National Lung Cancer Roundtable: Triage for Appropriate Treatment

Gerard A. Silvestri MD,MS
Hillenbrand Professor of Thoracic Oncology
Medical University of South Carolina
Charleston, SC

Disclosures

- All support for research funding only with no consultancies, SAB's or Paid lectures.
  - NCI
  - Patient Centered Outcomes Research Institute (PCORI)
  - Olympus America
  - Integrated Diagnostics
  - Cook Inc
  - Veran
  - Veracyte
  - Boston scientific Corporation
  - Auris
  - Exact Sciences

Opportunities for Intervention/Influence

1. Lack of expertise in lung nodule management
2. Lack of concordance with staging and management guidelines
3. Variability in access and use of mutational testing for expression of immune-markers and targeted therapy
4. Disparities in receipt of curative-intent surgery for early stage NSCLC
5. Variation in access to lung cancer specialists

Recent Trends in the Identification of Incidental Pulmonary Nodules

Michael K. Gould[1], Tania Tang[1], In-Lu Amy Liu[1], Janet Lee[1], Chengyi Zheng[1], Kim N. Danforth[1], Anne E. Kosco[2], Jamie L. Di Fiore[3], and David E. Suh[4]

Extrapolating to the US population

- 2010 Adult population: 234.5 million
- Estimate of chest CT scans: 4.8 million
- Estimate of lung nodules: 1.5 million
- New lung cancer diagnosis (within 2 years): 63,000
  - ~72,000 of 224,210 lung cancer cases in 2014 (US) were ≤ 30 mm

*This updated estimate of nodules highlights the magnitude of the problem which can be a diagnostic dilemma for clinicians and causes distress among patients.

-*8 million* people in the US are eligible for LCS

CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer?

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Michael K. Gould, MD, FCCP; Jessica Donington, MD; William R. Lynch, MD; Peter J. Mazzone, MD, MPH, FCCP; David E. Midthun, MD, FCCP; David P. Naidich, MD, FCCP; and Renda Soylemez Wiener, MD, MPH

British Thoracic Society guidelines for the investigation and management of pulmonary nodules

M E J Callister,[1] D R Baldwin,[2] A R Akram,[3] S Barnard,[4] P Cane,[5] J Draffan,[6] K Franks,[7] F Gleeson,[8] R Graham,[9] P Malhotra,[10] M Prokop,[11] K Rodger,[12] M Subesinghe,[13] D Waller,[14] I Woolhouse,[15] British Thoracic Society Pulmonary Nodule Guideline Development Group, on behalf of the British Thoracic Society Standards of Care Committee

Management of Pulmonary Nodules by Community Pulmonologists

A Multicenter Observational Study

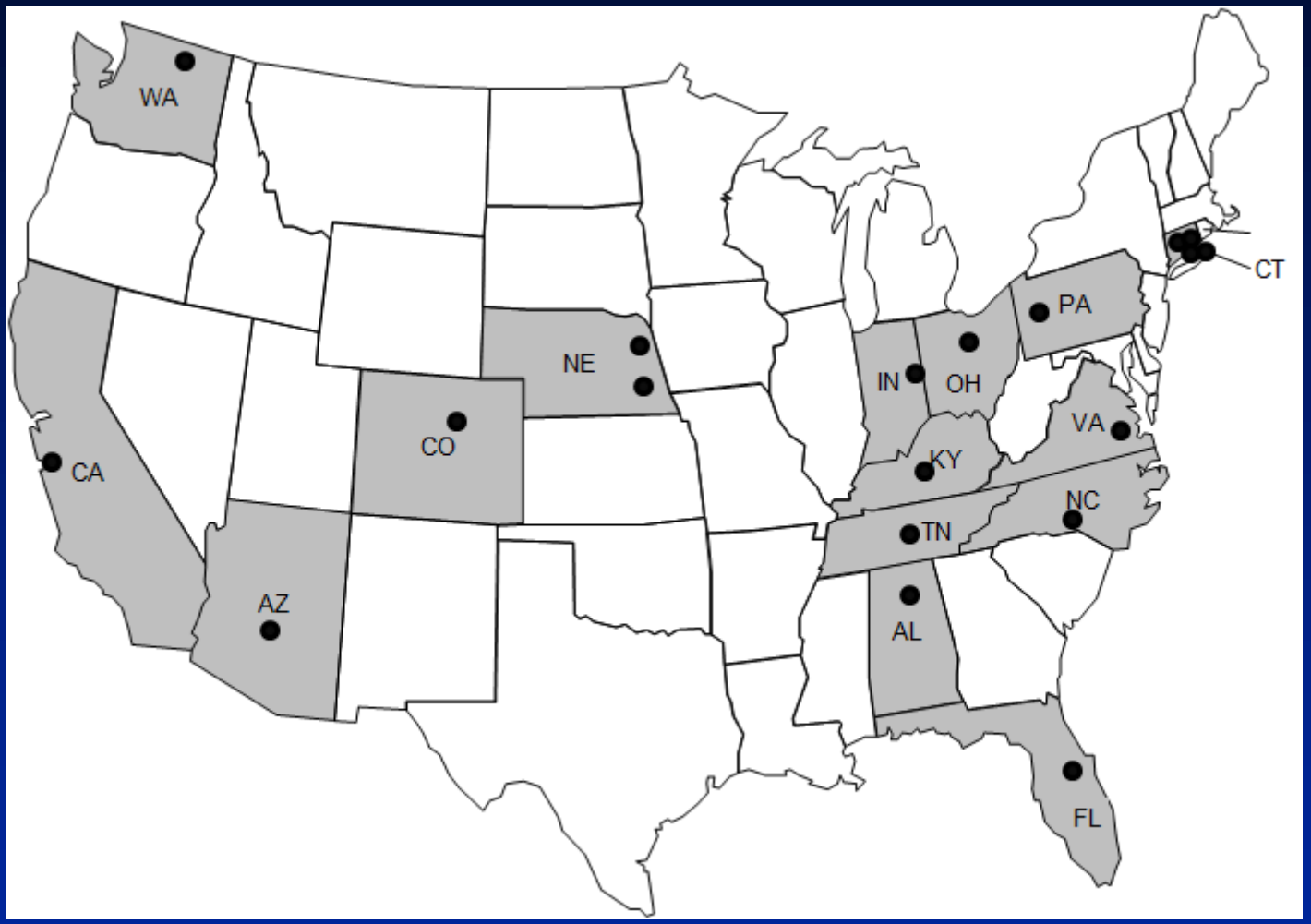
Nichole T. Tanner, MD, MSCR; Jyoti Aggarwal, MHS; Michael K. Gould, MD; Paul Kearney, PhD; Gregory Diette, MD, MHS; Anil Vachani, MD; Kenneth C. Fang, MD; and Gerard A. Silvestri, MD

PODCAST

- ***Objectives***:
  - **To estimate malignancy rate in PNs presenting to community pulmonologists.**
  - **Describe the management of PNs**
  - **Compare the relationship between pre-test probability of malignancy and management decisions**
- ***Design***: **Multicenter observational record review**
- ***Patients***: **Patients ages 40-89 presenting with PNs (8-20mm)**
- ***Measurements***: **Frequency of procedures, prevalence of malignancy, pre-test probability for malignancy**

Tanner et al. *Chest* 2015:148(6):1405-14

33 Geographically Diverse Outpatient Pulmonary Clinics



Tanner et al. *Chest* 2015:148(6):1405-14

Diagnosis and procedure use categorized by nodule pretest probability for cancer

	Low Risk < 5% n=36	Intermediate Risk >5 to <65% n=300	High Risk >65% n=41	p-value
Outcome				
Benign	36 (100%)	224 (75%)	23 (55%)	<0.0001
Malignant	0	76 (25%)	18 (45%)	<0.0001
Most Invasive Procedure Utilized				
Surgery	6 (17%)	64 (21%)	7 (17%)	0.6878
Biopsy	10 (28%)	95 (32%)	20 (49%)	0.0711
Surveillance	20 (56%)	141 (47%)	14 (34%)	0.1548

Nodule Management

- **Serial Imaging**
  - N= 175, 46%
  - Median # Scans: 3 (range1-7)
  - 4% underwent 7 repeat scans
  - All were benign by 2 years of stability
- **Biopsy**
  - N= 125, 33%
  - Malignant: 44 (35%)
  - Specific Benign Diagnosis: 71, (57%)
  - Non-diagnostic: 10, (8%), subsequently followed for two years
- **Surgery**
  - N= 77 (20%)
  - Malignant: 50 (65%)
  - Benign: 27(35%)

Nodules in the community

- **25% of patients presenting to pulmonologists ultimately have cancer**
- **44% of very low risk patients (pCA <0.05) underwent an invasive procedure for a benign nodule**
- **There was no difference in the rate of surgical resection for nodules based on pretest probability of cancer**
  - **Possible explanations:**
    - **Pulmonologists do not routinely consider pCA**
    - **They unaware that guidelines exist for nodule management**
    - **They choose not to follow them guidelines**

Tanner NT, et al. Chest.2015

Staging

- Accurate staging is critical
  - Treatment options are stage dependent
  - Prognosis is based upon stage
  - Enrollment in clinical trials by stage
  - Provides a common language when discussing cases
  - Allows for study of large cohorts of patients

Overview of NSCLC Treatment

Stage I	Surgery (Radiation if inoperable)
Stage II	Surgery With Adjuvant Chemotherapy
Stage III	Radiation With Chemotherapy
Stage IV or Recurrent Disease	Chemotherapy Targeted Therapy Immunotherapy

Patterns of Surgical Care of Lung Cancer Patients

- Survey with chart abstraction- 729 hospitals
- 40,000 patients, 11, 668 surgeries
- Staging:
  - Preoperative Mediastinoscopy was performed in only 27% of patients
  - Of those less than ½ had a biopsy taken
  - Thus of 11,668 patients operated upon, tissue was obtained from the mediastinum in only 1480 patients

- Little Ann Thorac Surg; 2005:80:2051

Multi-Modality Mediastinal Staging For Lung Cancer Among Medicare Beneficiaries

Farjah F, Flum D, Ramsey S, et al. J Thorac Oncol, 2009;4:355

Multi-modality Mediastinal Staging for Lung Cancer

- Use of non-invasive and invasive tests improves accuracy of mediastinal staging
- Unknown how frequently it is used and whether it improves health outcomes
- Cohort study using SEER data (1998-2005)
- Categorized as staged by
  - Single modality (CT)
  - Bimodality (CT & PET)
  - Trimodality (CT & PET & invasive staging)

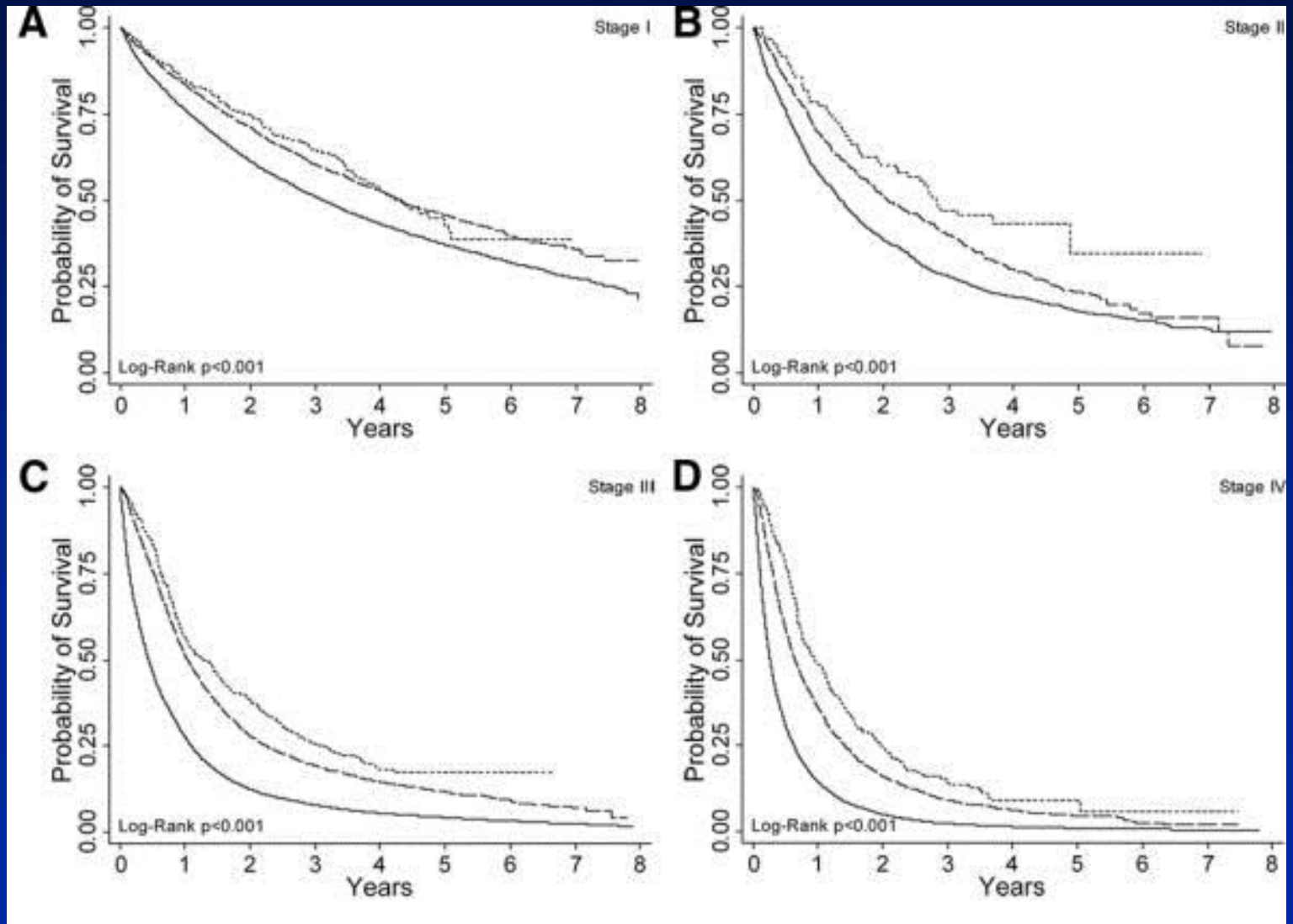
Findings

- 42,912 patients
- Median age 75
- Overall survival over 5 years – 13%
- 77% single modality
- 21% bi- modality
- 2% tri modality
- Over time PET increased, single mode decreased and invasive staging stayed about the same

Factors Associated With those Not Receiving Multi-Modality Staging

- Male sex
- Low SES
- Poorly Educated
- African Americans
- Residents of Rural areas
- Unmarried

Stage-Based Overall Survival by Number of Staging Modalities



Relationship Between Mediastinal Staging and Survival

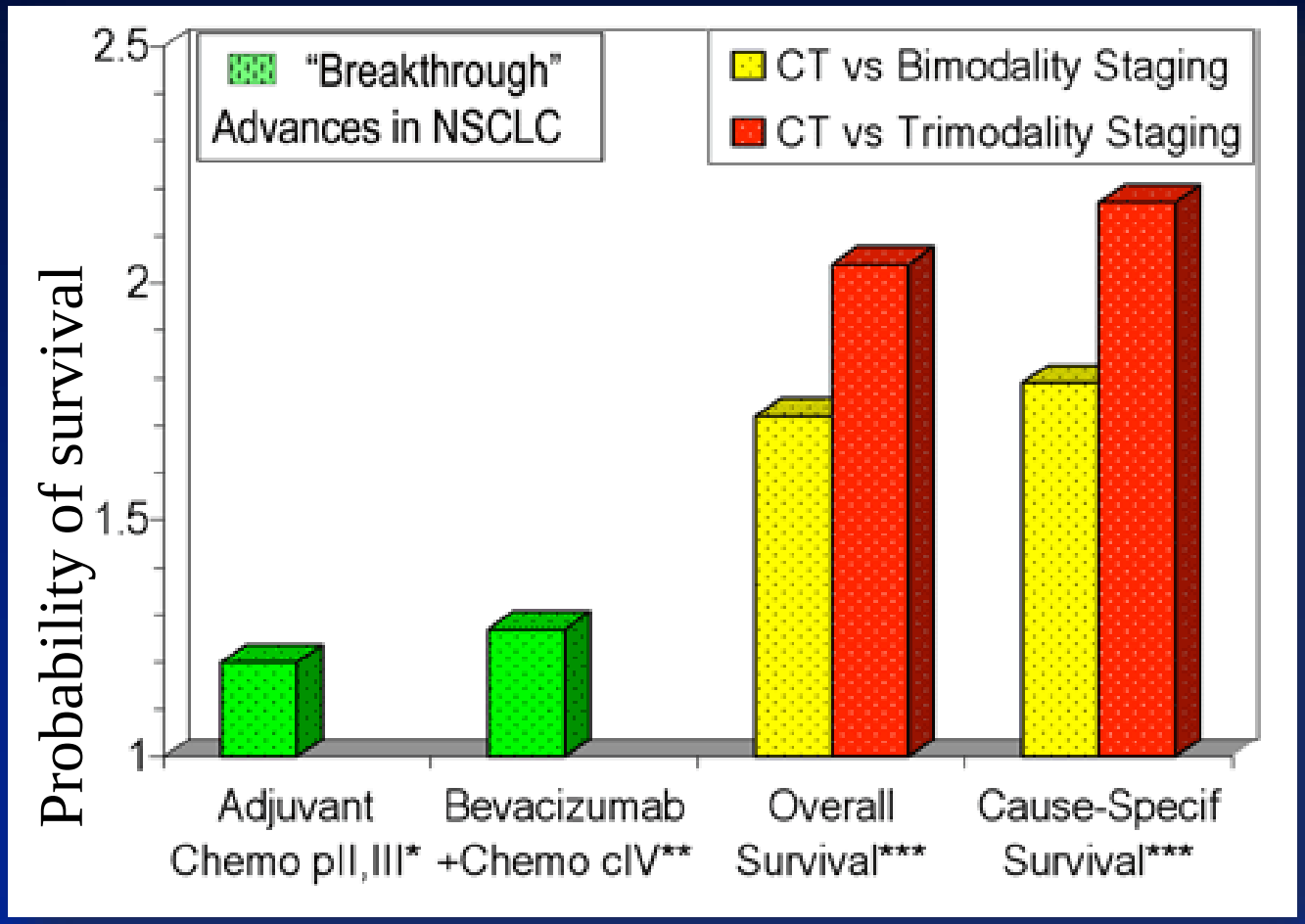
TABLE 4. Relationship Between Mediastinal Staging and Survival

	Overall survival Hazard ratio[a] (99% CI)	Lung cancer cause-specific survival Hazard ratio[a] (99% CI)
Bi- vs. single modality	0.58 (0.56–0.60)	0.56 (0.54–0.58)
Tri- vs. single modality	0.49 (0.45–0.54)	0.46 (0.42–0.52)
Tri- vs. bi-modality	0.85 (0.77–0.93)	0.83 (0.74–0.93)

[a] Adjusted for age, sex, race, income, education, marital status, geography, area of residence, history of prior malignancy, and comorbidity index.

CI, confidence interval.

Comparing the magnitude of survival benefit…



* LACE Clin Oncol (Meeting Abstracts) 2006; 24:7008

** ECOG 4599 Sandler A, NEJM 2006; 355:2542-2550

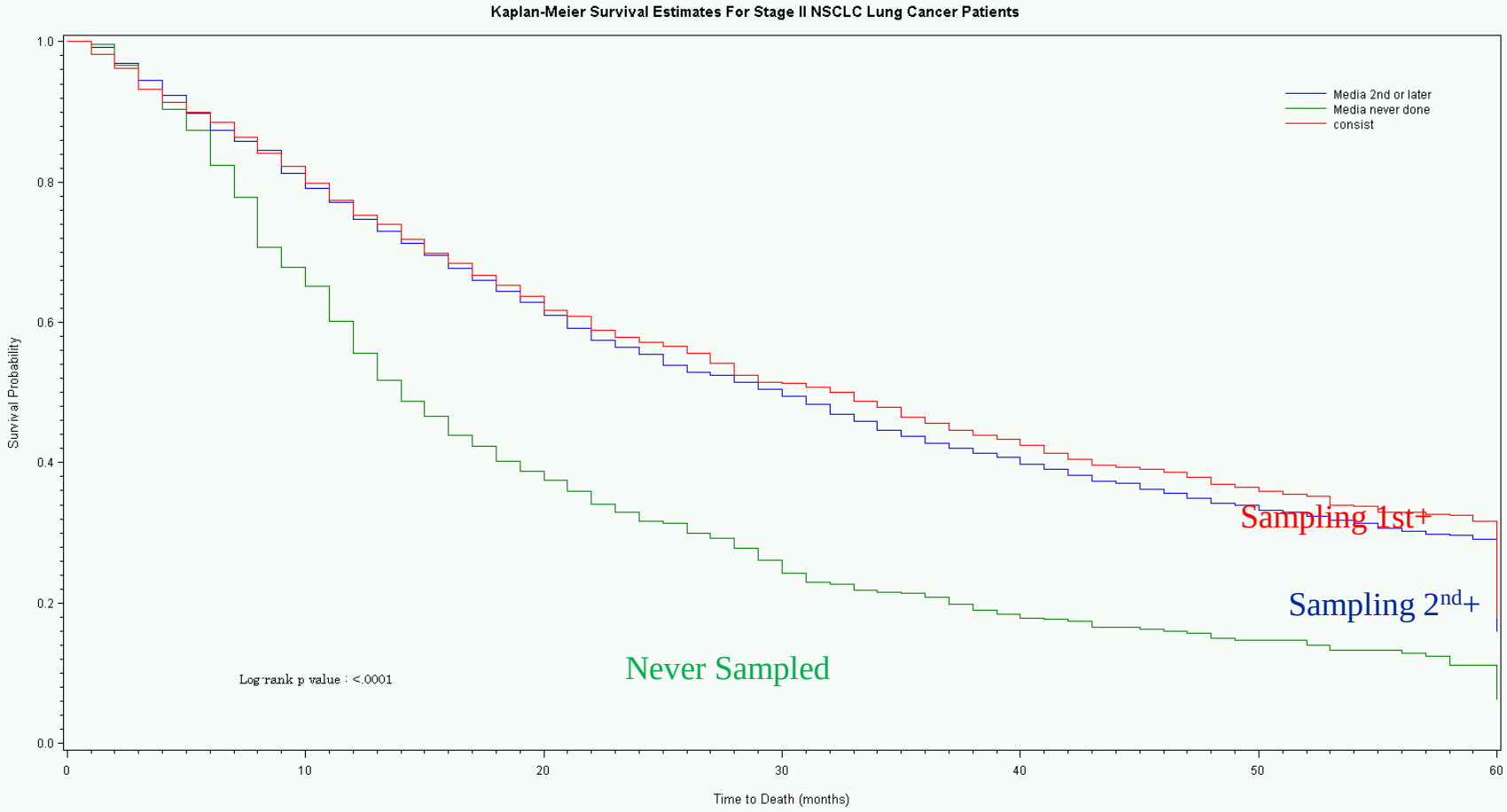
*** Data taken from a SEER-Medicare (1998-2005) analysis. Results are adjusted for all significant factors.6

SEER-Medicare and Texas Cancer Registry Data

- N=15,316
- Regional spread without distant metastasis
- Cancer and stage data from SEER and TCR
- CPT and ICD-9 for procedures and outcomes
- Guideline consistent defined as mediastinal sampling first vs. guideline inconsistent (2nd or later)
- Practice Patterns:
  - 21% Guideline consistent
  - 44% of NSCLC never had mediastinal sampling

Ost D, et al. CHEST 2014; 145:331-45

Practice Patterns and Survival in Stage II NSCLC



Ost D, et al. CHEST 2014; 145:331-45

Variability in access and use of mutational testing for expression of immune-markers and targeted therapy

Making Precision Medicine a Reality for More Patients

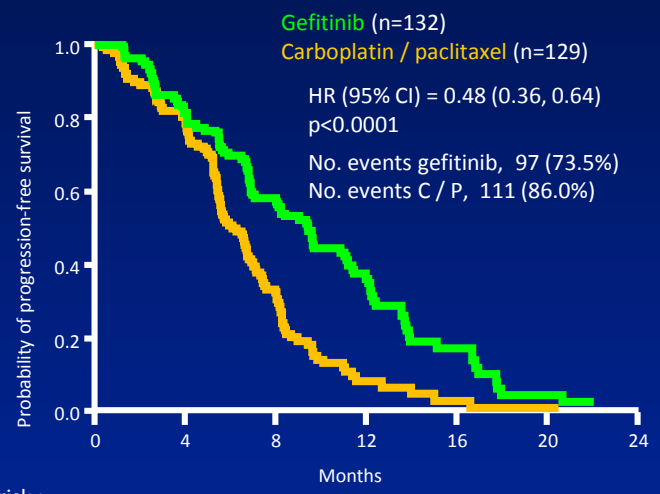
- **GOAL: To have every cancer center in the USA provide all patients the opportunity to have their cancer extensively characterized for mutations and other molecular abnormalities**

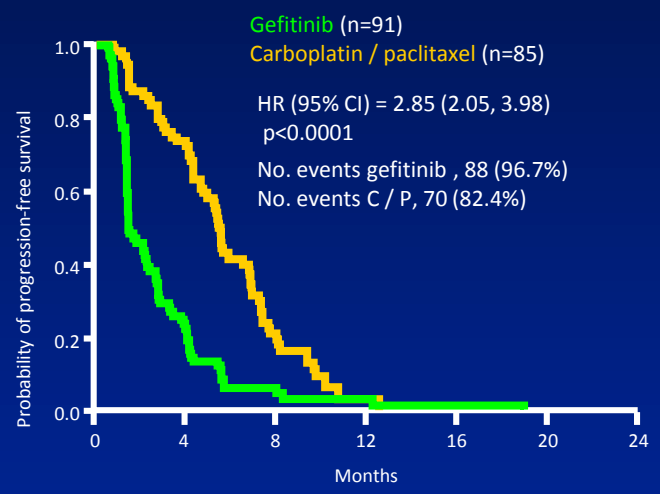
Dr Bruce Johnson: President ASCO 2017

Why actionable targets?

EGFR mutation positive

EGFR mutation negative





At risk :													
Gefitinib	132	108	71	31	11	3	0	91	21	4	2	1	0	0
C / P	129	103	37	7	2	1	0	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

Mok TS, et al. *N Engl J Med.* 2009;361:947-957.

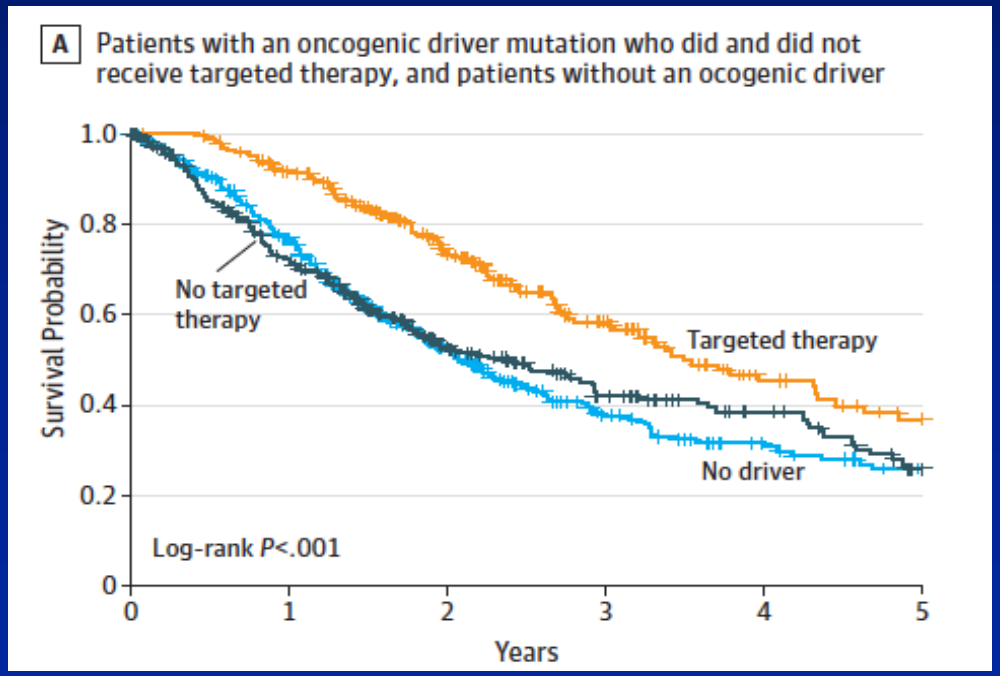
Original Investigation

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

- Lung Cancer Mutation Consortium
- Objective
  - Determine frequency of oncogenic drivers in patients with lung adenocarcinoma
  - Use data to select treatments targeting identified drivers
- 14 sites 2009-2012
- goal of 10 genes

Kris et al, JAMA, 2014

- 1007 patients tested for at least 1 gene
- 733 tested for all 10
- Driver mutation found in 64% (466/733)
- Results used to select therapy 28%

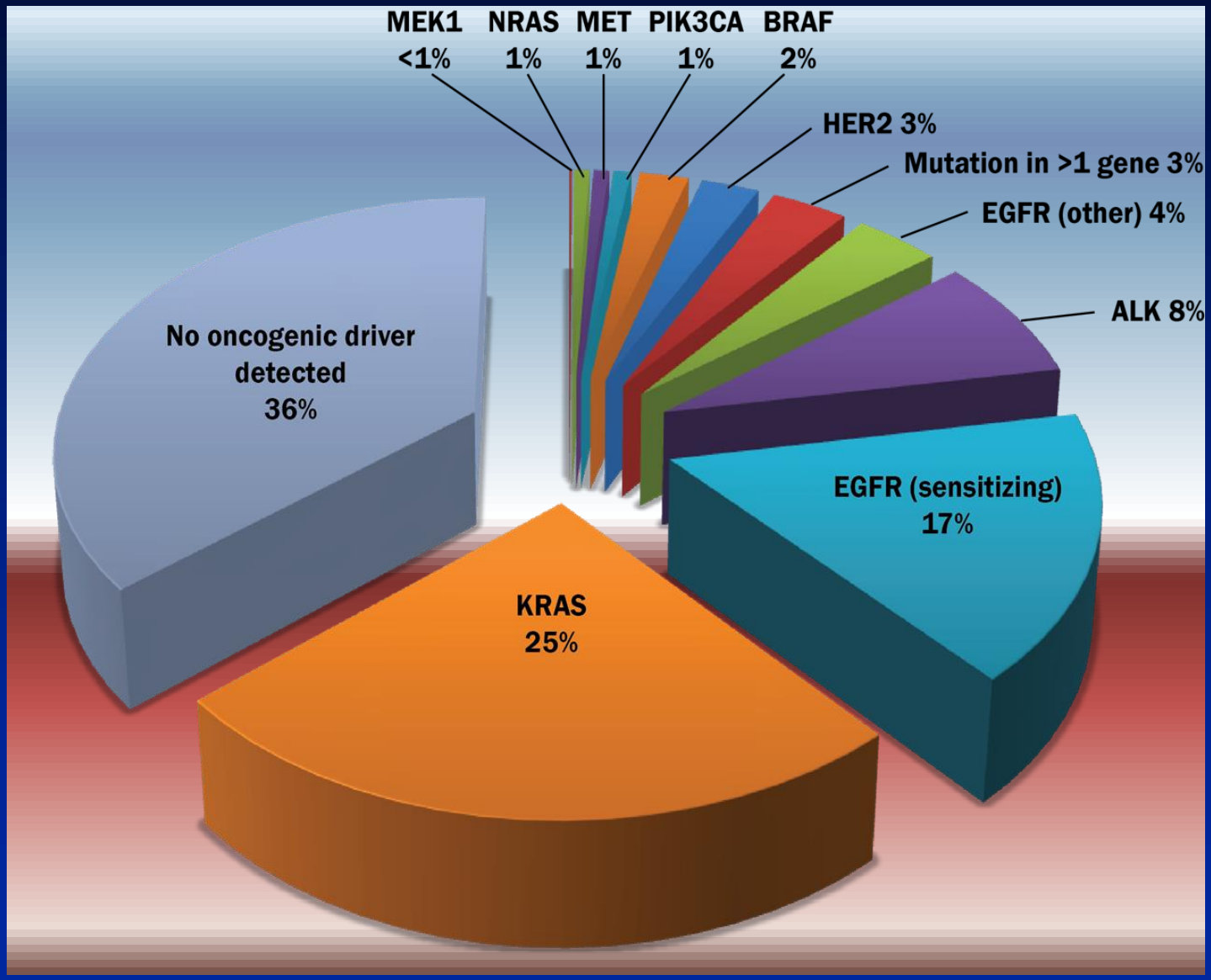


Median survival

- 3.5 vs 2.4 years

Kris et al, JAMA, 2014

Lung Cancer Mutation Consortium: Incidence of Drive Mutations

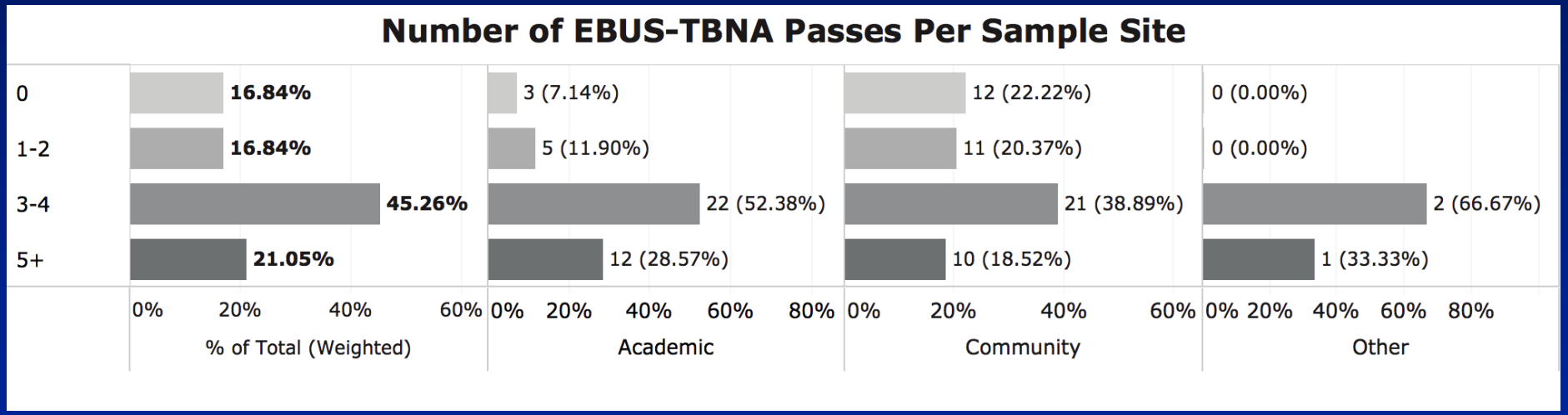


Frontline Therapies Based on Molecular Testing: Lung Cancer

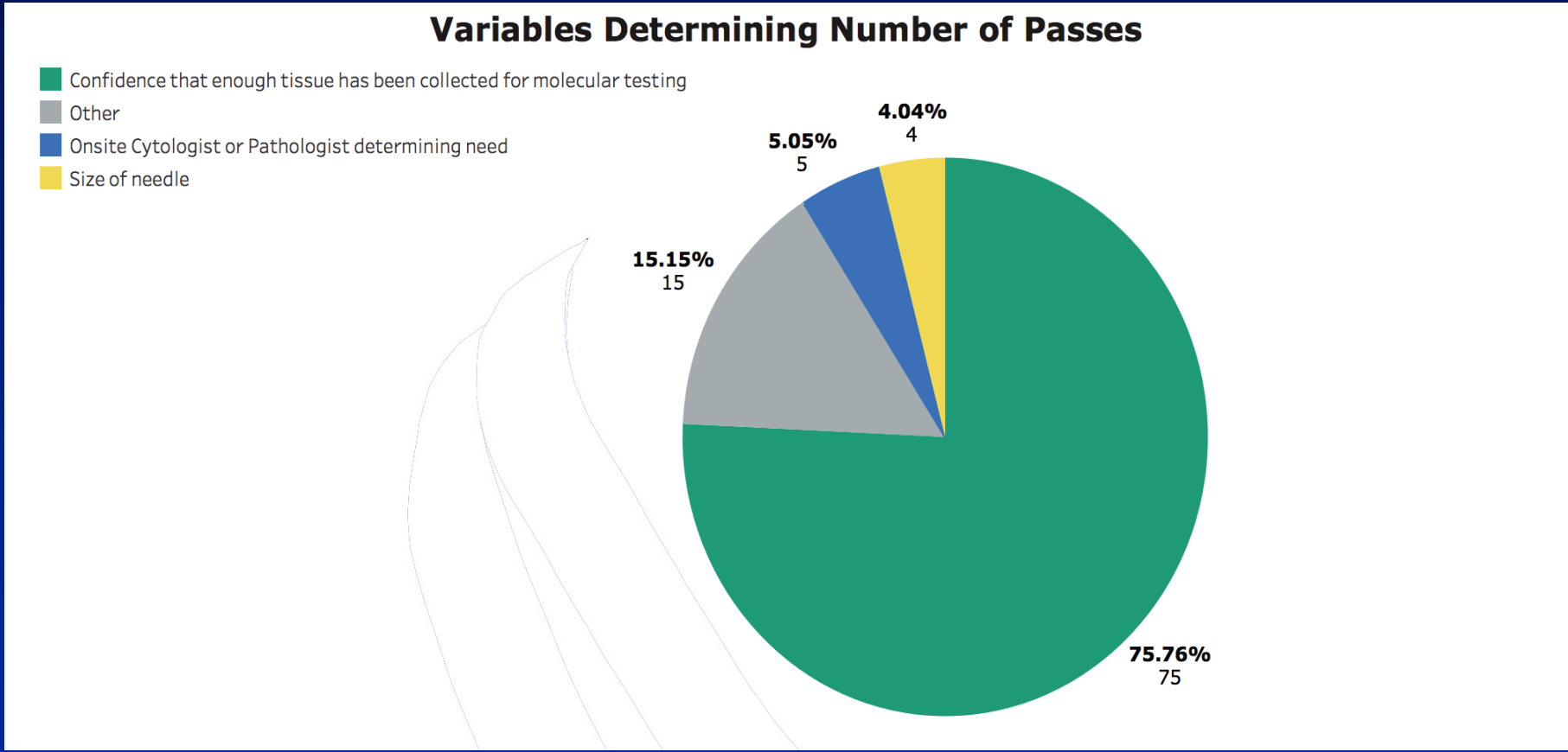
- EGFR
- ALK
- ROS-1
- BRAF-V600E
- PD-L1 (>50%)

TISSUE SAMPLING PRACTICES
ACCP Pilot Study

No consistency in number of needle passes reported when collecting tissue samples using EBUS-TBNA.



TISSUE SAMPLING PRACTICES



EBUS samples and Molecular Testing

- 195 cases of adeno or NSCLC-NOS
  - Suitable for molecular analysis
  - KRAS 96%, EGFR 97%, ALK 98%
- Frequency of mutations by EBUS same as for mutations in 1000 resected specimen.
- Mean quantity of DNA extracted was 1.74 microgram (360 ng-32 microgram)
  - 10-20 ng DNA is sufficient for NGS

Casadio C et al Am J Clin Path 2015; 144:629

Randomized Trial of EBUS With or Without ROSE for Molecular Testing

- Complete Genotyping (KRAS, EGFR, and ALK) Was Achieved in 108 of 126 Patients (85%)
  - 90% Success on EBUS Plus ROSE
  - 80% Success in EBUS Alone Arm
- 18 Failures (6 ROSE; 12 EBUS)
  - Pathology failures only (0 ROSE; 6 EBUS)

Trisolini, et al, *Chest* 2015; 148: 1430-1437

Summary

Multiple opportunities for improvement in areas that have guideline evidence for better outcomes

- **Goals:**
  - **Reduce unnecessary surgery for patients with benign nodules**
  - **Improve staging for patients newly diagnosed disease such that they receive appropriate treatment**
  - **Insure that every patient with newly diagnosed advanced lung cancer have their tumor individually profiled such that they receive personalized therapy.**
  - **Insure that underserved/at risk populations have access to the same opportunities for treatment as do everyone else.**