

ADENOCARCINOMA: WHAT ARE THE ISSUES?

New 2015 WHO Classification: Putting it into practice

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***EUROPEAN LUNG CANCER
CONFERENCE***

GENEVA, SWITZERLAND

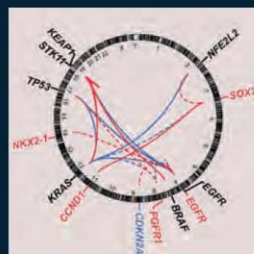
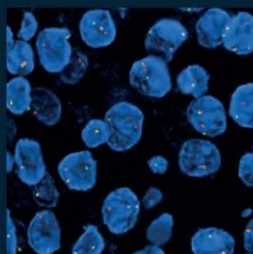
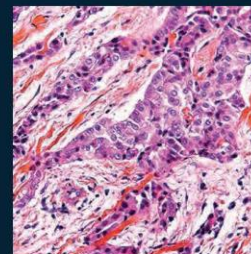
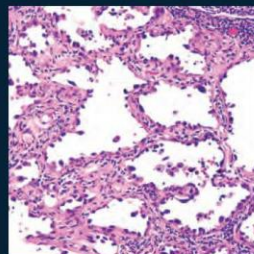
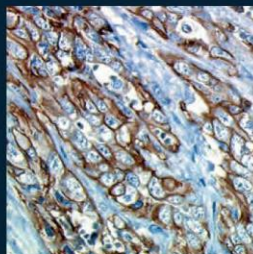
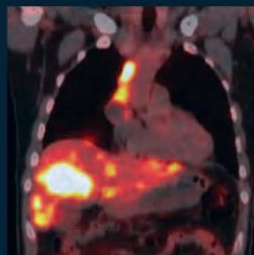
APRIL 17, 2015

Disclosure slide

- Board Member of IASLC

WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

Edited by
William D. Travis, Elisabeth Brambilla, Allen P. Burke, Alexander Marx, Andrew G. Nicholson



WHAT ARE THE QUESTIONS?

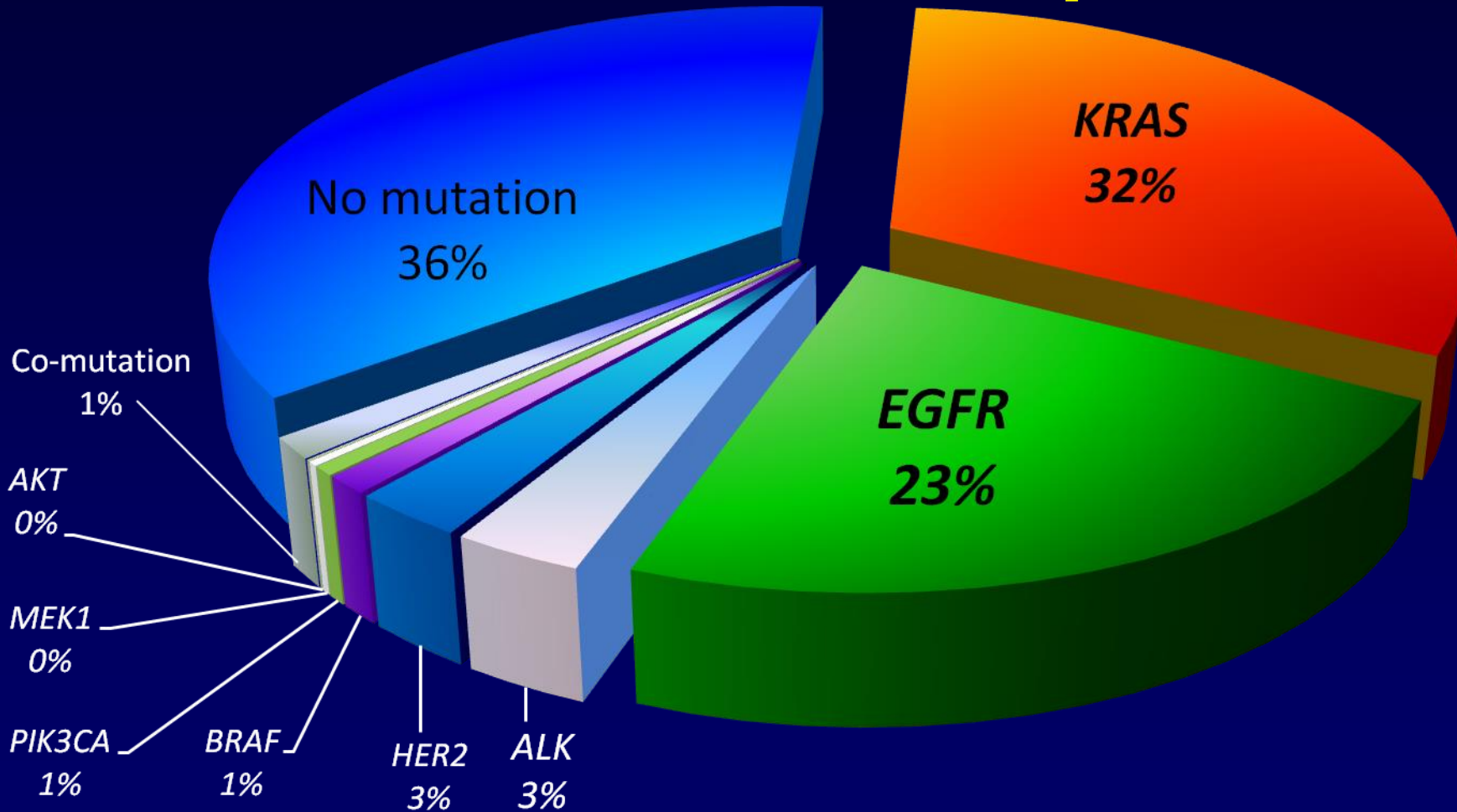
- What happened to BAC?
- Do AIS and MIA have a 100% DFS?
- Does predominant subtyping have prognostic significance?
- What is the reproducibility?
- Are there any new concepts?
- Does it help comparing multiple tumors?
- What is impact on TNM?

2011 IASLC/ATS/ERS ADC CLASSIFICATION – DISCONTINUE BAC CONCEPT FIVE PLACES IN NEW CLASSIFICATION

- 1. Adenocarcinoma in situ (AIS) which can be non-mucinous and rarely mucinous**
- 2. Minimally invasive adenocarcinoma**
- 3. Invasive adenocarcinoma with predominant nonmucinous lepidic pattern**
- 4. Invasive adenocarcinoma with less than predominant nonmucinous lepidic pattern (probably most formerly clinically advanced adenocarcinomas with BAC pattern)**
- 5. Invasive mucinous adenocarcinoma**

Lung Cancer Molecular Analysis Project 2009-10

Driver Mutations found in 65% of Adenocarcinoma Specimens



–Courtesy of Mark Kris
–JAMA 311:1998-2006, 2014

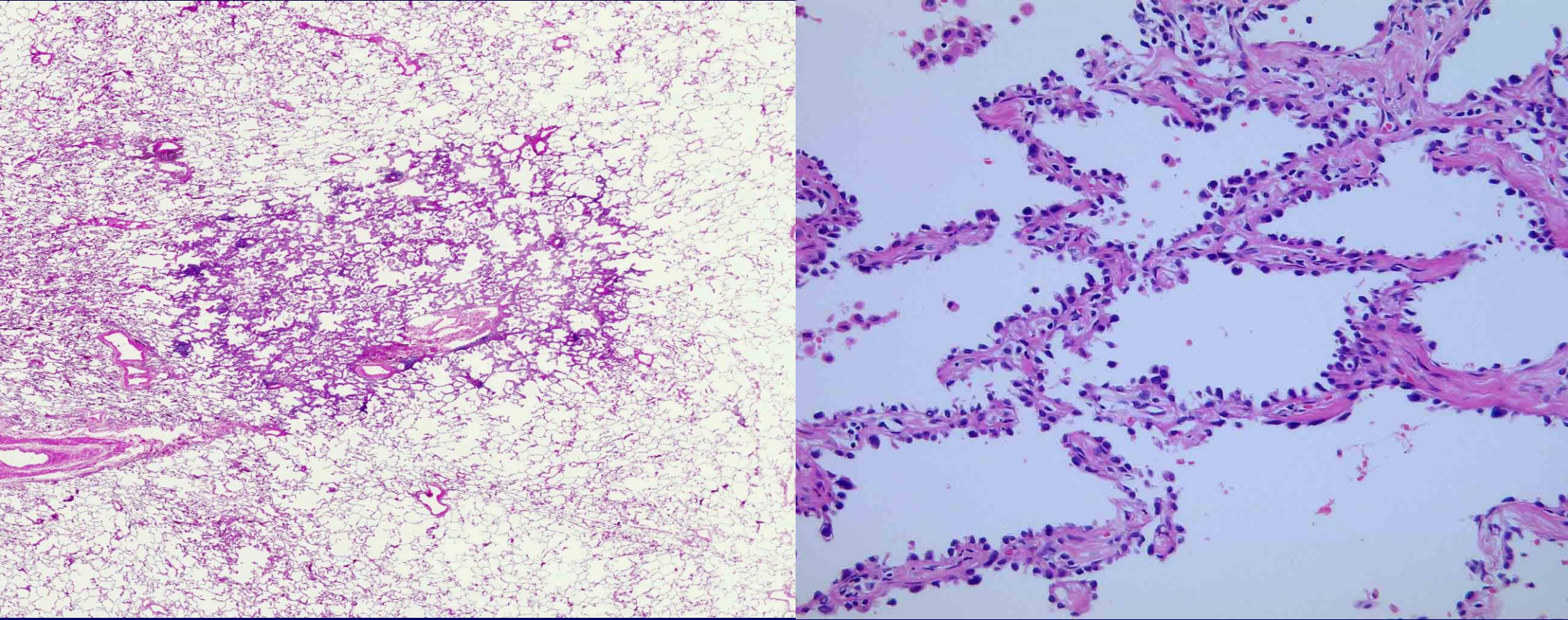
2015 WHO (IASLC/ATS/ERS) ADENOCARCINOMA CLASSIFICATION

- **PREINVASIVE LESIONS**
 - **ATYPICAL ADENOMATOUS HYPERPLASIA**
 - **ADENOCARCINOMA IN SITU (≤ 3 cm, formerly BAC pattern) †**
 - non-mucinous
 - mucinous
- **MINIMALLY INVASIVE ADENOCARCINOMA (≤ 3 cm, a lepidic predominant tumor with ≤ 5 mm invasion)**

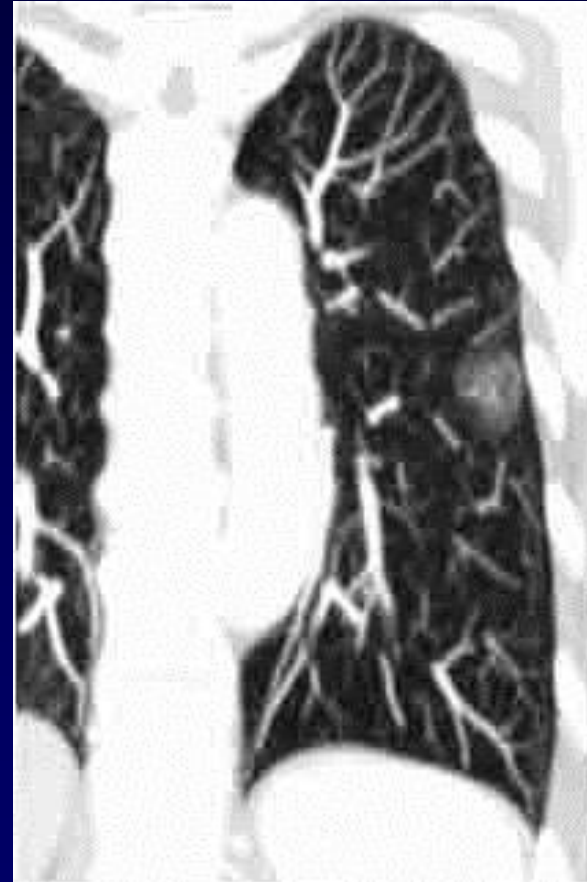
- **INVASIVE ADENOCARCINOMA**

† Size should be specified. AIS and MIA should be completely sampled histologically

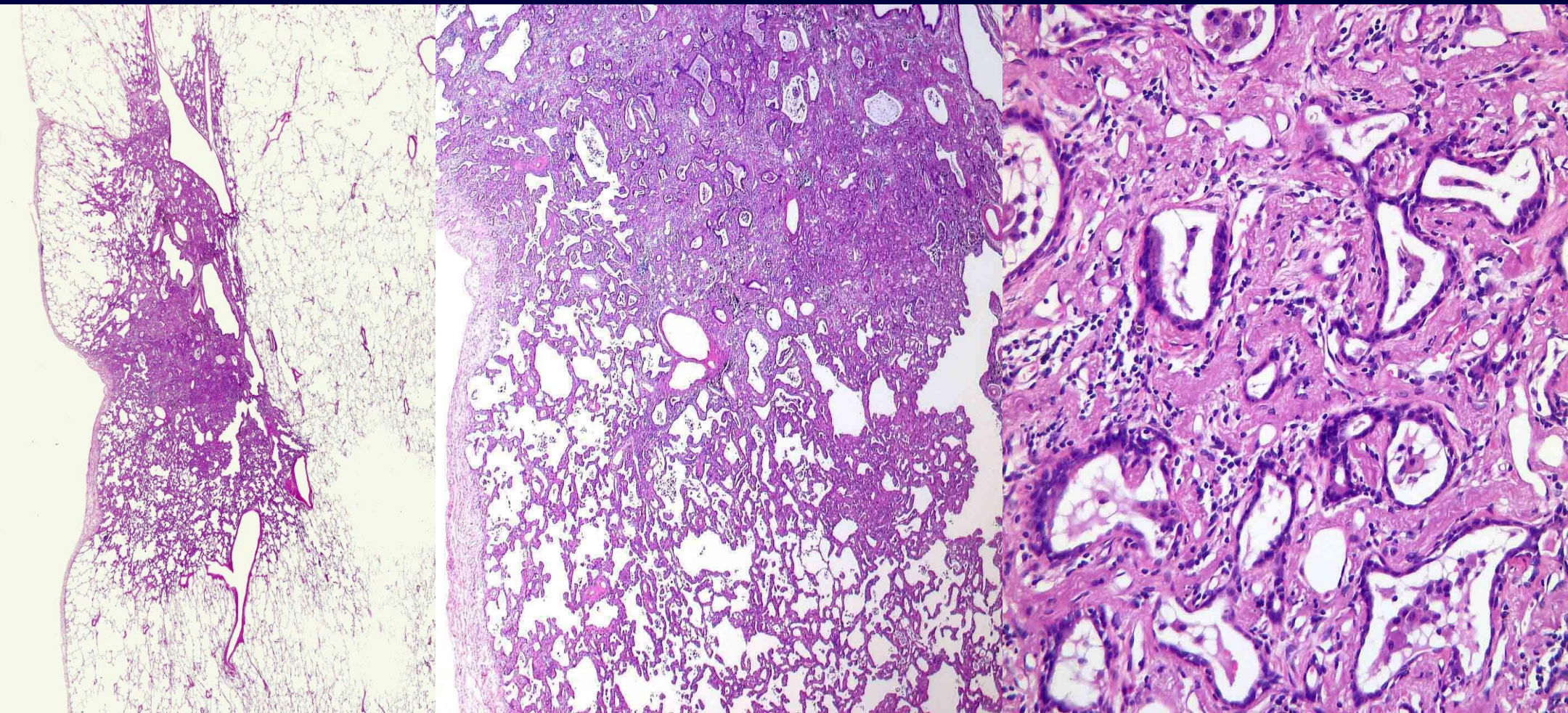
ADENOCARCINOMA IN SITU NONMUCINOUS



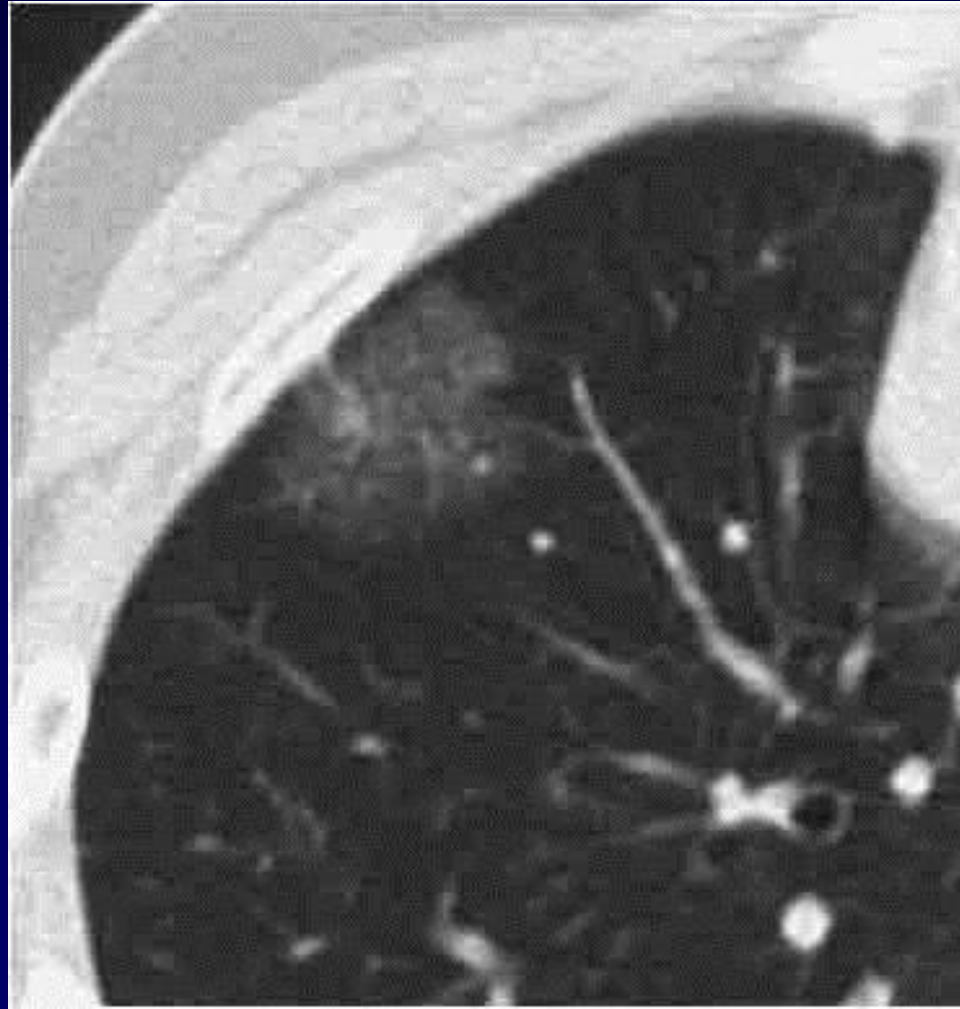
ADENOCARCINOMA IN SITU NONMUCINOUS



MINIMALLY INVASIVE ADENOCA NONMUCINOUS



MINIMALLY INVASIVE ADENOCA NONMUCINOUS



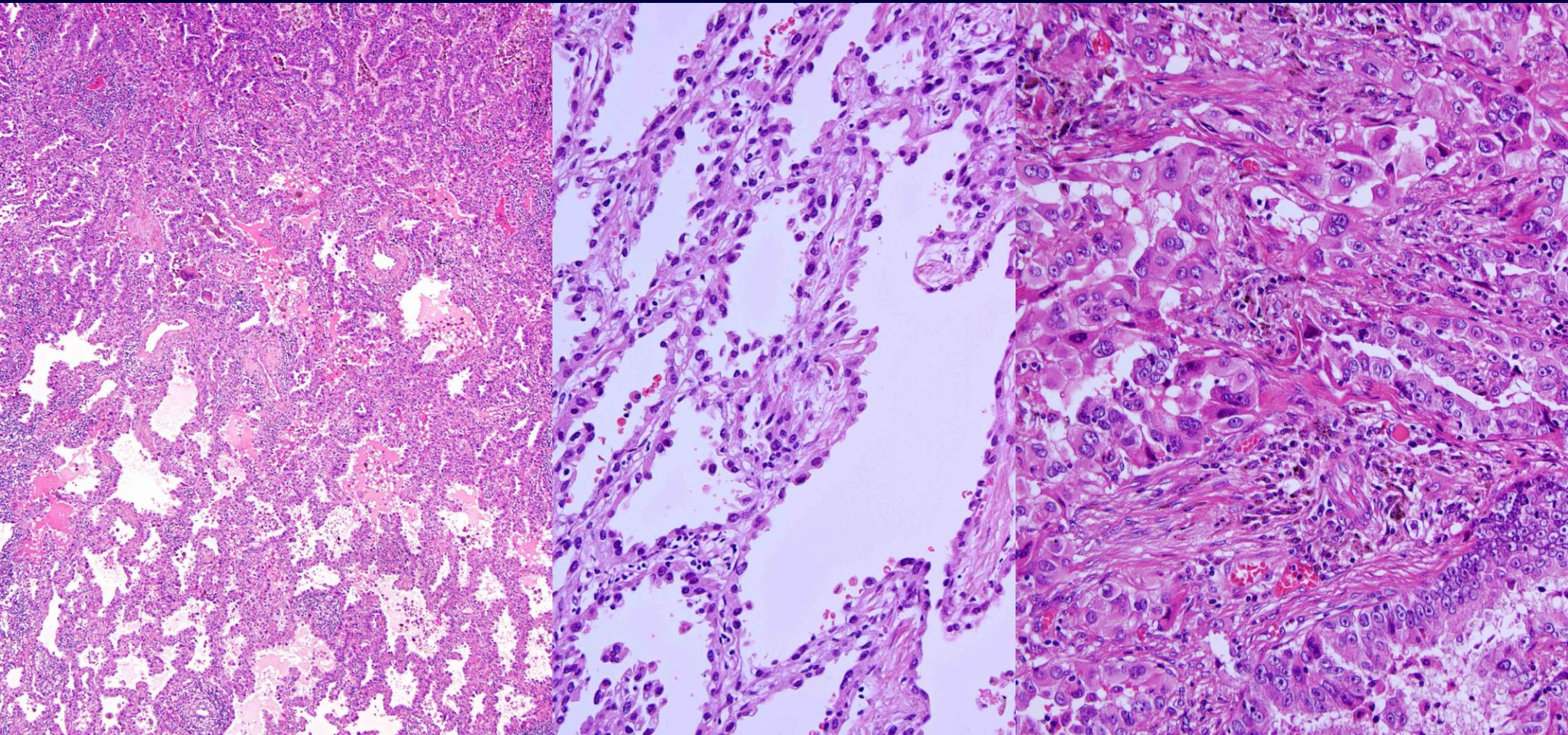
2015 WHO (IASLC/ATS/ERS) ADENOCARCINOMA CLASSIFICATION

INVASIVE ADENOCARCINOMA

- **Lepidic (predominant, formerly non-mucinous BAC pattern)**
- Acinar
- Papillary
- **Micropapillary**
- Solid

(Comprehensive histologic subtyping: semiquantitative assessment of patterns in 5-10% increments)

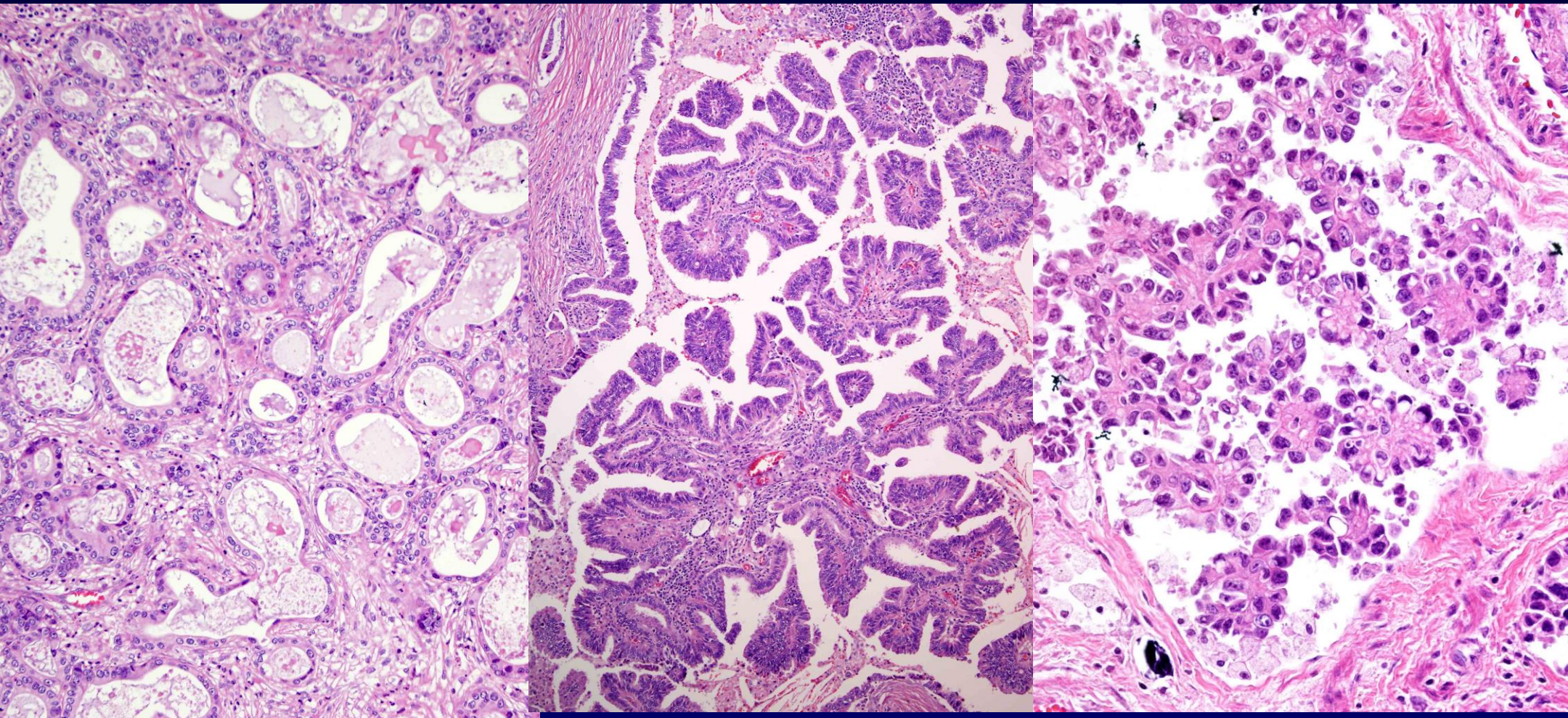
LEPIDIC



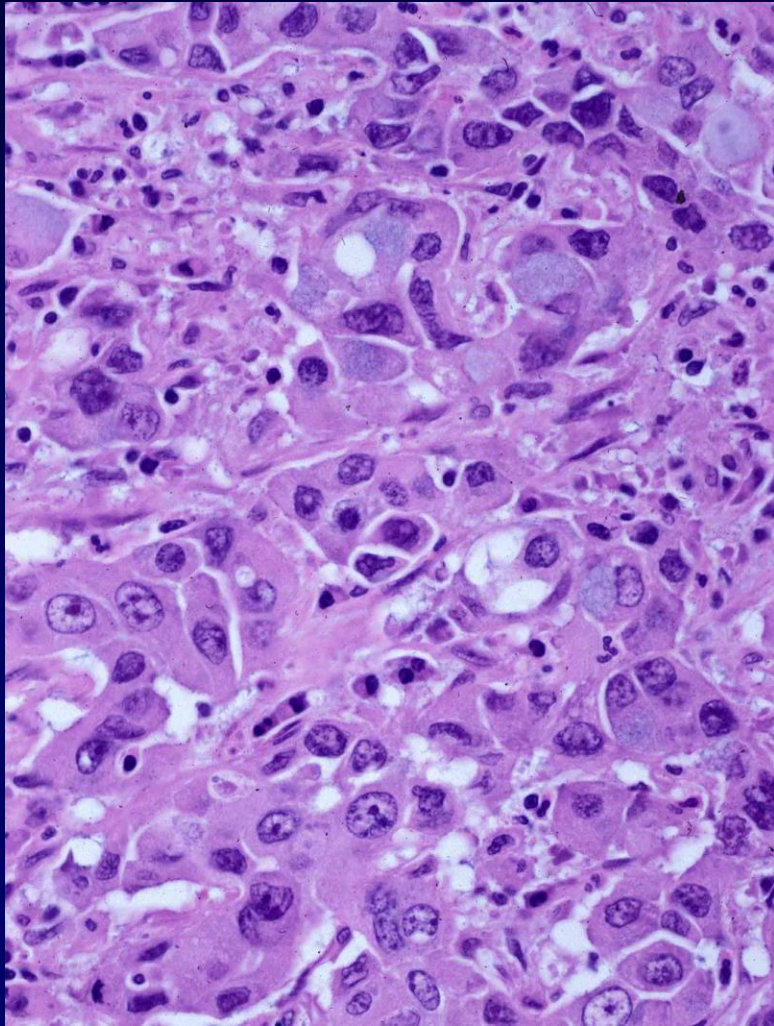
ACINAR

PAPILLARY

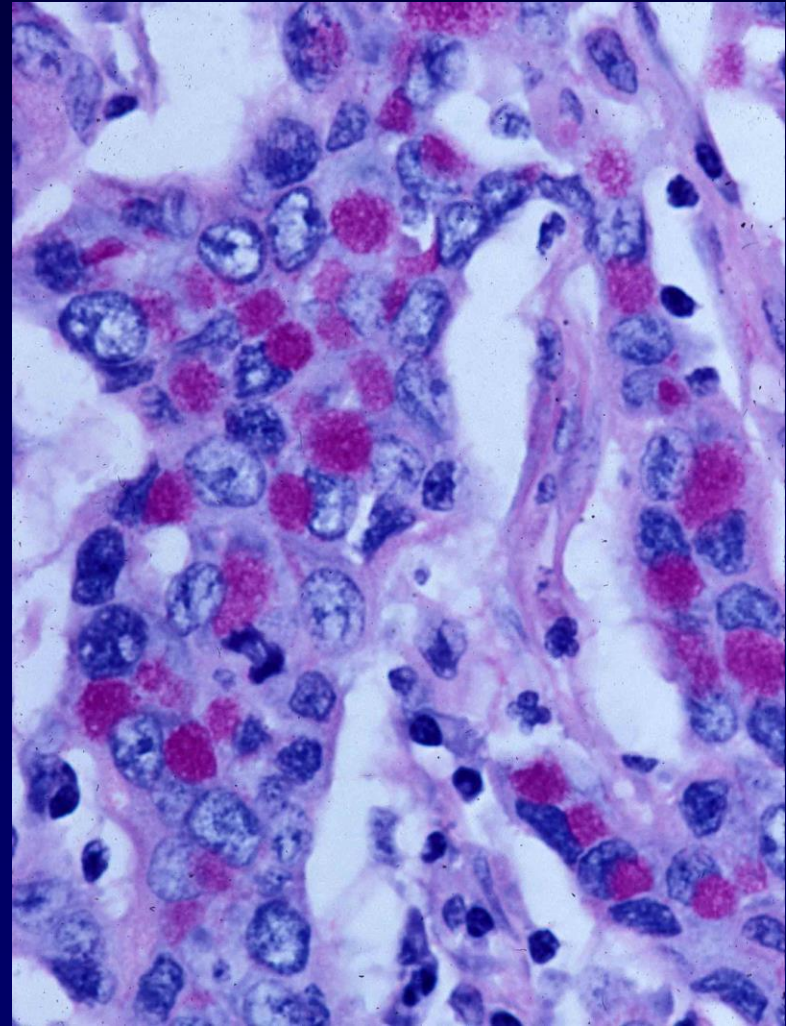
**MICRO-
PAPILLARY**



SOLID WITH MUCIN

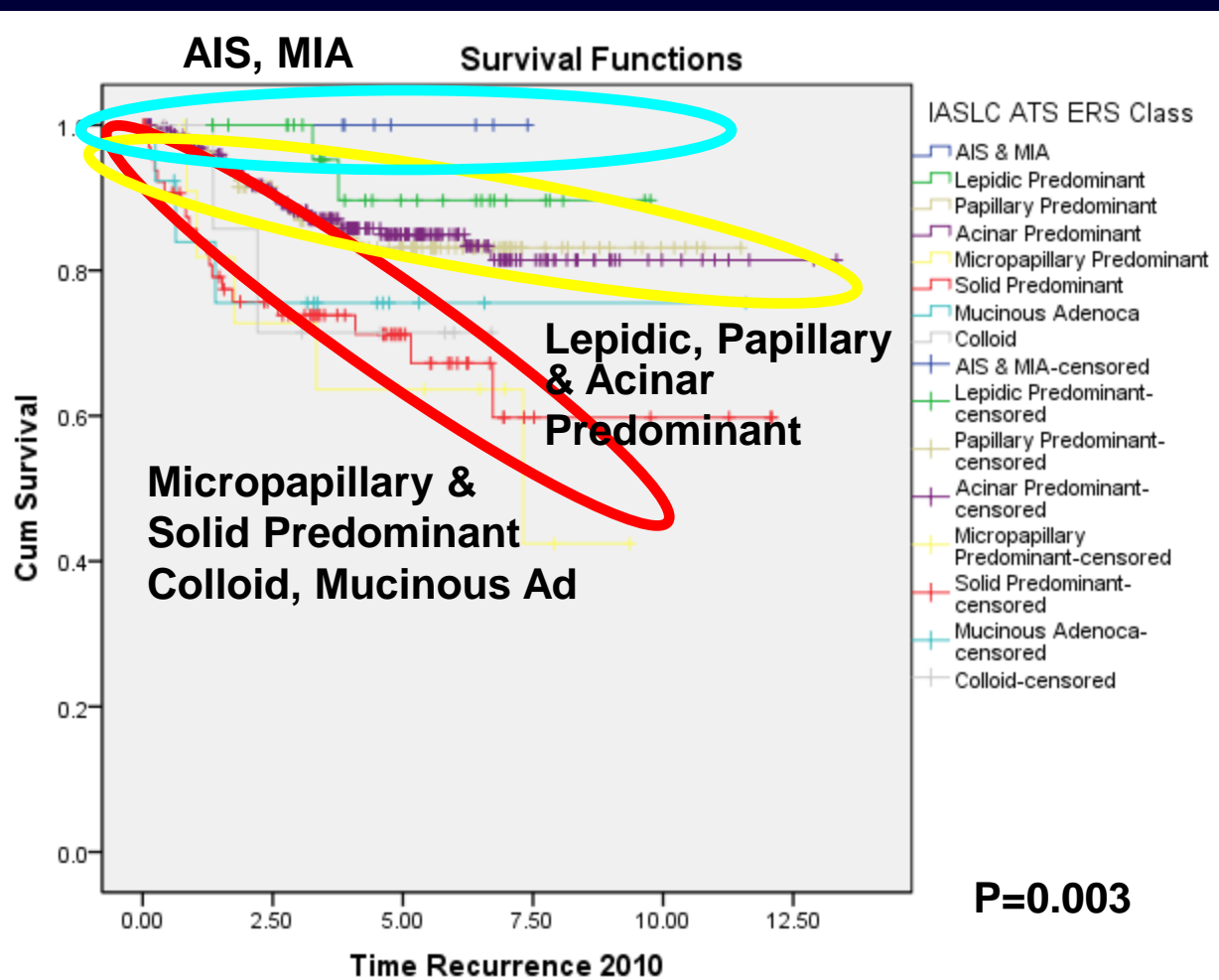


DPAS STAIN



STAGE I ADENOCARCINOMA (N=514)

RECURRENCE-FREE SURVIVAL (RFS) BY IASLC HISTOLOGIC TYPE



Histologic Type (N)	5 Year RFS %
AIS (1)	100
MIA (8)	100
Lepidic NM (29)	90
Papillary (143)	83
Acinar (232)	85
Inv Mucinous Ad (13)	76
Solid (67)	71
Micropapillary (12)	64
Colloid (9)	71

Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011

The Novel Histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification System of Lung Adenocarcinoma Is a Stage-Independent Predictor of Survival

Arne Warth, Thomas Muley, Michael Meister, Albrecht Stenzinger, Michael Thomas, Peter Schirmacher, Philipp A. Schnabel, Jan Budczies, Hans Hoffmann, and Wilko Weichert

Does Lung Adenocarcinoma Subtype Predict Patient Survival?

A Clinicopathologic Study Based on the New International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Lung Adenocarcinoma Classification

Prudence A. Russell, MBBS, FRCPA, Zoe Wainer, BMBS,†‡ Gavin M. Wright, MBBS, FRACS,†‡§ Marissa Daniels, MBBS,§ Matthew Conron, MBBS, FRACP,|| and Richard A. Williams, MBBS, FRCPA, PhD**

Warth A, J Clin Oncol 2013; 30: 1438-46

Russell PA et al: J Thor Oncol 2011;6:1496-1504

Adenocarcinomas With Prominent Lepidic Spread: Retrospective Review Applying New Classification of the American Thoracic Society

Lauren Xu, MD, Fabio Tavora, MD,† Richard Battafarano, MD,‡ and Allen Burke, MD**

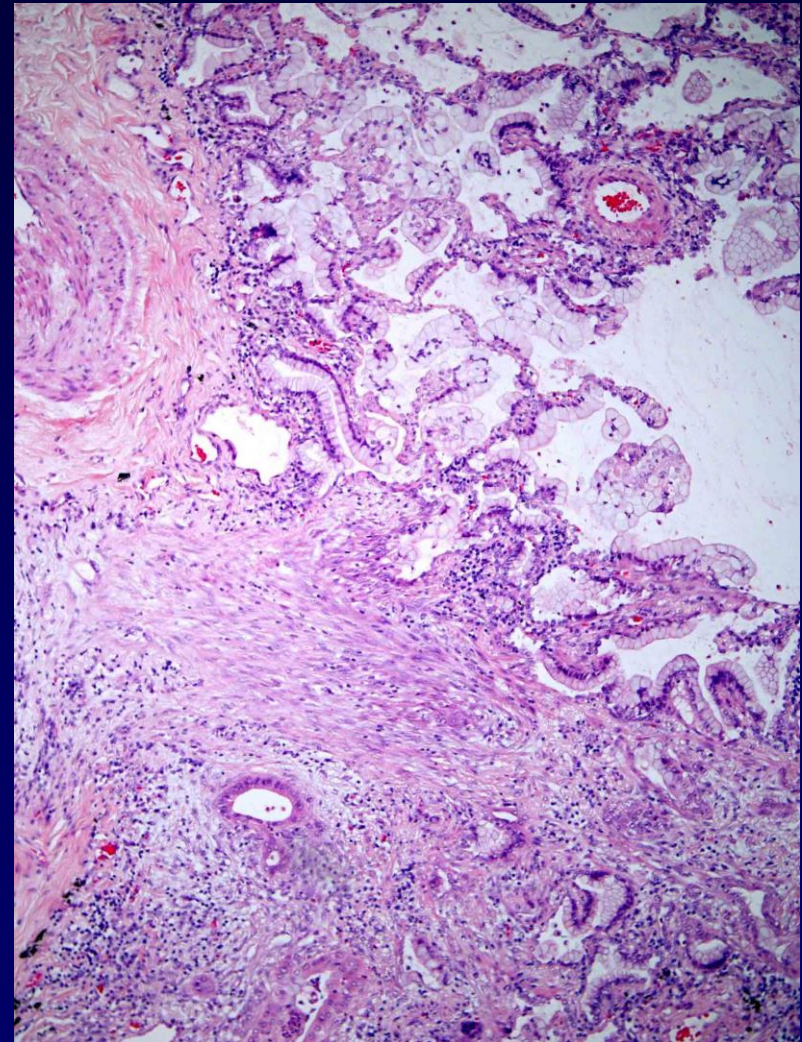
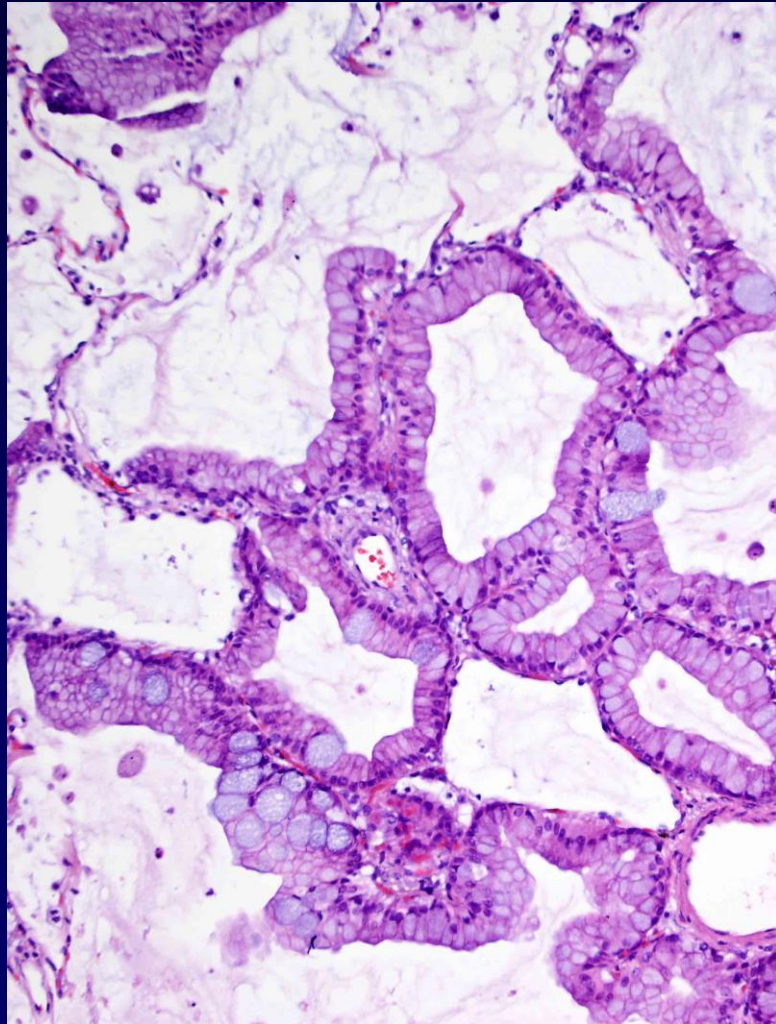
Validation of the IASLC/ATS/ERS Lung Adenocarcinoma Classification for Prognosis and Association with *EGFR* and *KRAS* Gene Mutations

Analysis of 440 Japanese Patients

Xu L et al: AJSP 2012;36:273-282

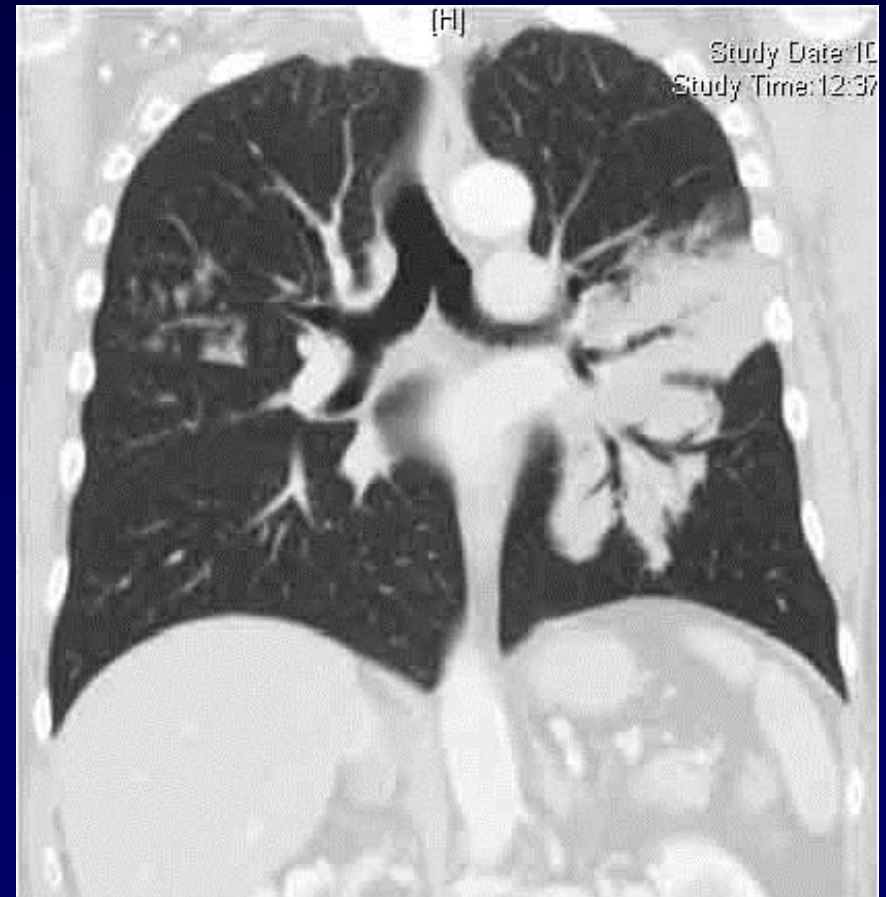
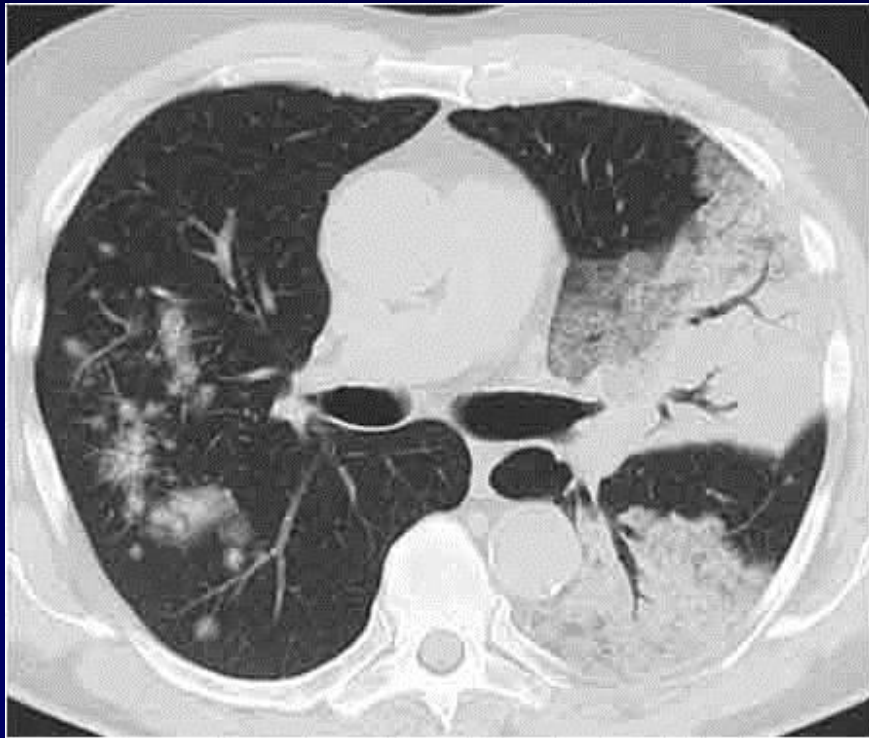
Yoshizawa A, et al: J Thor Oncol 2013;8: 52-61

INVASIVE MUCINOUS ADENOCARCINOMA

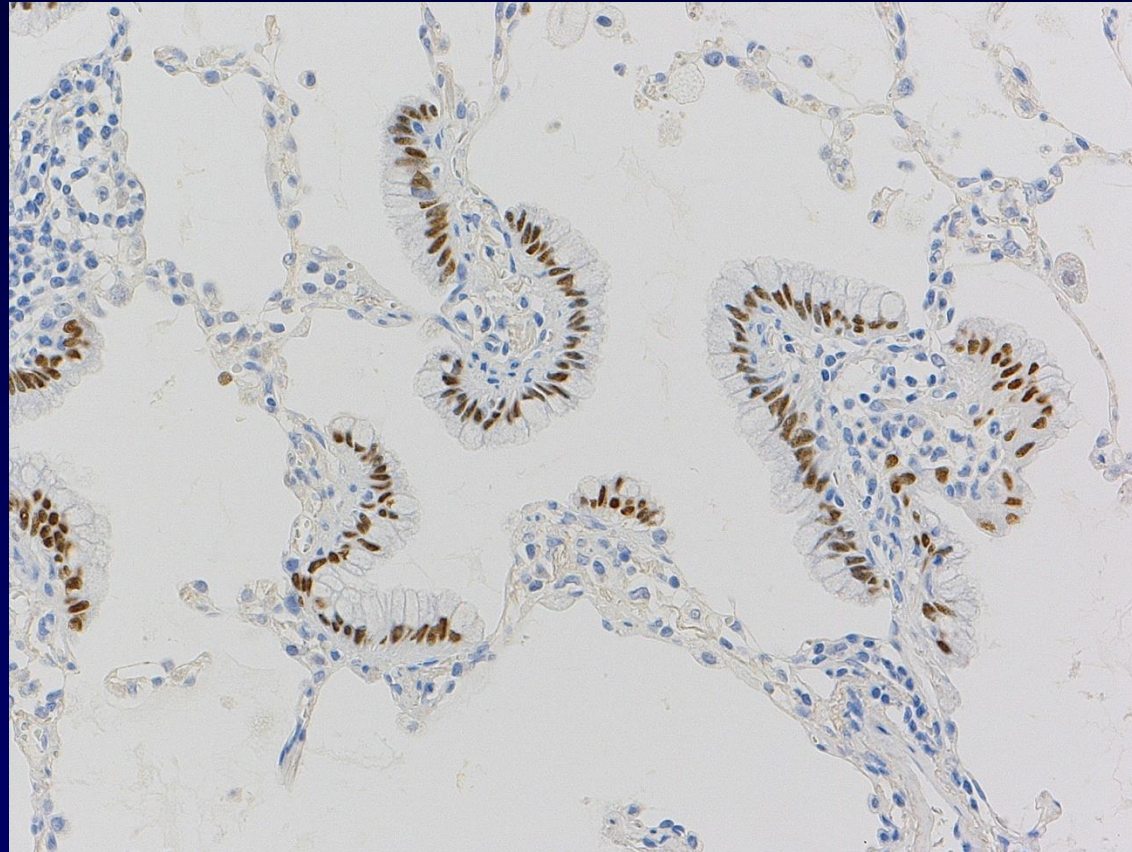


INVASIVE MUCINOUS ADENOCARCINOMA

Frequent *KRAS* mutations

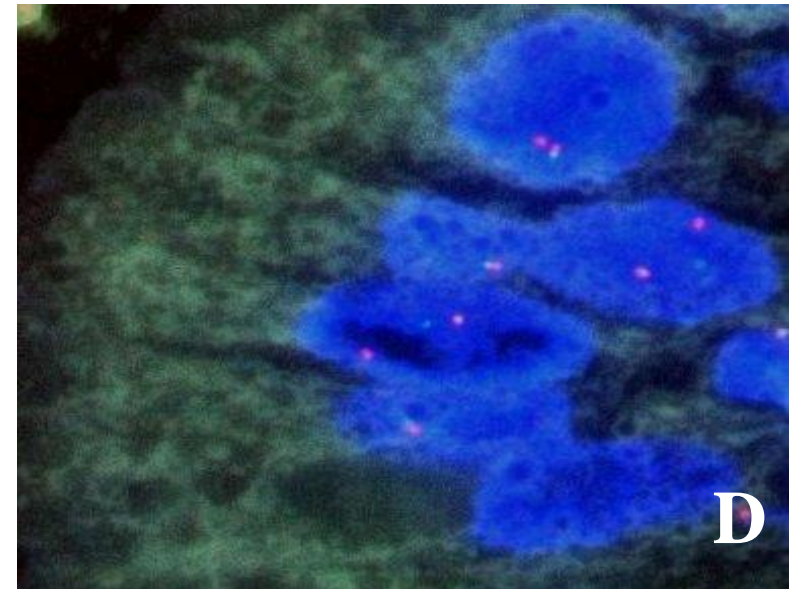
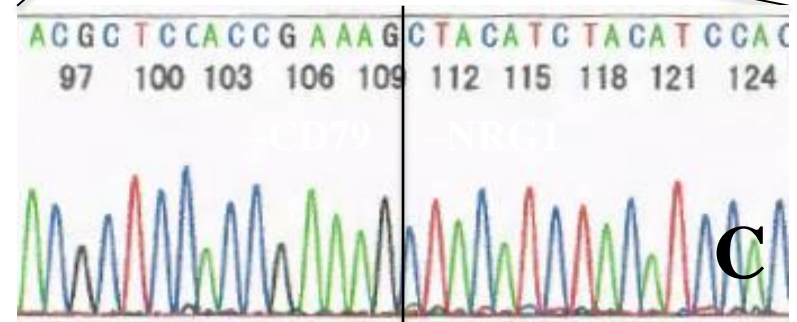
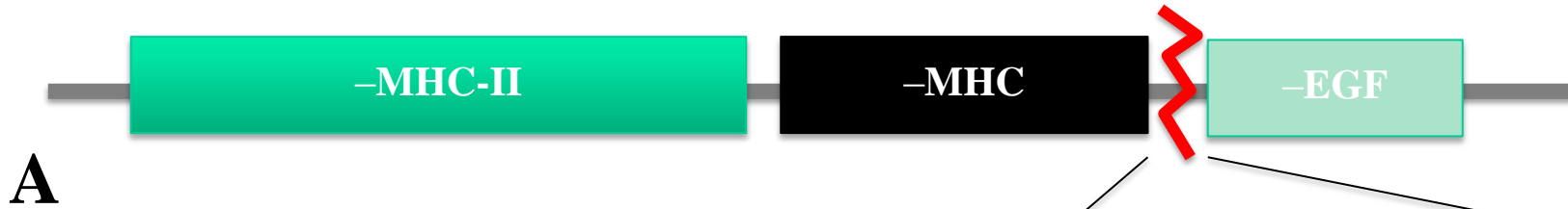


HNF4- α AS A MARKER FOR INVASIVE MUCINOUS ADENOCARCINOMA



Sugano M et al: Am J Surg Pathol 37:211-8, 2013

INVASIVE MUCINOUS ADENOCARCINOMA WITH *CD74-NRG1* FUSION (Cancer Discov 2014;4:415-22)



Provided by Y. Yatabe

REPRODUCIBILITY

Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study

Erik Thunnissen¹, Mary Beth Beasley², Alain C Borczuk³, Elisabeth Brambilla⁴,

–Mod Path 25:1574, 2012

Selected images: kappa

Typical patterns: 0.77

Difficult cases: 0.38

Invasion vs noninvasion

Typical: 0.55

Difficult: 0.08

Interobserver variability in the application of the novel IASLC/ATS/ERS classification for pulmonary adenocarcinomas

Arne Warth*, Albrecht Stenzinger*, Ann-Christin von Brünneck[#], Benjamin Goeppert*, Judith Cortis*, Iver Petersen[†], Hans Hoffmann⁺, Philipp A. Schnabel* and Wilko Weichert*

–ERJ 40:1221-27, 2012

Predominant pattern : Kappa
Lung Pathologists: substantial
(0.44-.72)

Residents: fair (0.38-0.47)

Training increases concordance in classifying pulmonary adenocarcinomas according to the novel IASLC/ATS/ERS classification

Arne Warth • Judith Cortis • Ludger Fink • Annette Fisseler-Eckhoff • Helene Geddert • Thomas Hager • Klaus Junker • Gian Kayser • Julia Kitz • Florian Länger • Alicia Morresi-Hauf • German Ott • Iver Petersen • Albrecht Stenzinger • Alex Soltermann • Saskia Ting • Verena Tischler • Ekkehard Vollmer • Philipp A. Schnabel • Wilko Weichert • on behalf of the Pulmonary Pathology Working Group of the German Society of Pathology

–Virch Arch 461:185-93, 2012

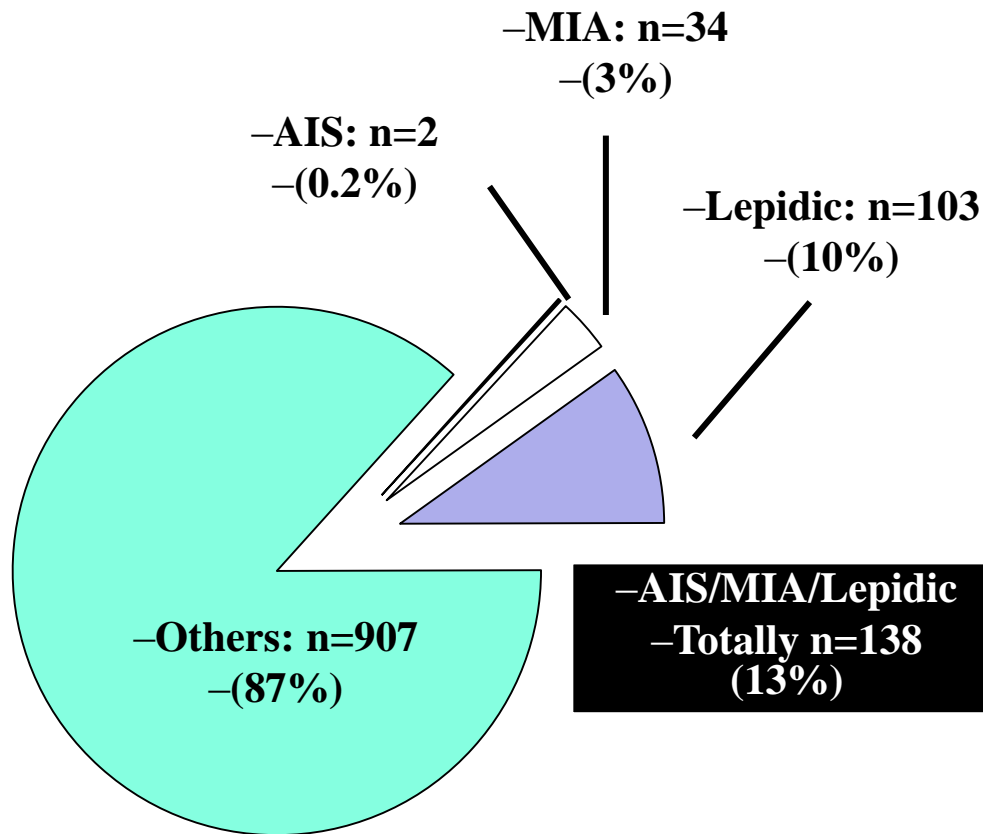
Digital images:

Consensual votes: 59.6-75%

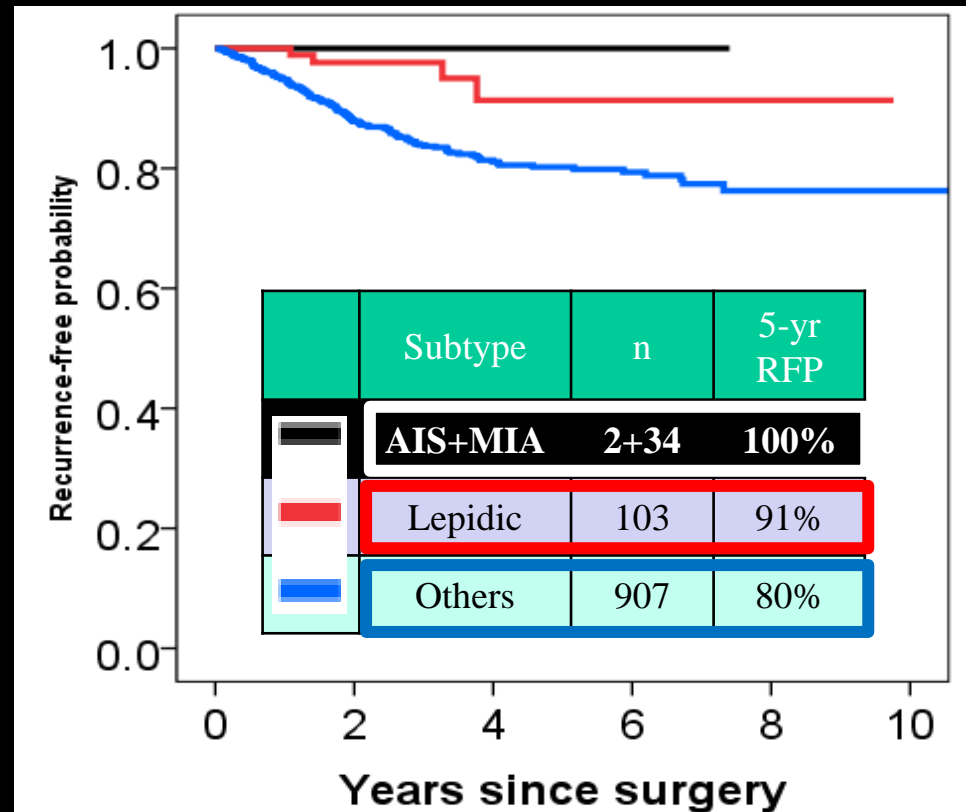
Disagreement decreased
significantly after educational
sessions (p<0.001)

Patients distribution by lepidic pattern and their recurrence-free probability (RFP)

–Lepidic pattern (patient, %)



–RFP by lepidic pattern



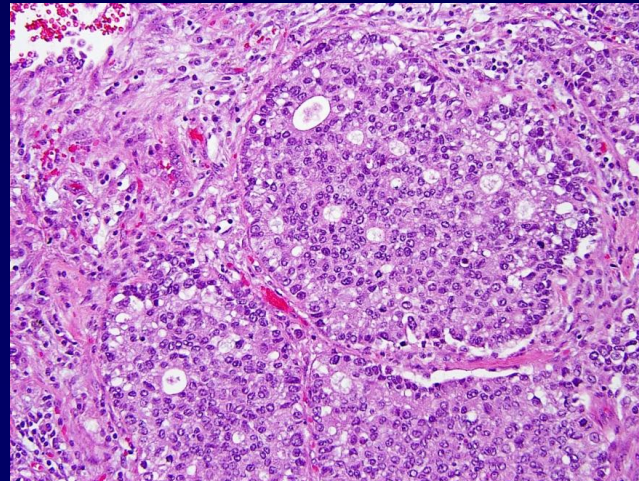
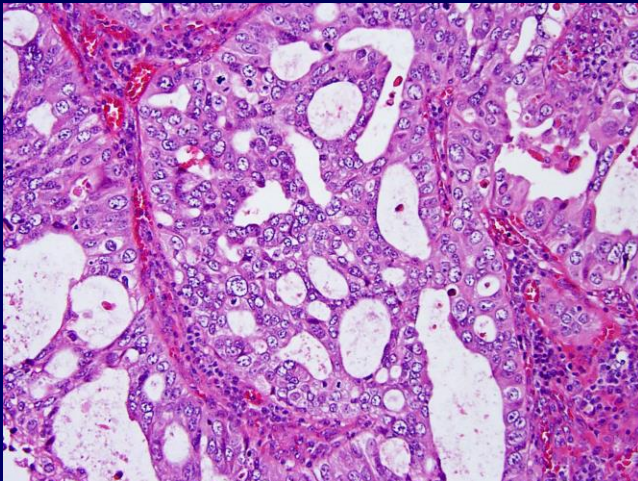
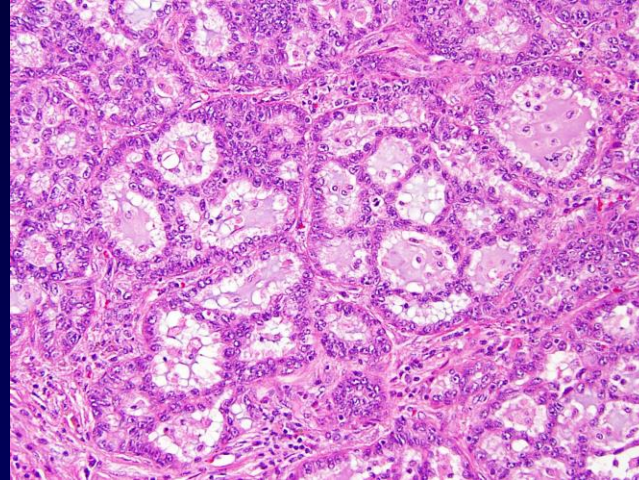
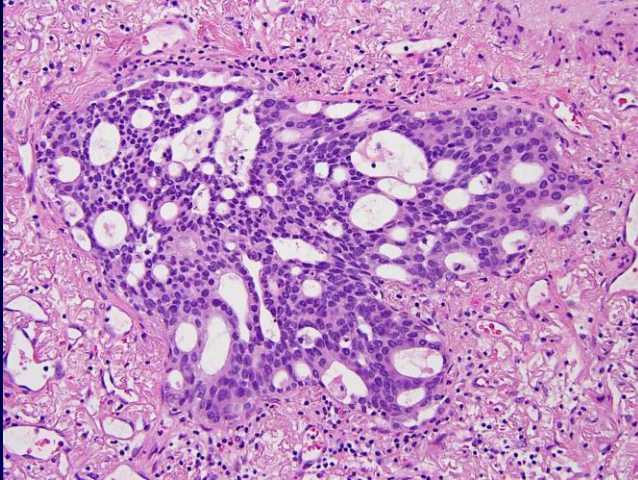
Clinicopathologic characteristics of four recurrent cases in lepidic predominant ADC

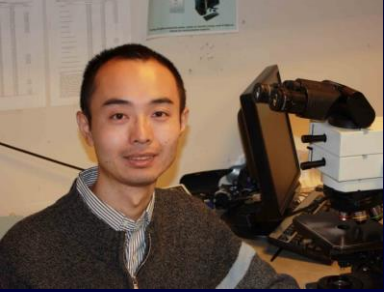
Case	surgical procedure	type of rec.	duration until rec.	staple margin	stage	Ly	V	PL	micro-papillary
1	lobectomy	distant (bone)	1.4 yrs	NA	IA	+	+	0	30
2	wedge resection	local rec. (lung)	1.1 yrs	2 mm	IA	+	-	0	20
3	wedge resection	distant (chest wall)	3.3 yrs	5 mm	IA	-	-	0	0
4	lobectomy	local rec. (lung)	3.8 yrs	NA	IA	-	-	0	0

–Lepidic predominant ADC with no recurrence (n=99)

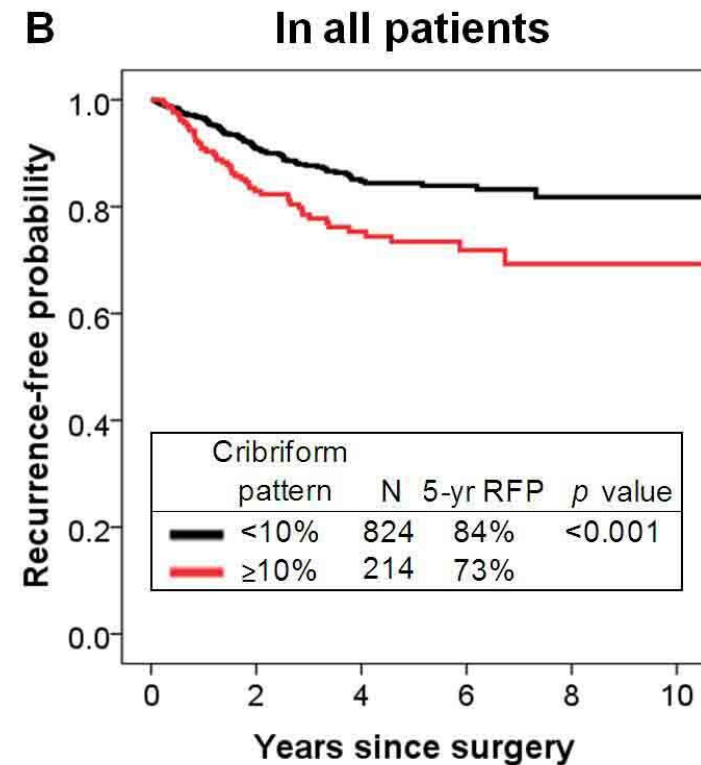
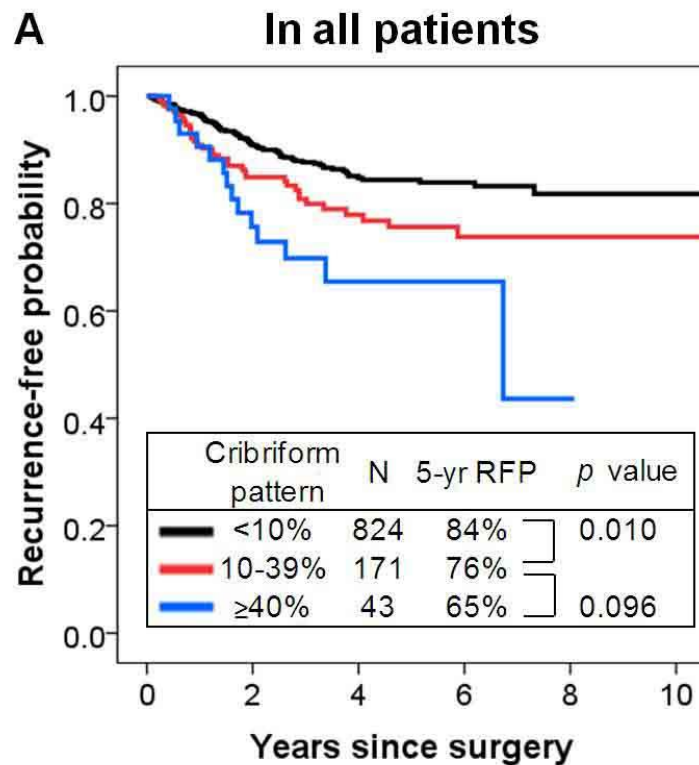
- lymphatic invasion: 6% (n=6)
- vascular invasion: 4% (n=4)
- micropapillary pattern: 2% (average)

CRIBRIFORM PATTERN





POOR SURVIVAL FOR CRIBRIFORM ADENOCA



—Kadota K et al: Mod Pathol 2014; 27: 690-700

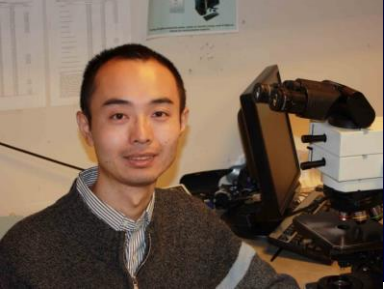
SHOULD CRIBRIFORM BE ADDED TO CLASSIFICATION?

NOT YET (high grade acinar)

INVASIVE ADENOCARCINOMA

- **Lepidic pattern predominant** (formerly non-mucinous BAC pattern)
- Acinar pattern predominant
- Papillary pattern predominant
- **Micropapillary pattern, predominant**
- Solid pattern predominant
- **??? Cribriform predominant???**

(Comprehensive histologic subtyping: semiquantitative assessment of patterns in 5-10% increments)



MODERN PATHOLOGY (2012), 1–11

© 2012 USCAP, Inc. All rights reserved 0893-3952/12 \$32.00

A grading system combining architectural features and mitotic count predicts recurrence in stage I lung adenocarcinoma

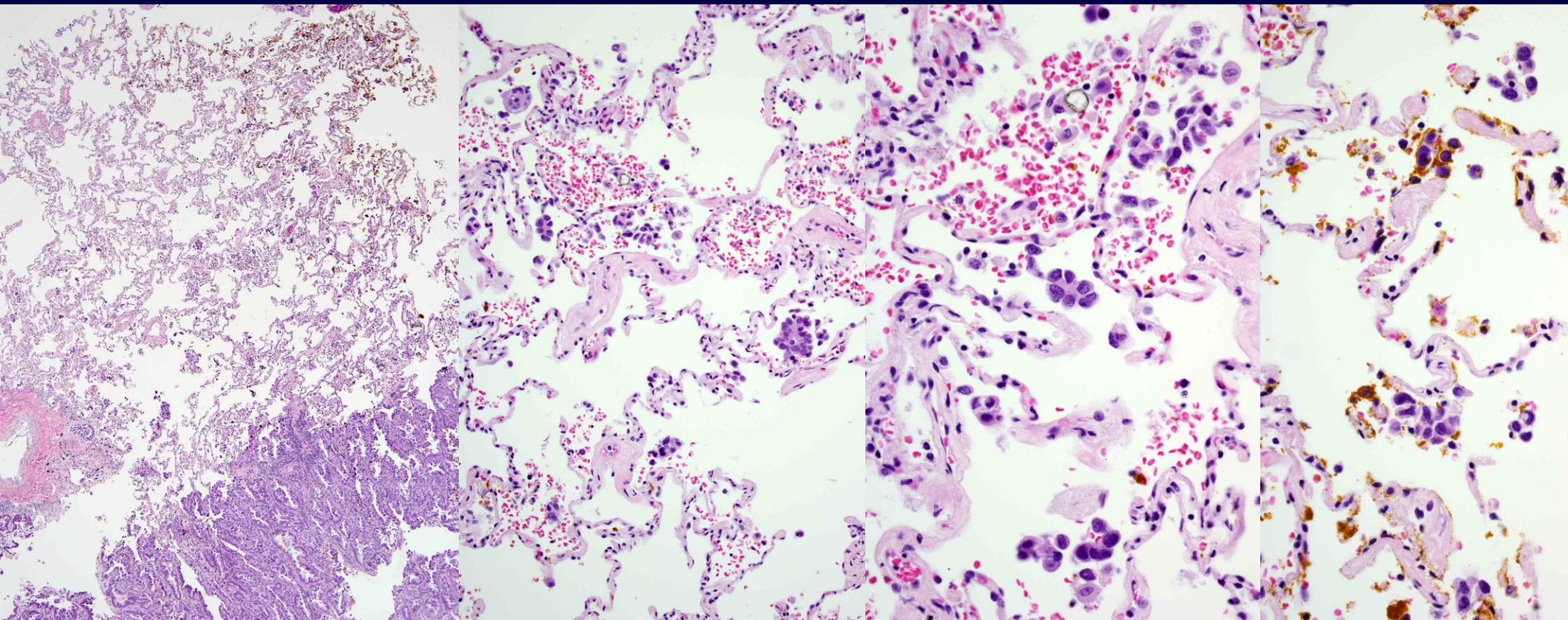
Kyuichi Kadota^{1,2}, Kei Suzuki¹, Stefan S Kachala¹, Emily C Zabor³, Camelia S Sima³, Andre L Moreira⁴, Akihiko Yoshizawa^{4,5}, Gregory J Riely⁶, Valerie W Rusch¹, Prasad S Adusumilli^{1,7} and William D Travis⁴

–Kadota K et al: Mod Pathol 25:1117-1127, 2012

**SPREAD THROUGH AIR SPACES
(STAS)
IS AN IMPORTANT PATTERN OF
INVASION IN LUNG
ADENOCARCINOMA**

MICROPAPILLARY ADCA IS AN INDEPENDENT PREDICTOR OF RECURRENCE IN LIMITED RESECTIONS (≤ 2 CM)

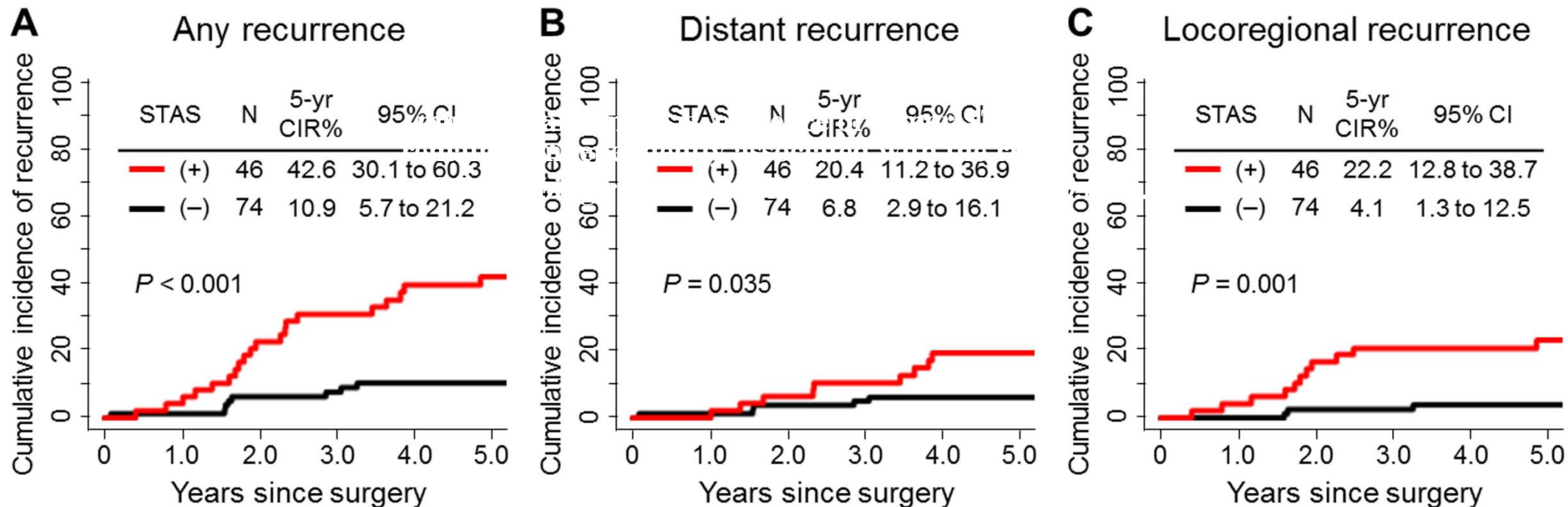
Nitadori J & Adusumilli P, et al JNCI ; 2013: 105:1212-20



STAS – Cumulative Incidence of Recurrence in Limited Resections

Figure 3

CIR by STAS in the limited resection group



Multivariate analysis, presence of tumor STAS remained independently associated with the risk of recurrence (hazard ratio, 3.08; $P=0.014$).

Kadota K et al; JTO 2015; epub ahead

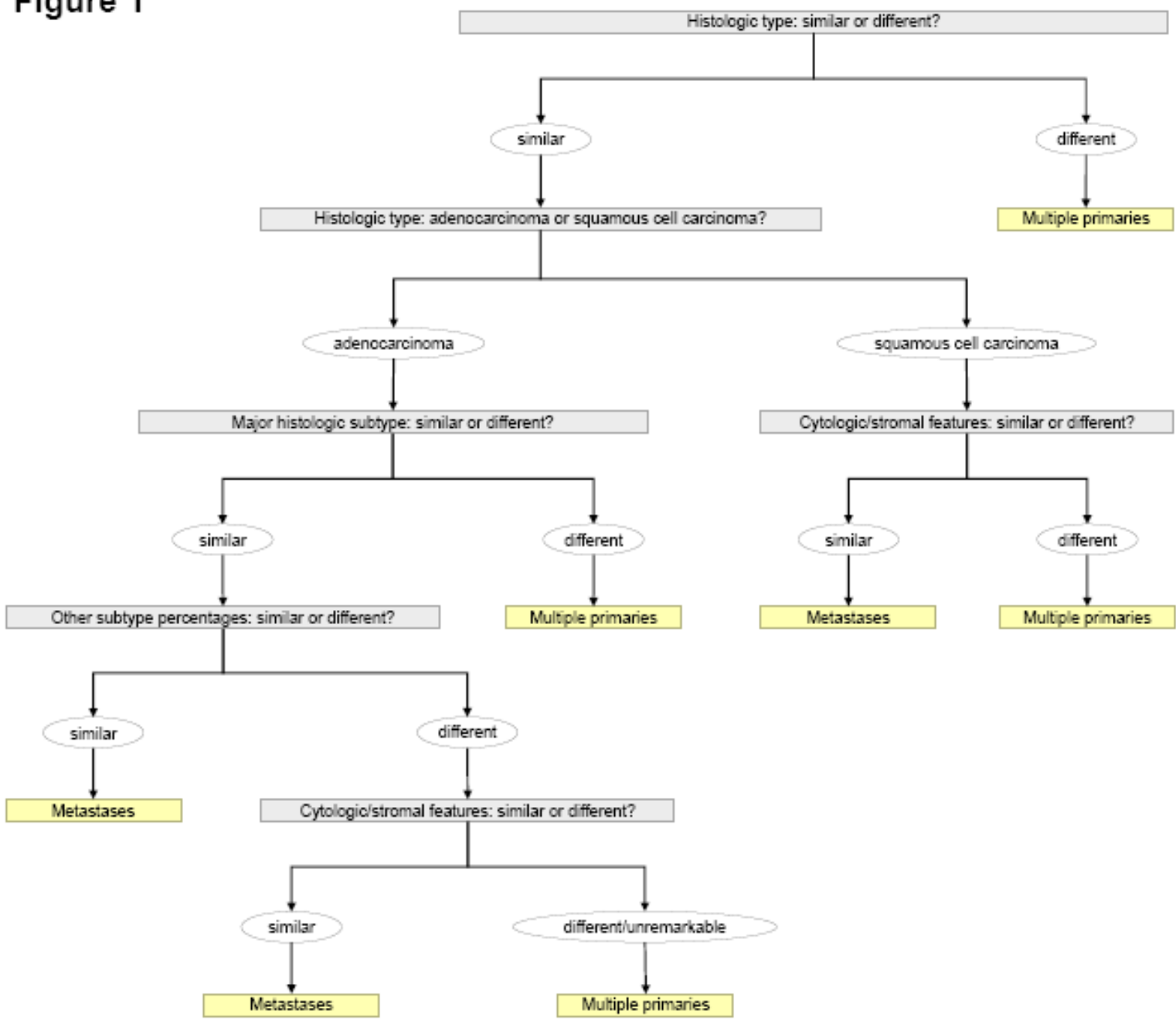
Spread Through Air Spaces (STAS)

- **Is true invasion, not an artifact**
- **Introduced into the definition of invasion in lung adenocarcinoma**
- **Should not be included in tumor size**
- **Should not be included in subtyping**
- **Should be searched for in staple line margins**

IMPLICATIONS OF NEW CLASSIFICATION FOR TNM STAGING OF ADENOCARCINOMAS

- Multiple tumors: Metastasis vs synchronous/metachronous primaries
- Terminology: implication of AIS and MIA
- Tumor size

Figure 1



**Girard, N, et al:
AJSP 33: 1752-64,
2009**

DISEASE FREE SURVIVAL COMPARING MARTINI MELAMED VS MOLECULAR VS SURGICAL PATHOLOGY

Martini Melamed

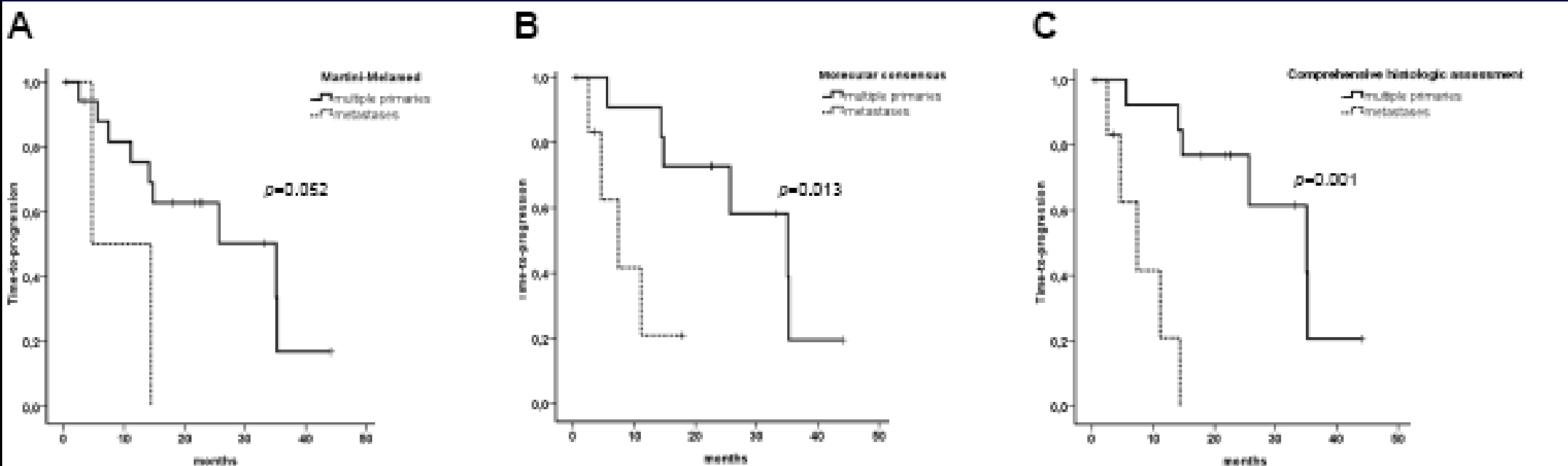
$P=0.052$

Molecular

$P=0.013$

Surgical Pathology

$P=0.001$

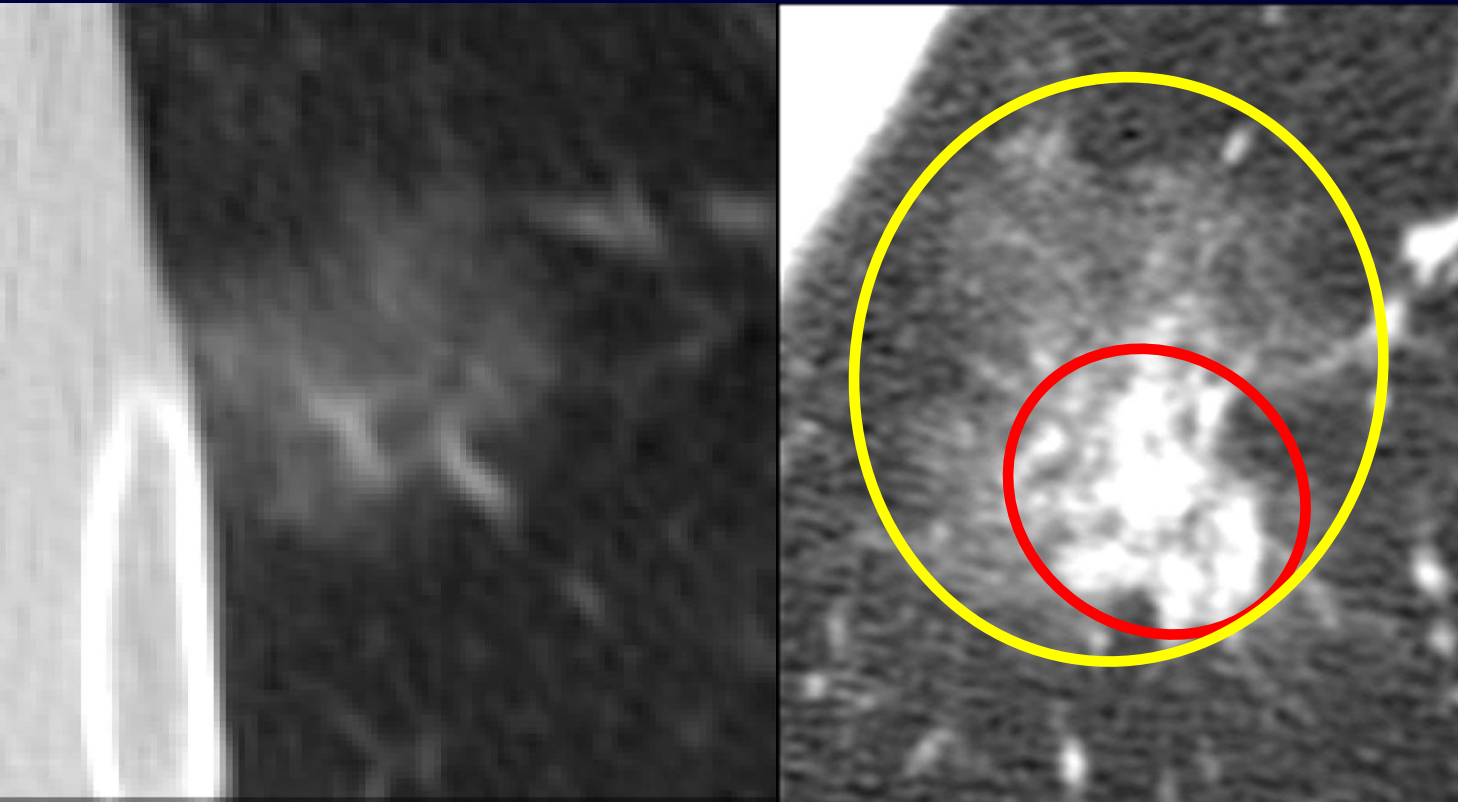


Girard, N, et al: AJSP AJSP 33: 1752-64, 2009

IMPLICATIONS OF NEW CLASSIFICATION FOR TNM STAGING OF ADENOCARCINOMAS

- **Multiple tumors: Metastasis vs synchronous/metachronous primaries**
- **Tumor size (use only invasive size)**
- **Terminology: implication of AIS and MIA**

IMPLICATIONS OF IN SITU CONCEPT ON CT MEASUREMENT OF TUMOR SIZE: GGO VS SOLID



–GROUND GLASS OPACITY

–PART SOLID

POTENTIAL NEW
APPROACH
TO TUMOR SIZE
MEASUREMENT

–Contributed by C. Henschke & colleagues

2012 UICC TNM Supplement, p 6

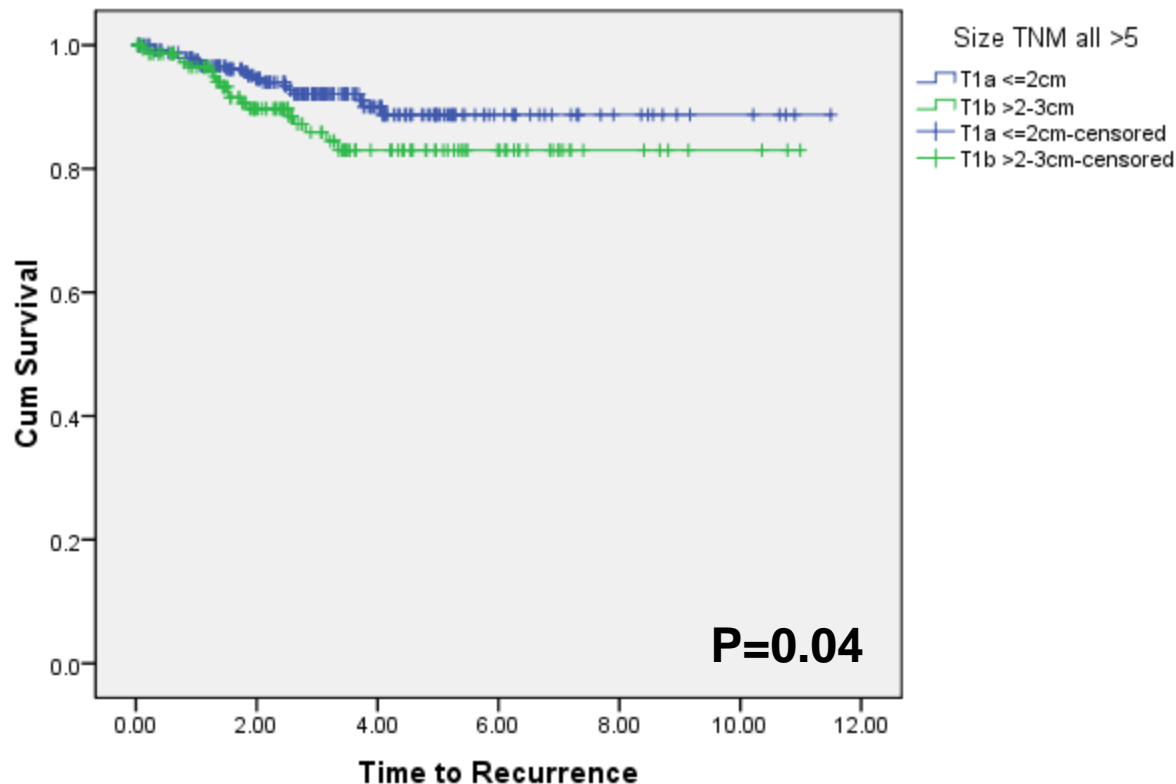
- **When size is a criterion for the T/pT category, it is a measurement of the invasive component. If in the breast, for example, there is a large in situ component (e.g. 4 cm) and a small invasive component (e.g. 0.5cm), the tumor is coded for the invasive component only, i.e. pT1a.**

STAGE 1 ADENOCARCINOMA

Standard Gross Size

T1a ≤ 2 cm vs. T1b $>2-3$ cm

Survival Functions



Stage (N)

5 Year RFS
%

T1a (259)

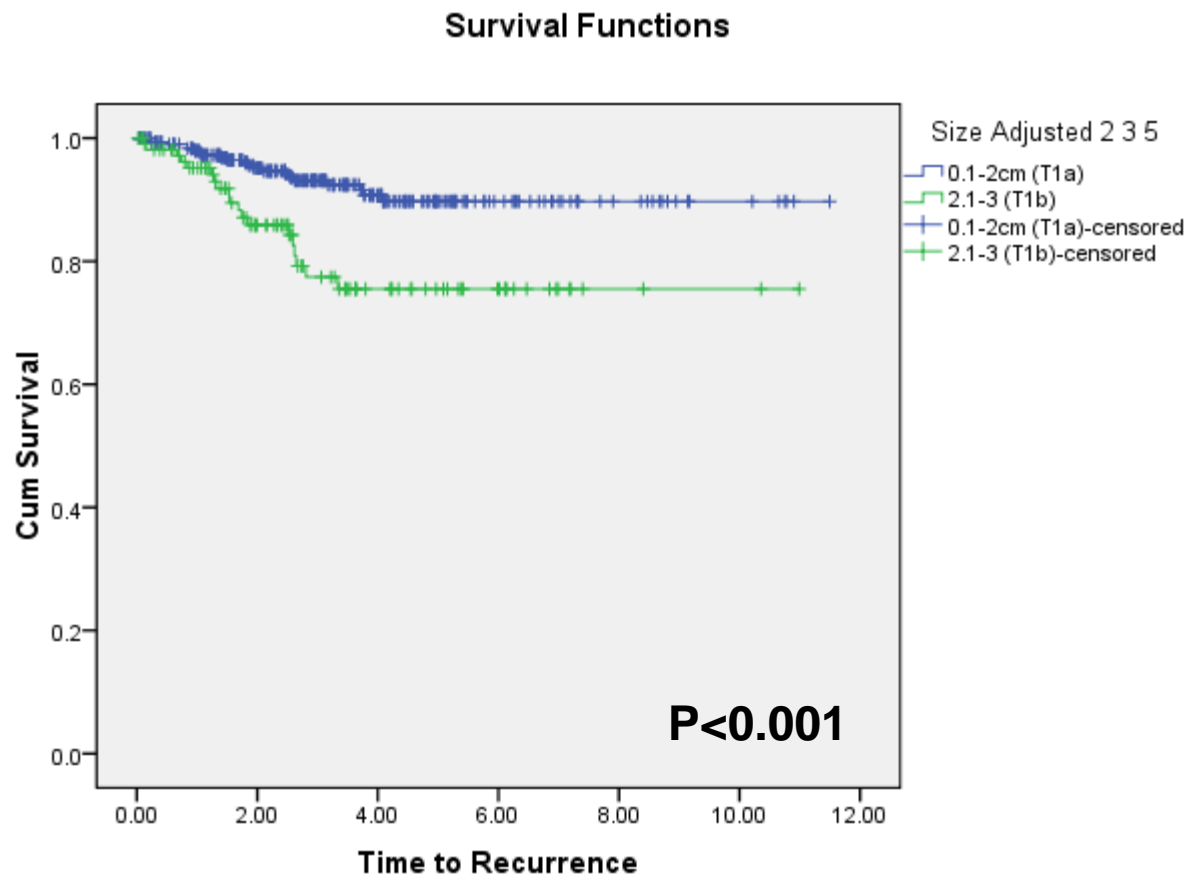
88

T1b (152)

80

STAGE 1 ADENOCARCINOMA

Size adjusted by % invasion (not in situ)
T1a \leq 2 cm vs. T1b >2 -3cm



Stage (N)	5 Year RFS %
T1a (320)	88
T1b (111)	73

514 Stage I Adenocarcinomas

Multivariate Analysis

Factor	HR (95% CI)	p-value
IASLC/ATS/ERS classification (High vs. Intermediate/Low Grade)	1.7 (1.0 – 2.8)	0.038
Gender (Male vs Female)	1.8 (1.2 – 2.7)	0.007
Stage (IB vs IA)	1.4 (0.8 – 2.3)	0.19
Invasive Tumor size*	1.3 (1.0 – 1.6)	0.026
2004 WHO Histologic grade (Poor vs Moderate/Well)	1.1 (0.6 – 1.8)	0.86
Necrosis (Yes vs. No)	2.1 (1.3 – 3.5)	0.002
Vascular invasion (Yes vs No)	1.5 (0.9 – 2.3)	0.085

Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011

* Tumor size adjusted by subtracting percentage of lepidic growth

IMPLICATIONS FOR TNM STAGING

- **ALS would be classified as Tis**
 - **Tis (squamous CIS)**
 - **Tis (AIS)**
- **Similar to breast cancer**
 - **Tis (DCIS)**
 - **Tis (LCIS)**
- **MIA would be classified as Tmi**
- **T factor size -change to invasive size?**

WHAT ARE THE QUESTIONS?

- What happened to BAC?
- Do AIS and MIA have a 100% DFS?
- Does predominant subtyping have prognostic significance?
- What is the reproducibility?
- Are there any new concepts?
- Does it help comparing multiple tumors?
- What is impact on TNM?

