 80 | 95 | (100)[a] | (100)[a] | 83 |
| Rintoul[344] | 2009 | 109 | cN1-3 | Sys | 77 | 91 | (100)[a] | (100)[a] | 60 |
| Gilbert[339] | 2009 | 67 | cN1-3 | Sel | 70 | 93 | (100)[a] | (100)[a] | 83 |
| Yasufuku[349] | 2005 | 108 | cN1-3 | Sys | 69 | 95 | (100)[a] | (100)[a] | 90 |
| Yasafuku[350] | 2004 | 70 | cN1-3 | Sys | 67 | 96 | (100)[a] | (100)[a] | 92 |
| Szlubowski[343] | 2009 | 226 | cN0-3 | Sys | 64 | 89 | (100)[a] | (100)[a] | 84 |
| Ye[333] | 2011 | 101 | cN1-3 | Sel | 63 | 95 | (100)[a] | (100)[a] | 93 |
| Cerfolio[336] | 2010 | 92 | cN2 | Sys | 63 | 57 | (100)[a] | (100)[a] | 79 |
| Lee BE[329] | 2012 | 73 | cN0-3 | Sys | 62 | 95 | (100)[a] | (100)[a] | 94 |
| Bauwens[345] | 2008 | 106 | cN1-3 | Sys | 58 | 95 | (100)[a] | (100)[a] | 91 |
| Sun[337] | 2010 | 49 | cN1-3 | Sys | 53 | 85 | 96 | 96 | 85 |
| Herth[307] | 2010 | 139 | cN1-3 | Sel | 52 | 91 | (100)[a] | (100)[a] | 92 |
| Memoli[331] | 2011 | 100 | cN1-3 | Sys | 47 | 87 | (100)[a] | (100)[a] | 89 |
| Omark Petersen[340] | 2009 | 151 | cN2-3 | Lim | 43 | 85 | (100)[a] | (100)[a] | 89 |
| Yasufuku[330] | 2011 | 153 | cN0-3 | Sys | 35 | 81 | (100)[a] | (100)[a] | 91 |
| Hwangbo[335] | 2010 | 150 | cN2-3 | Sys | 31 | 84 | (100)[a] | (100)[a] | 93 |
| Wallace[296] | 2008 | 138 | cN2-3 | Sys | 30 | 69 | (100)[a] | (100)[a] | 88 |
| Lee HS[346] | 2008 | 102 | cN2-3 | Sys | 30 | 94 | (100)[a] | (100)[a] | 97 |
| Hwangbo[342] | 2009 | 117 | cN2-3 | Sys | 26 | 90 | (100)[a] | (100)[a] | 97 |
| Yasufuku[348] | 2006 | 102 | cN1-3 | Sys | 25 | 92 | (100)[a] | (100)[a] | 97 |
| Szlubowski[343] | 2010 | 120 | cN0 | Sel | 22 | 46 | 99 | 93 | 86 |
| Herth[211] | 2006 | 100 | cN0 | Sys | 21 | 92 | (100)[a] | (100)[a] | 96 |
| Nakajima[338] | 2010 | 49 | cN1-3 | Sys | 18 | 67 | (100)[a] | (100)[a,c] | 93 |
| Herth[210] | 2008 | 97 | cN0 | Sys | 10 | 89 | (100)[a] | (100)[a,c] | 99 |
| **Median: Prevalence ≥ 80** | | | | | | **96** | | | **83** |
| **Median: Prevalence 60-79** | | | | | | **91** | | | **83** |
| **Median: Prevalence 40-59** | | | | | | **87** | | | **89** |
| **Median: Prevalence 20-39** | | | | | | **87** | | | **95** |
| **Median: Prevalence < 20** | | | | | | **78** | | | **96** |
| **Median: cN1-3** | | | | | | **91** | | | **89** |
| **Median: cN0** | | | | | | **89** | | | **96** |
| **Summary: median** | | **2,756** | | | **58** | **89** | **(100)[a]** | **(100)[a]** | **91** |

Overall sensitivity: 89% (46-97%)

NPV 91% (n=2756)

*Silvestri et al. Chest. 2013*

# EBUS TBNA

Risk EBUS-TBNA

Gu et al. *Eur J Cancer* – 1299 pts (11 studies)

Systematic review of EBUS-TBNA for lung ca staging

0.07% morbidity (pneumothorax)

Varela-Lema et al. *Eur Respir J* 2009 – 1627 pts (15 studies)

Systematic review of EBUS-TBNA for lung ca staging

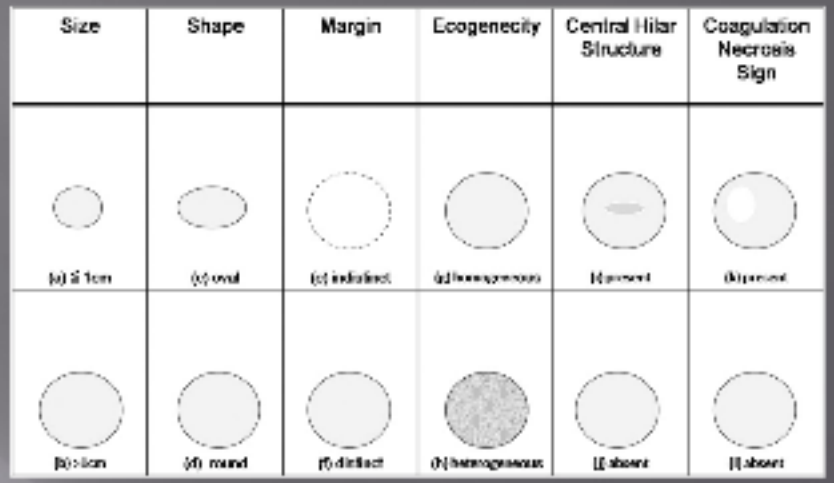
No complications

Agitation, cough and blood at puncture site

# EBUS TBNA

Ultrasonographic features

- Round shape
- Distinct margin
- Heterogeneous
- Central necrosis

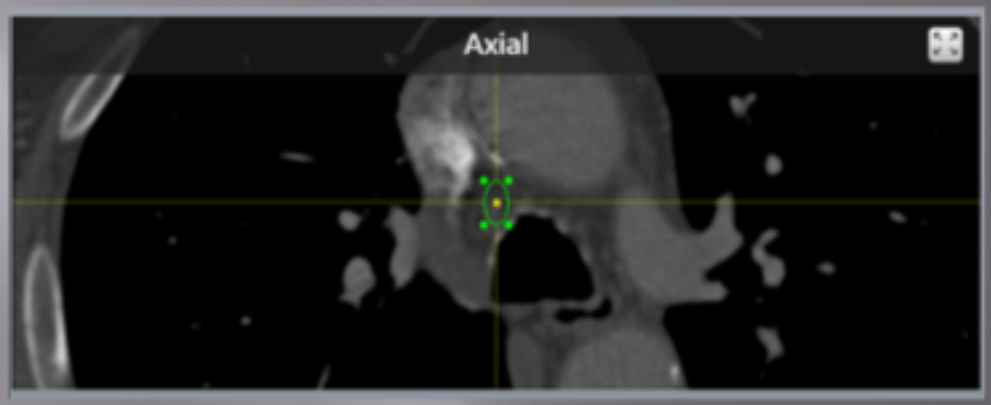


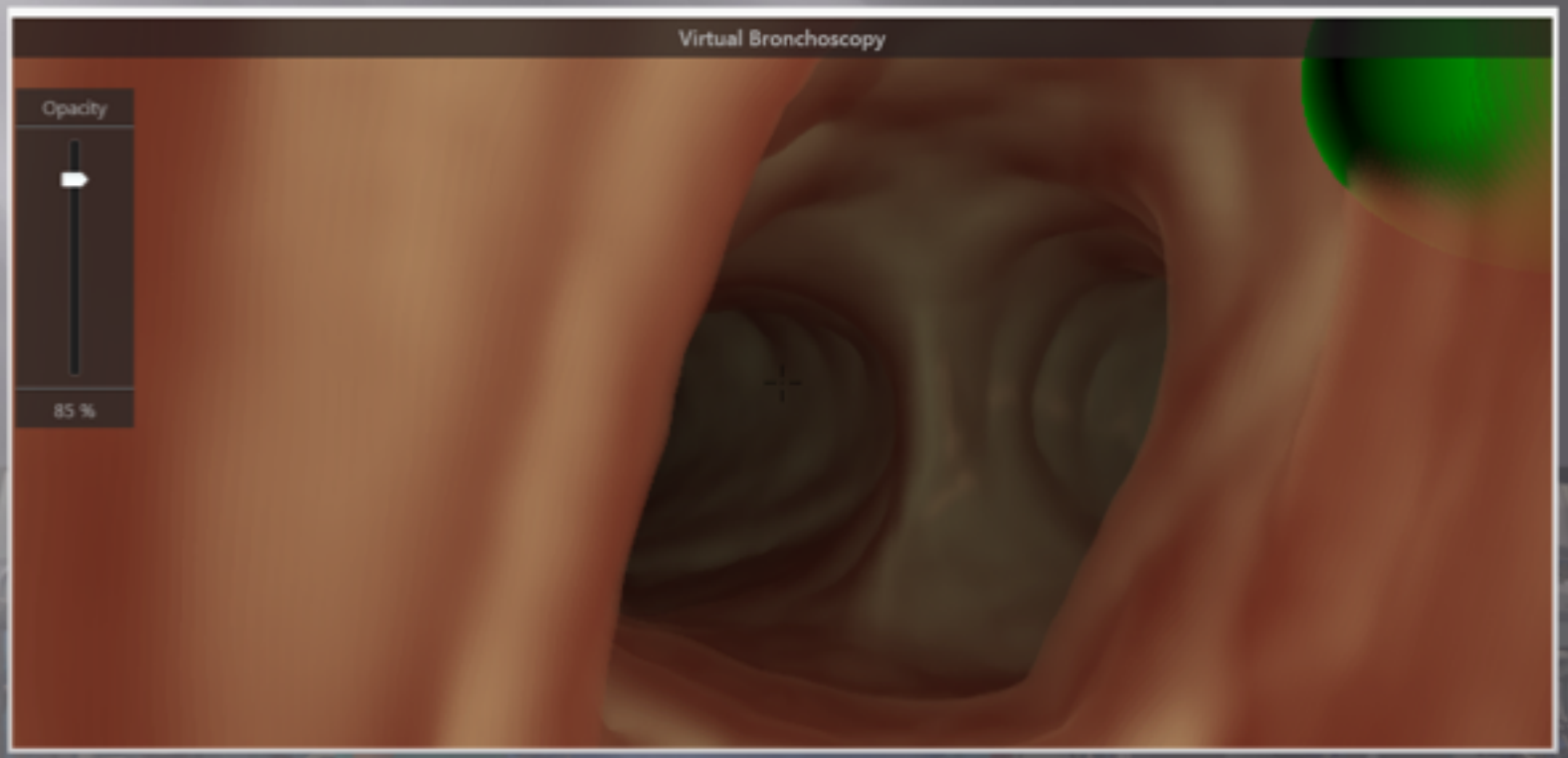

Independent predictor for malignancy
All four absent 96% nodes benign

*CHEST 2010; 138(3):641–647*

# EBUS TBNA

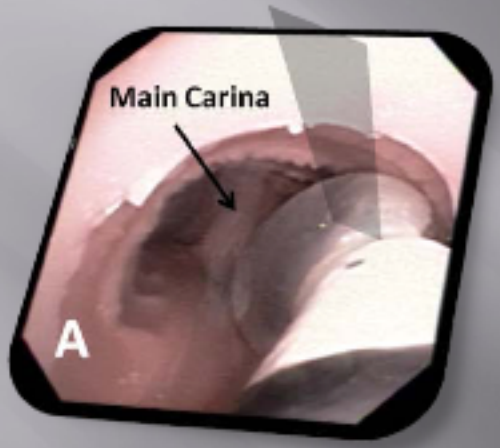
## Anatomy 4R

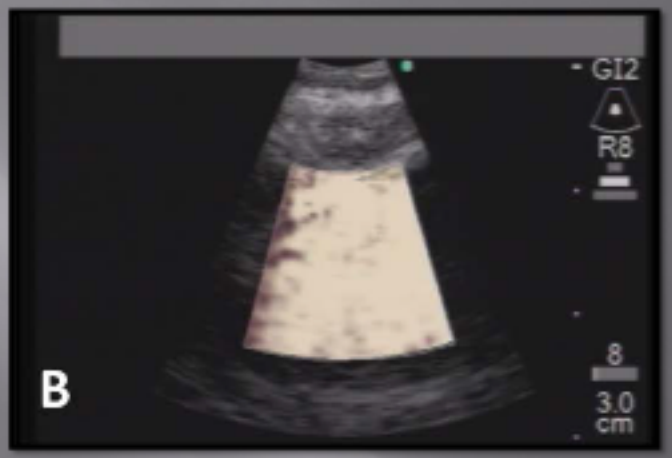


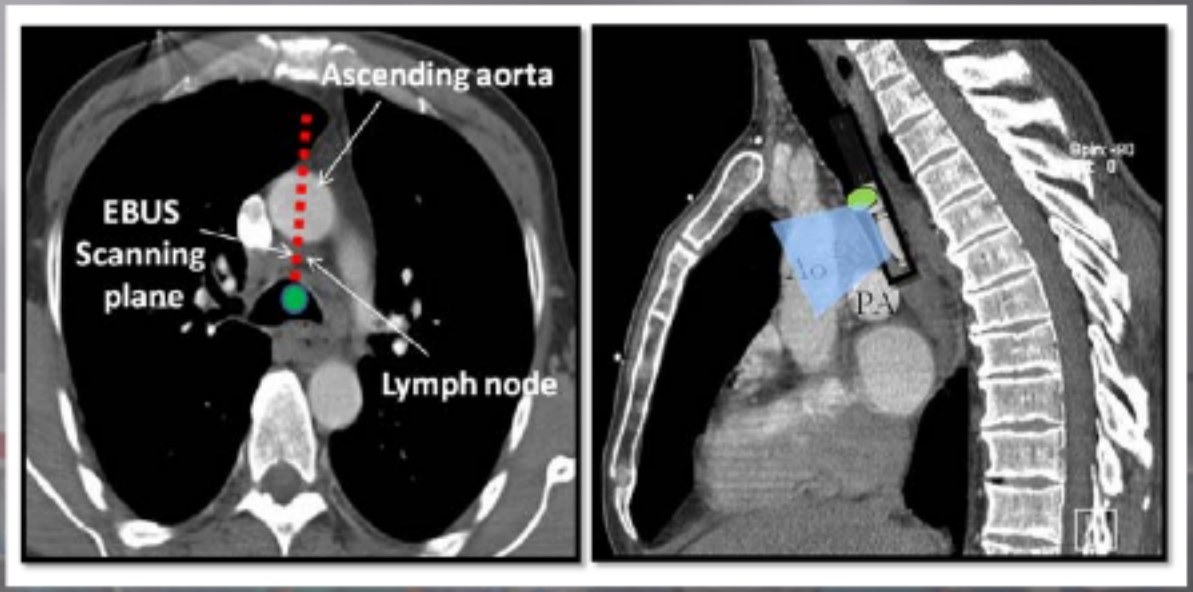



# EBUS TBNA

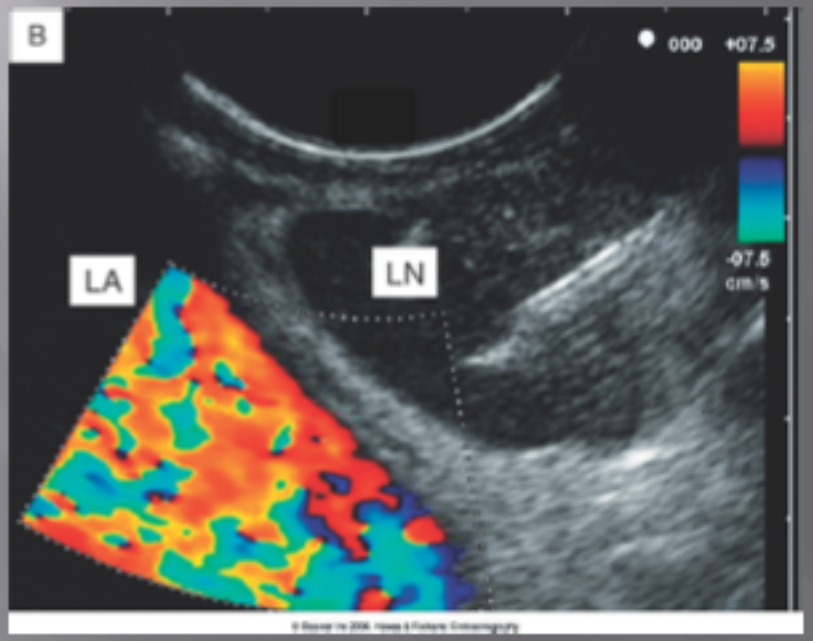
## Anatomy 4R



# Endobronchial Ultrasound




# Diagnostic Yield Molecular Analysis

## The Efficacy of EBUS-Guided Transbronchial Needle Aspiration for Molecular Testing in Lung Adenocarcinoma

Julissa Jurado, MD, Anjali Saqi, MD, MBA, Roger Maxfield, MD, Alexis Newmark, BS, Matt Lavelle, MSE, Matthew Bacchetta, MD, Lyall Gorenstein, MD, Frank Dovidio, MD, Mark E. Ginsburg, MD, Joshua Sonett, MD, and William Bulman, MD

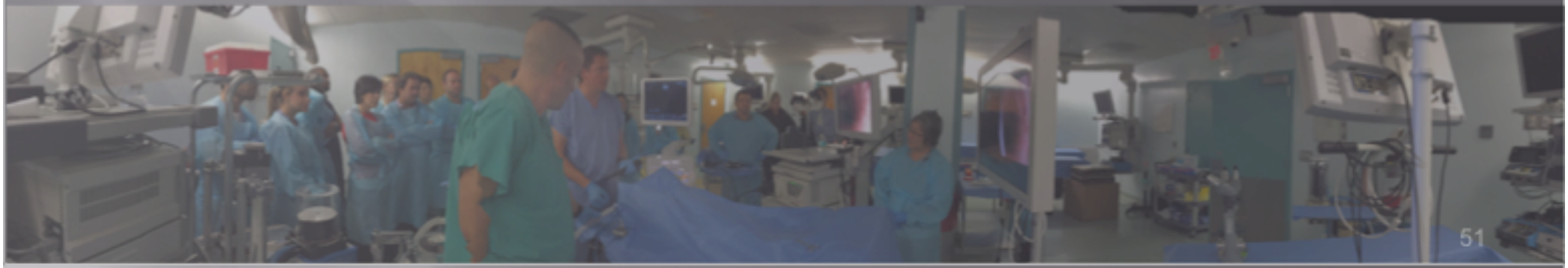
Department of General Thoracic Surgery, Department of Pathology and Cell Biology, and Division of Pulmonary and Critical Care Medicine, Columbia University Medical Center, New York, New York

(Ann Thorac Surg 2013;96:1196–202)

| Sample Type | No. of Samples Tested | Positive (%) | Negative (%) | Insufficient (%) | Sufficient for Testing |
|---|---|---|---|---|---|
| EGFR | 51 | 5 (10%) | 41 (80%) | 5 (10%) | 46 (90%) |
| ALK | 43 | 5 (12%) | 34 (79%) | 4 (9%) | 39 (91%) |
| Kras | 40 | 10 (25%) | 20 (50%) | 10 (25%) | 30 (75%) |

Numbers in parentheses represent proportion in total number of samples tested.

ALK = anaplastic lymphoma; EGFR = epidermal growth factor receptor; Kras = Kirsten rat sarcoma.



# Diagnostic Yield Molecular Analysis

## EBUS-TBNA Provides Highest RNA Yield for Multiple Biomarker Testing from Routinely Obtained Small Biopsies in Non-Small Cell Lung Cancer Patients - A Comparative Study of Three Different Minimal Invasive Sampling Methods

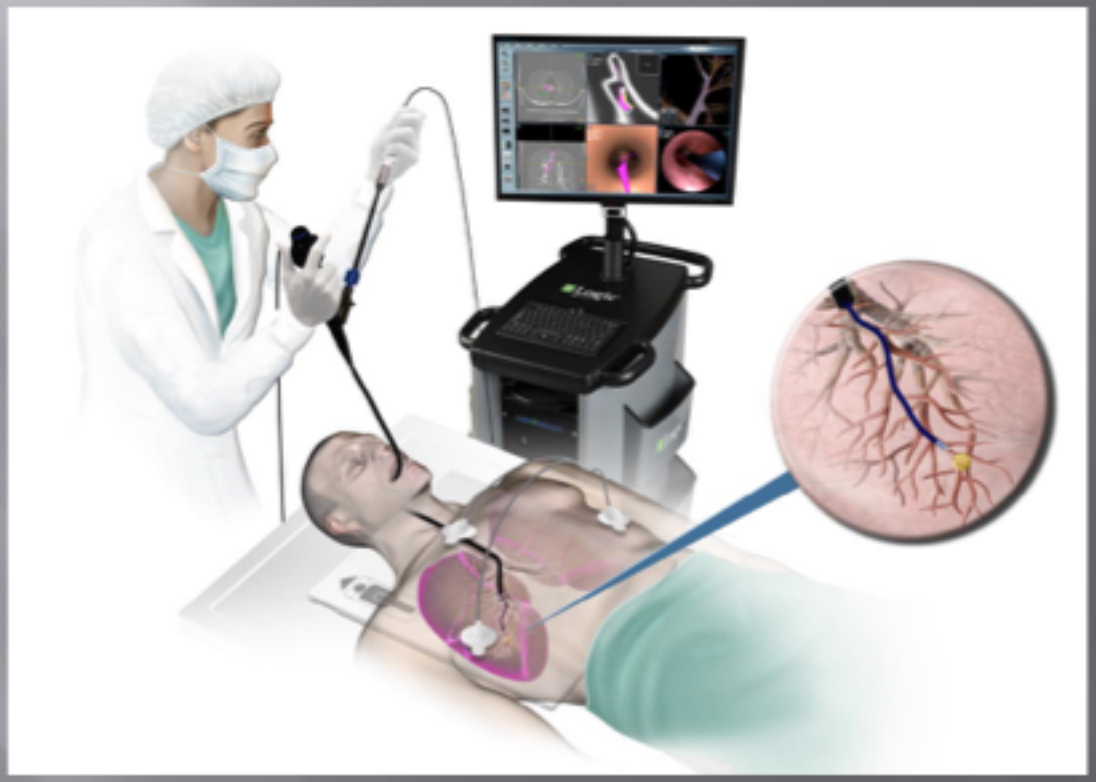
Gerald Schmid-Bindert[1], Yongsheng Wang[2,3], Hongbin Jiang[4], Hui Sun[2], Thomas Henzler[5], Hao Wang[6], Lothar R. Pilz[7], Shengxiang Ren[2]*, Caicun Zhou[2]

***Methods:*** 106 small biopsies were prospectively collected by three different methods forceps biopsy, endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA), and CT-guided core biopsy. Samples were split into two halves. One part was formalin fixed and paraffin embedded for standard pathological evaluation. The other part was put in RNAlater for immediate RNA/DNA extraction. If the pathologist confirmed the diagnosis of non-small cell lung cancer(NSCLC), the following molecular markers were tested: EGFR mutation, ERCC1, RRM1 and BRCA1.

***Conclusion:*** All three methods can provide sufficient tumor material for multiple biomarkers testing from routinely obtained small biopsies in lung cancer patients. In our study EBUS guided needle aspiration provided the highest amount of tumor RNA compared to bronchoscopy or CT guided core biopsy. Thus EBUS should be considered as an acceptable option for tissue acquisition for molecular testing.

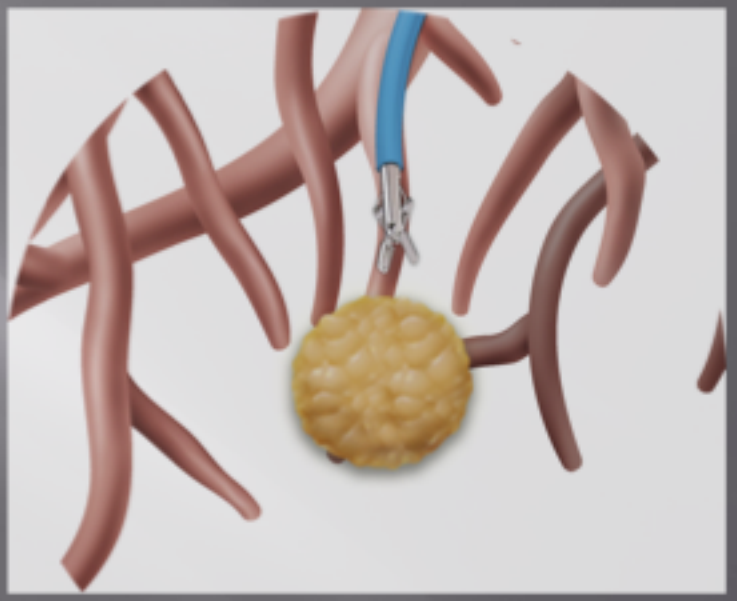
PLOS ONE October 2013 | Volume 8 | Issue 10

# Electromagnetic Navigational Bronchoscopic Biopsy



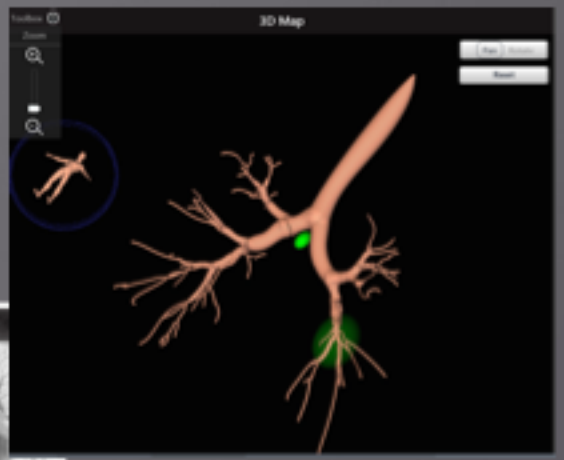
# Electromagnetic Navigational Bronchoscopic

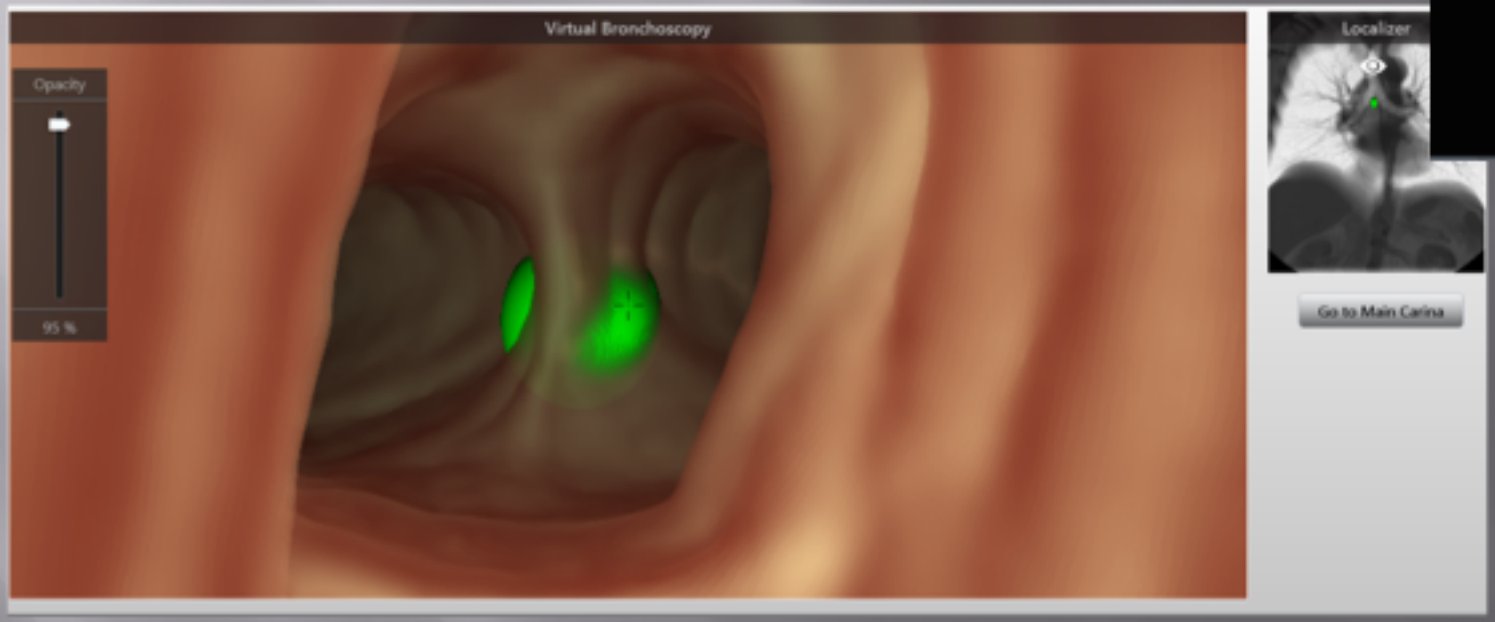
# Electromagnetic Navigational Bronchoscopic Biopsy



Electromagnetic Navigational Bronchoscopic

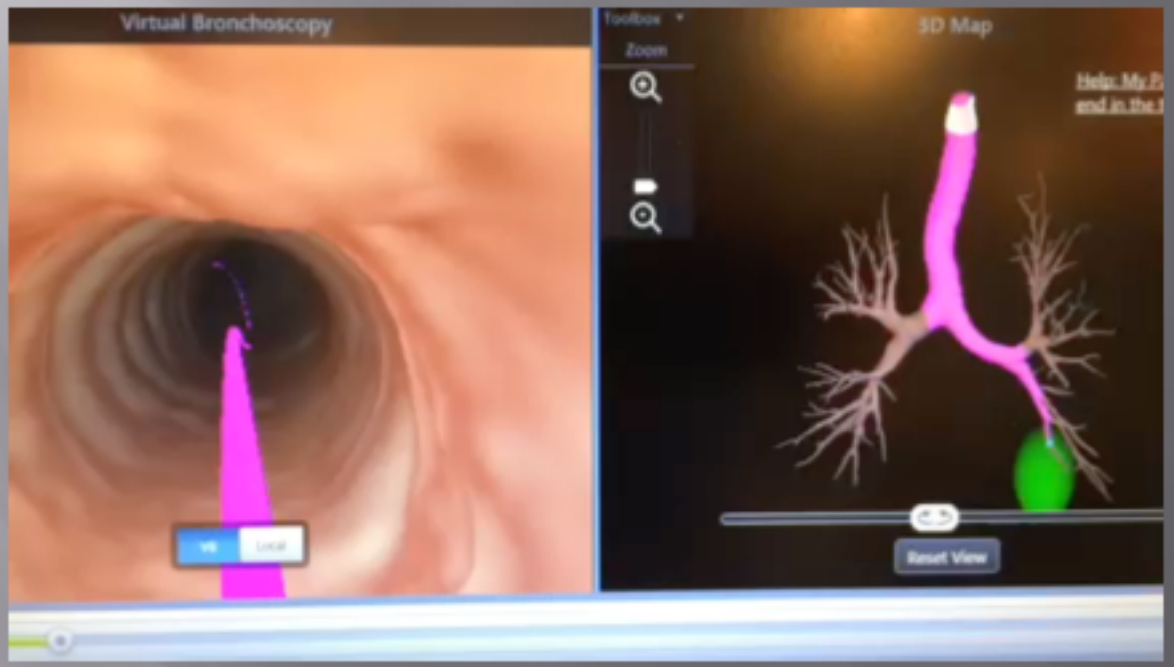
Biopsy




# Electromagnetic Navigational Bronchoscopic Biopsy

# Biopsy




# Diagnostic Yield ENB

FIGURE 6. [Section 3.4] Diagnostic yield of electromagnetic navigation for peripheral pulmonary nodules.

FIGURE 6. [Section 3.4] Diagnostic yield of electromagnetic navigation for peripheral pulmonary nodules.

| First Author | Year | No. | ROSE used? | Size mm[a] | Diagnostic Yield (%) | Pneumo -thorax rate (%) |
|---|---|---|---|---|---|---|
| **Prospective** | | | | | | |
| Eberhardt[148] | 2007 | 120 | no | 26 | 59[b] | 6 |
| Eberhardt[137] | 2007 | 89 | no | 24 | 67 | 2 |
| Gildea[146] | 2006 | 60 | no | 24 | 74 | 3 |
| Bertoletti[157] | 2009 | 54 | no | 28 | 71 | 4 |
| Eberhardt[154] | 2009 | 54 | no | 23 | 76 | 2 |
| Seijo[153] | 2010 | 51 | yes | 25 | 67[c] | - |
| Makris[147] | 2007 | 40 | no | 24 | 63 | 8 |
| Schwarz[144] | 2006 | 13 | no | 34 | 69 | 0 |
| **Subtotal** | | | | | 68 | 4 |
| **Retrospective** | | | | | | |
| Wilson[151] | 2007 | 248 | yes | 21 | 70 | 3 |
| Pearlstein[158] | 2012 | 104 | yes | 28 | 85 | 6 |
| Mahajan[155] | 2011 | 48 | no | 20 | 77 | 10 |
| Becker[142] | 2005 | 29 | no | 40 | 69 | 3 |
| Lamprecht[152] | 2009 | 13 | yes | 30 | 77 | 0 |
| Weiser[156] | 2008 | 9 | yes | - | 67 | - |
| **Subtotal** | | | | | 74 | |
| **Total** | | **932** | | | **71** | **4** |

Inclusion criteria: studies reporting the yield of electromagnetic navigation bronchoscopy in patients with peripheral lung lesions, up to December 2011. ROSE = rapid on-site cytologic evaluation.
[a]Mean or median.
[b]88% yield when combined with endobronchial ultrasound.
[c]Higher yield with positive bronchus sign.


# Diagnostic Yield Molecular Analysis

# Histologic and Molecular Characterization of Lung Cancer With Tissue Obtained by Electromagnetic Navigation Bronchoscopy

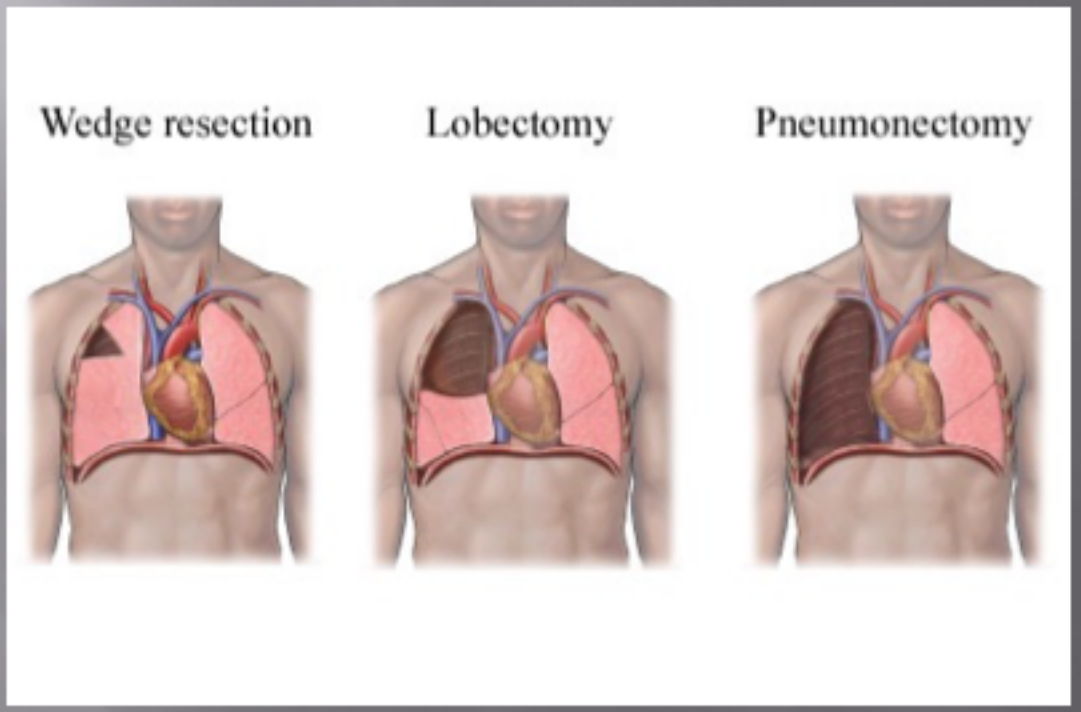
**TABLE 4.** Immunohistochemical and Molecular Characterization of Lung Cancer by ENB

| IHC/Molecular Analysis | Samples Sent, n | Adequate Samples, n (%) |
|---|---|---|
| TTF-1 | 12 | 12 (100) |
| p63 | 4 | 4 (100) |
| Cytokeratin 5/6 | 6 | 6 (100) |
| EGFR mutation | 15 | 14 (93.3) |
| EML4-ALK gene rearrangements | 2 | 2 (100) |

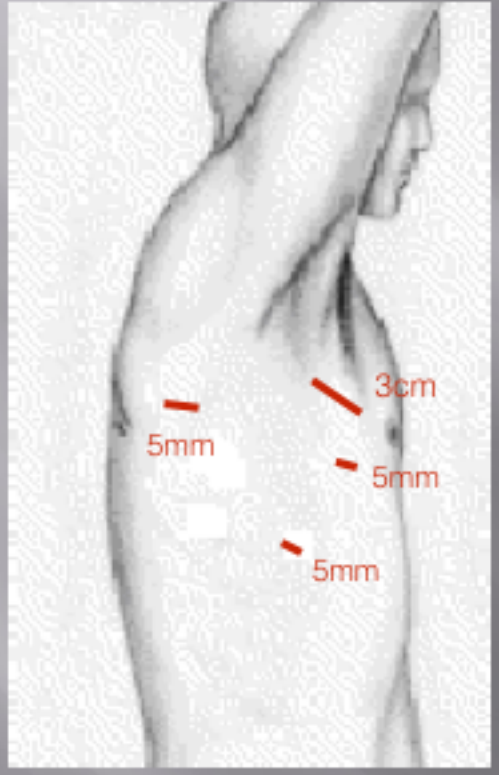
EGFR indicates epidermal growth factor receptor; EML4-ALK, echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase; ENB, electromagnetic navigation bronchoscopy; IHC, immunohistochemical.

*J Bronchol Intervent Pulmonol* 2013;20:10–15

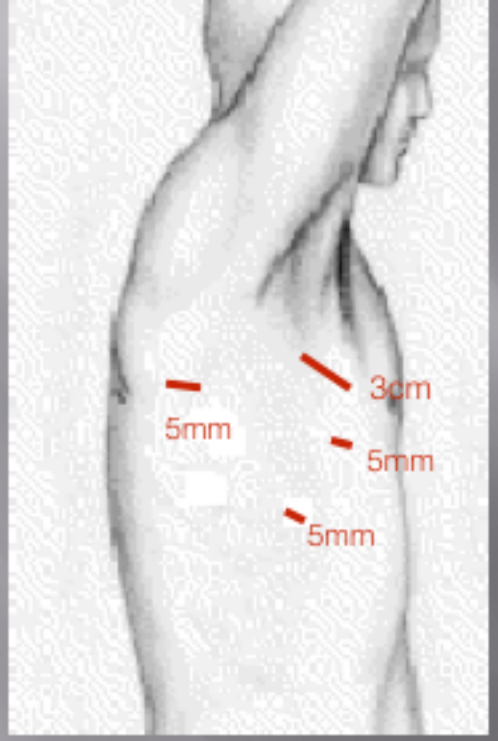

# Minimally Invasive Lung Resection

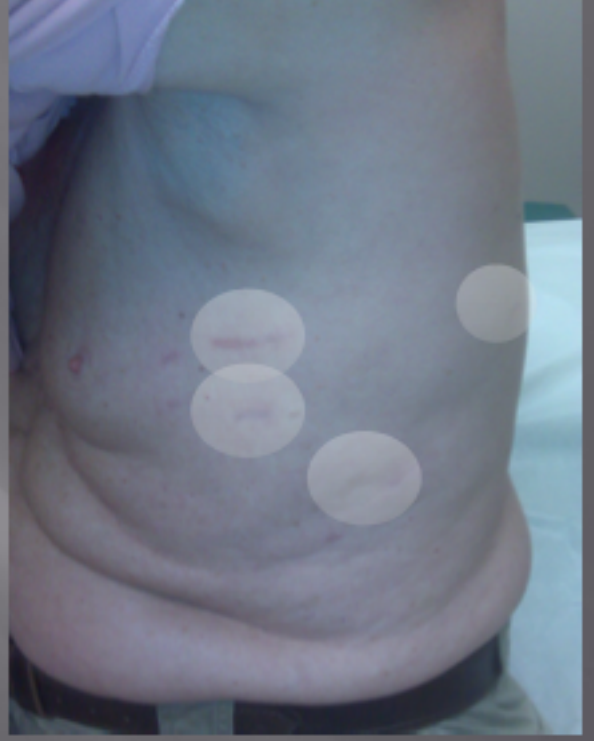



# Minimally Invasive Lung Resection




# Minimally Invasive Lung Resection

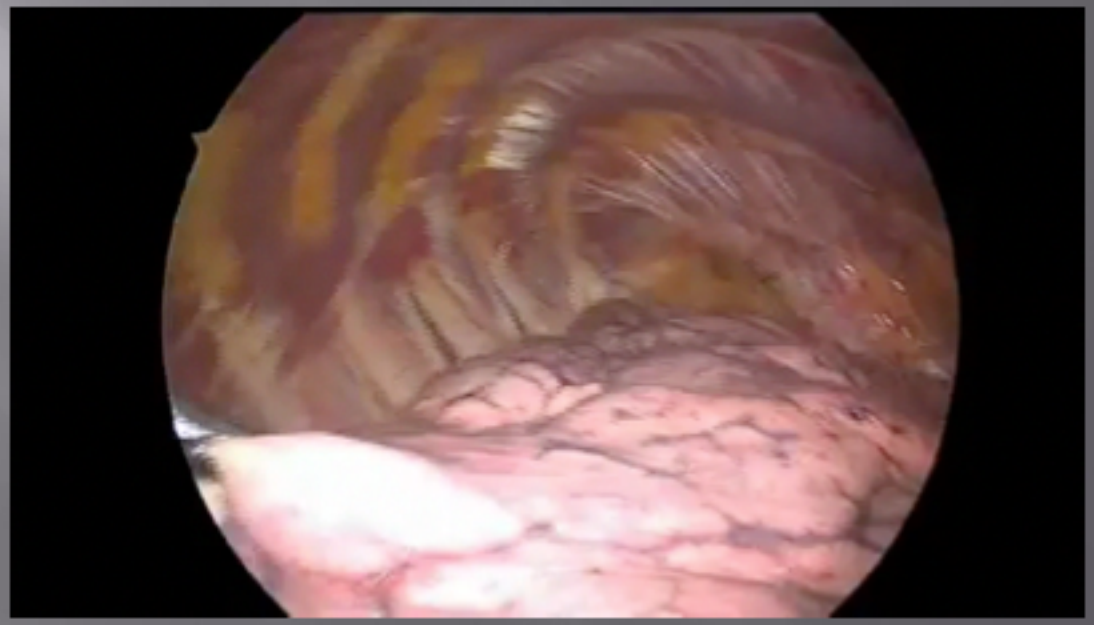


# Minimally Invasive Surgery

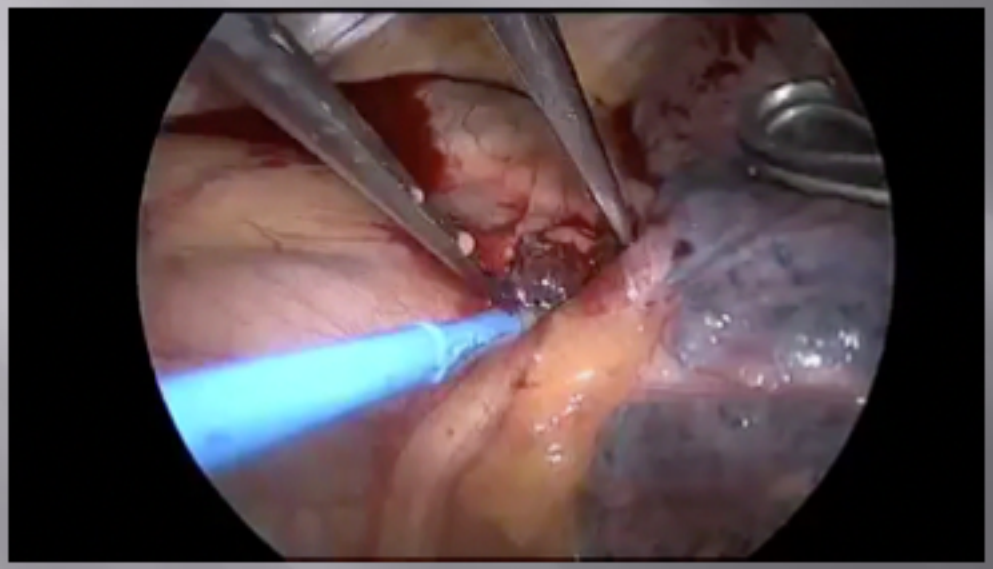
## Wedge resection

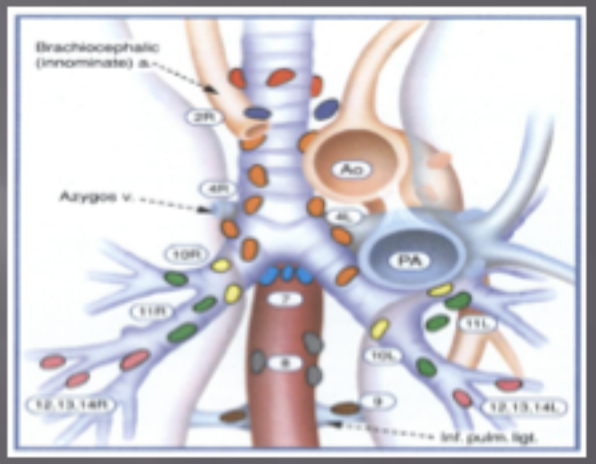
Wedge resection



# Minimally Invasive Surgery

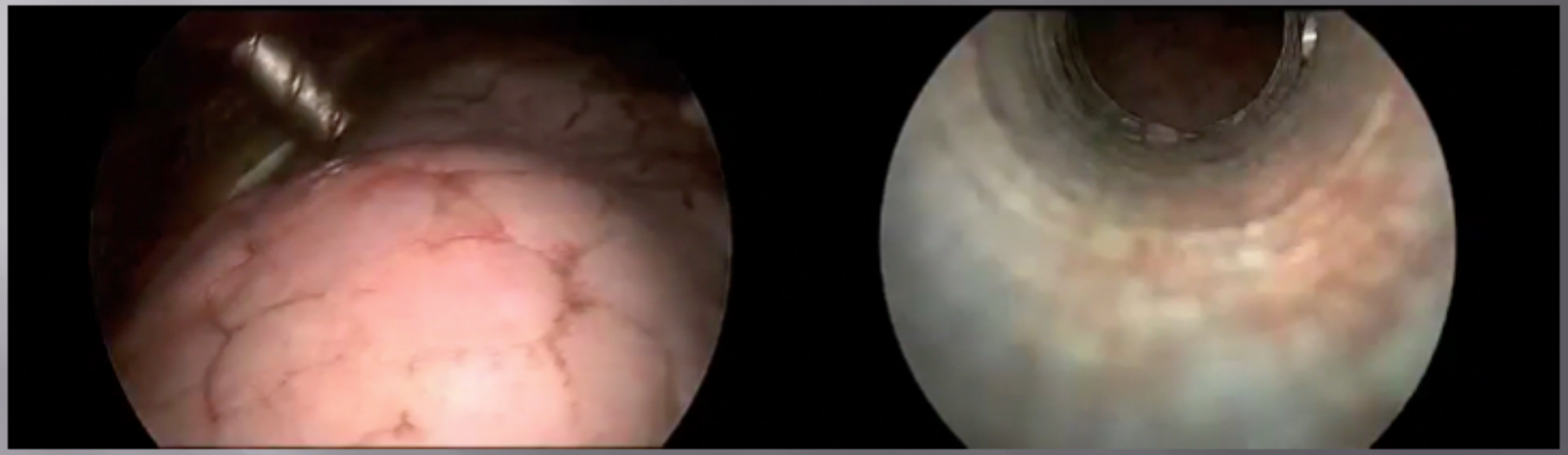
## Mediastinal nodes



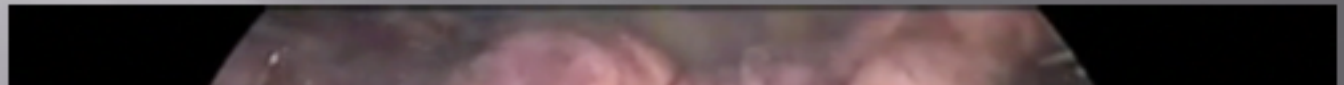

# Minimally Invasive Surgery

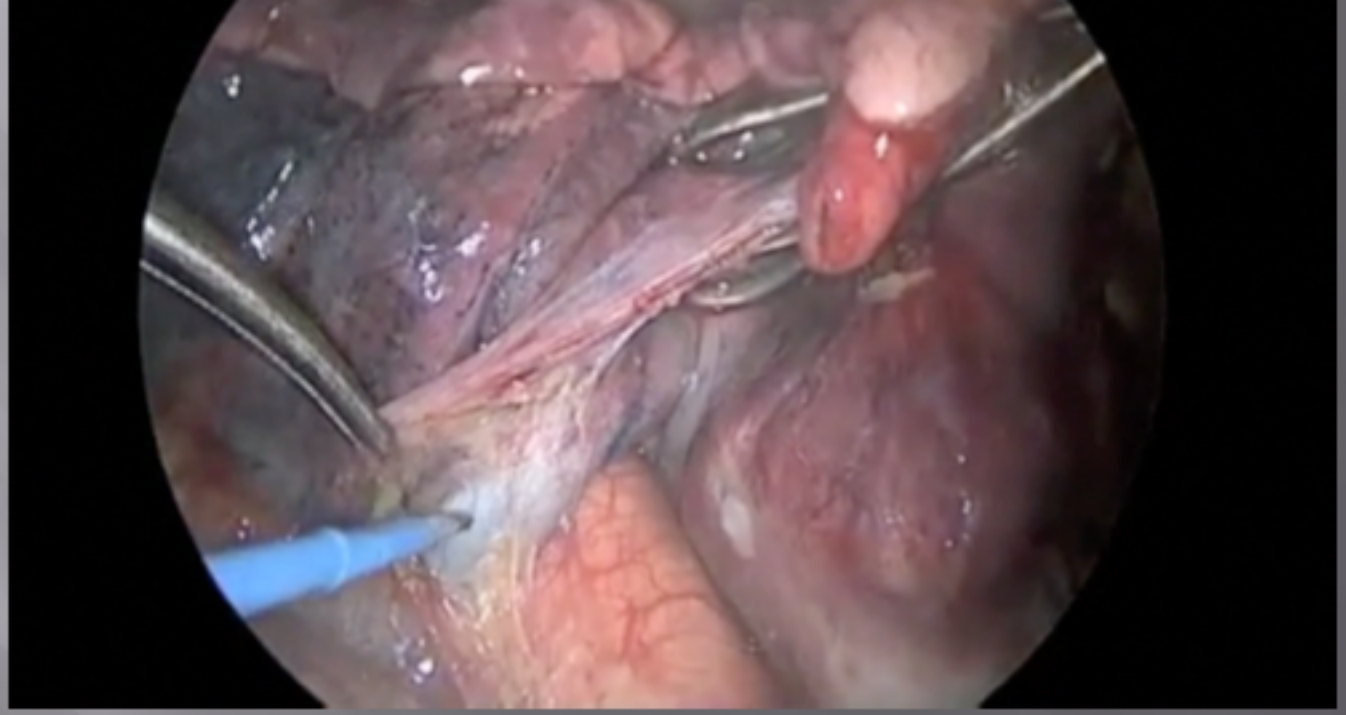
## Pleural biopsy



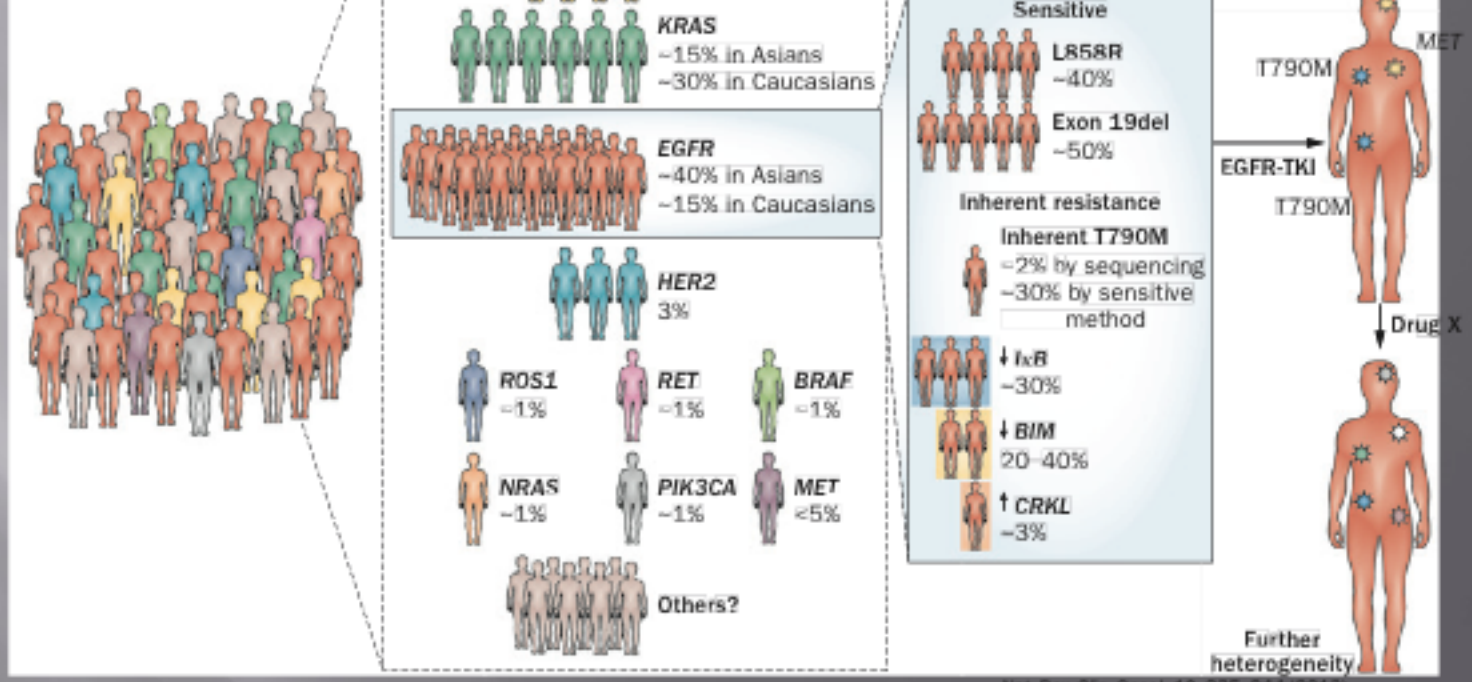
# Minimally Invasive Surgery

## Lobectomy, LLL





# Tumor heterogeneity




Nat. Rev. Clin. Oncol. 10, 235–244 (2013)

# EGFR

Summary of Studies of the Concordance of *EGFR* Mutations in Primary Versus Metastatic Tumors in the Same Patient[a]

Same Patient[a]

| | Primary Tumor | |
|---|---|---|
| Metastatic Lesions | EGFR+ | EGFR− |
| EGFR+ | 108 | 6 |
| EGFR− | 11 | 183 |

[a]Data derived from Park et al[57]; Yatabe et al[80]; and Sun et al.[303]

*J Thorac Oncol*. 2013 July ; 8(7): 823–859.

# Lung Cancer and Personalized Treatment

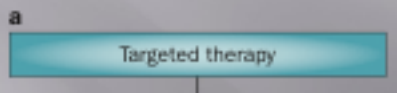
**Table 1** | Comparison of three fundamental treatment of cancer

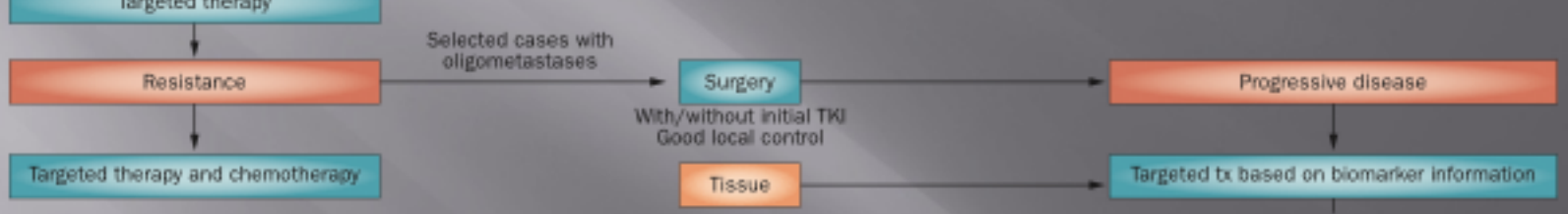
**Table 1** | Comparison of three fundamental treatment of cancer

| Treatment modality | Mode | Indication | Treatment period | Response rate | Treatment-related death | Tissue availability |
|---|---|---|---|---|---|---|
| Drug therapy | Systemic | Adjuvant<br>Neoadjuvant<br>Metastatic | Months to years (~12 weeks platinum-doublet therapy, ~1 year EGFR-TKI) | EGFR-TKI 60–70%[3,4]<br>Cytotoxic platinum-doublet 17–31%[8,45] | EGFR-TKI ~1%[3,4]<br>Platinum-doublet 1.6%,[8] ~1%[45] | No |
| Radiation | Local | Localized<br>Metastatic | Weeks | Chemoradiotherapy 50–60%[46] | 2.4%[46] | No |
| Surgery | Local | Localized | Hours | 100% | <1%[10] | Yes |

Abbreviation: TKI, tyrosine kinase inhibitor.

# Lung Cancer and Personalized Treatment






# Lung Cancer and Personalized Treatment

- NSCLC subdivided by presence mutated driver oncogene
- Surgery is safer and less invasive due to technology and preoperative management

management

- Surgical specimens more valuable due to heterogeneous nature genetic alterations
- Surgery as an efficient method to treat patients with acquired resistance
- Surgery combined with drug therapy post or preoperatively for selected biomarkers
- Personalization of treatment!

## Personalized Treatment for Lung Cancer

**Lung Cancer**

Cola enhances absorption of erlotinib in NSCLC

By: JENNIFER SHEPPHIRD, Frontline Medical News

FEBRUARY 8, 2016

FEBRUARY 8, 2016

FROM JOURNAL OF CLINICAL ONCOLOGY

## VITALS

**Key clinical point:** Taking oral erlotinib with cola significantly increased the drug's bioavailability in patients concomitantly taking the acid-reducing agent esomeprazole.

**Major finding:** Patients treated with erlotinib and esomeprazole had significantly better absorption after drinking cola, compared with water (AUC0-12h was 39% higher; range, –12% to +136%; $P = .004$ and $C_{max}$ was 42% higher; range, –4% to +199%; $P = .019$).

**Data source:** 28 evaluable patients with lung cancer; 14 received erlotinib and esomeprazole and 14 received erlotinib only.

**Disclosures:** Research was supported by Stichting de Merel and Roche. Dr. van Leeuwen reported research funding from Roche. Several of his coauthors reported ties to industry.