LUNG CANCER PATHOLOGY: UPDATE ON LUNG ADENOCARCINOMAS

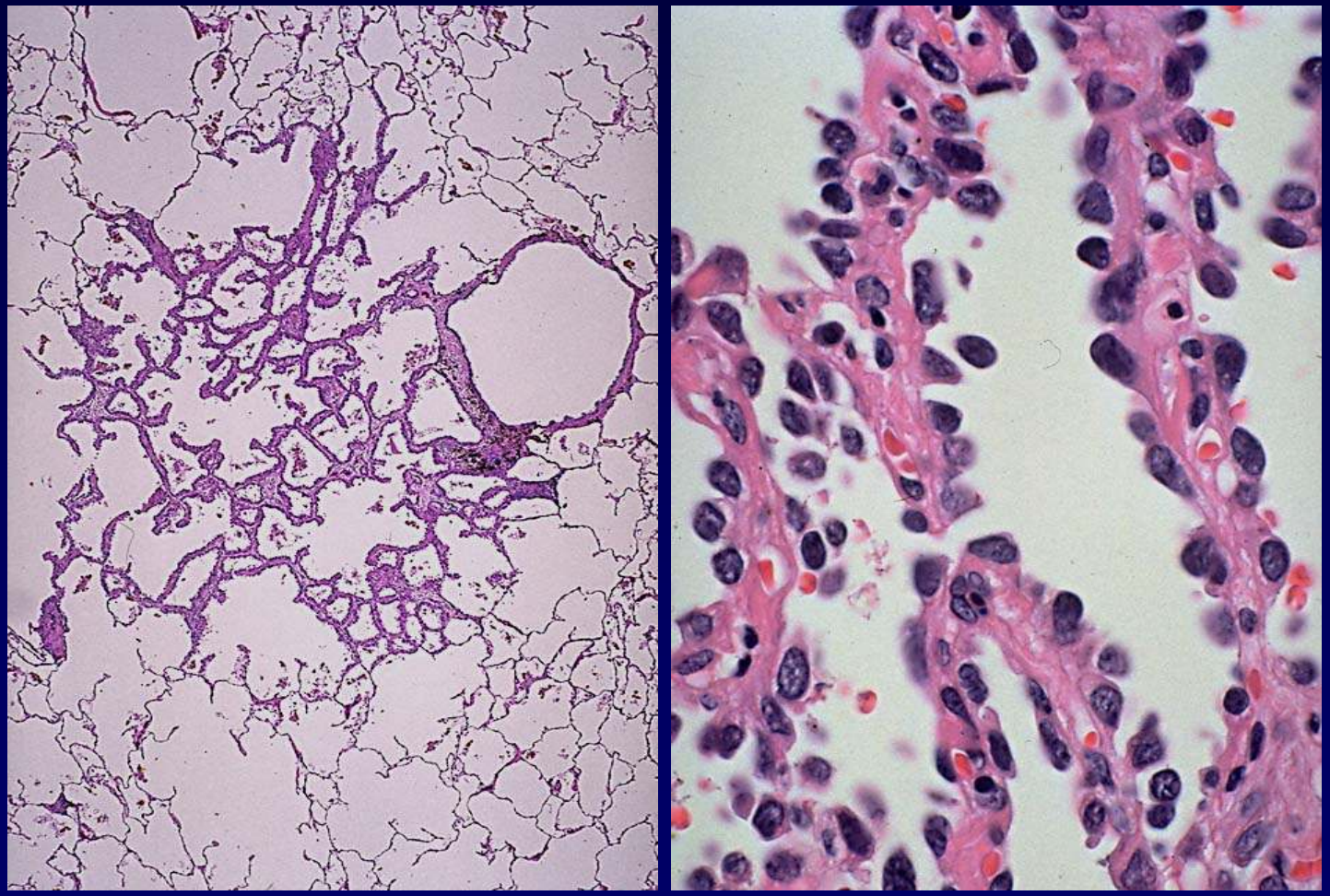
William D. Travis

Attending Thoracic Pathologist

Memorial Sloan Kettering Cancer Center

New York, NY

ATYPICAL ADENOMATOUS HYPERPLASIA



ATYPICAL ADENOMATOUS HYPERPLASIA

- Incidental finding in 9-16% of lung CA pts
- Most often associated with ADCA
- Multiple in 5-7% of lung CA pts
- Accepted as preinvasive lesion for ADCA
- May explain relatively high incidence of multicentric synchronous and metachronous lung CA

LUNG ADENOCARCINOMA

- Most common type (30-70%) of lung cancer
- Very heterogeneous (path, rad, clinical, molecular)
- Literature confusing:
  - Divergent use of term BAC
  - Multiple different classifications - increasing
- Major Molecular pathways:
  - EGFR (10-40%): nonsmokers, women, East Asians, adenocarcinoma, BAC, response to TKIs
  - KRAS (15-20%): worse prognosis, lack of response to chemotherapy/TKI's
  - Unknown major pathway in 30-70% cases

ADENOCARCINOMA
WHO CLASSIFICATION

1967 WHO

1. Bronchogenic
   - a. acinar
   - b. papillary

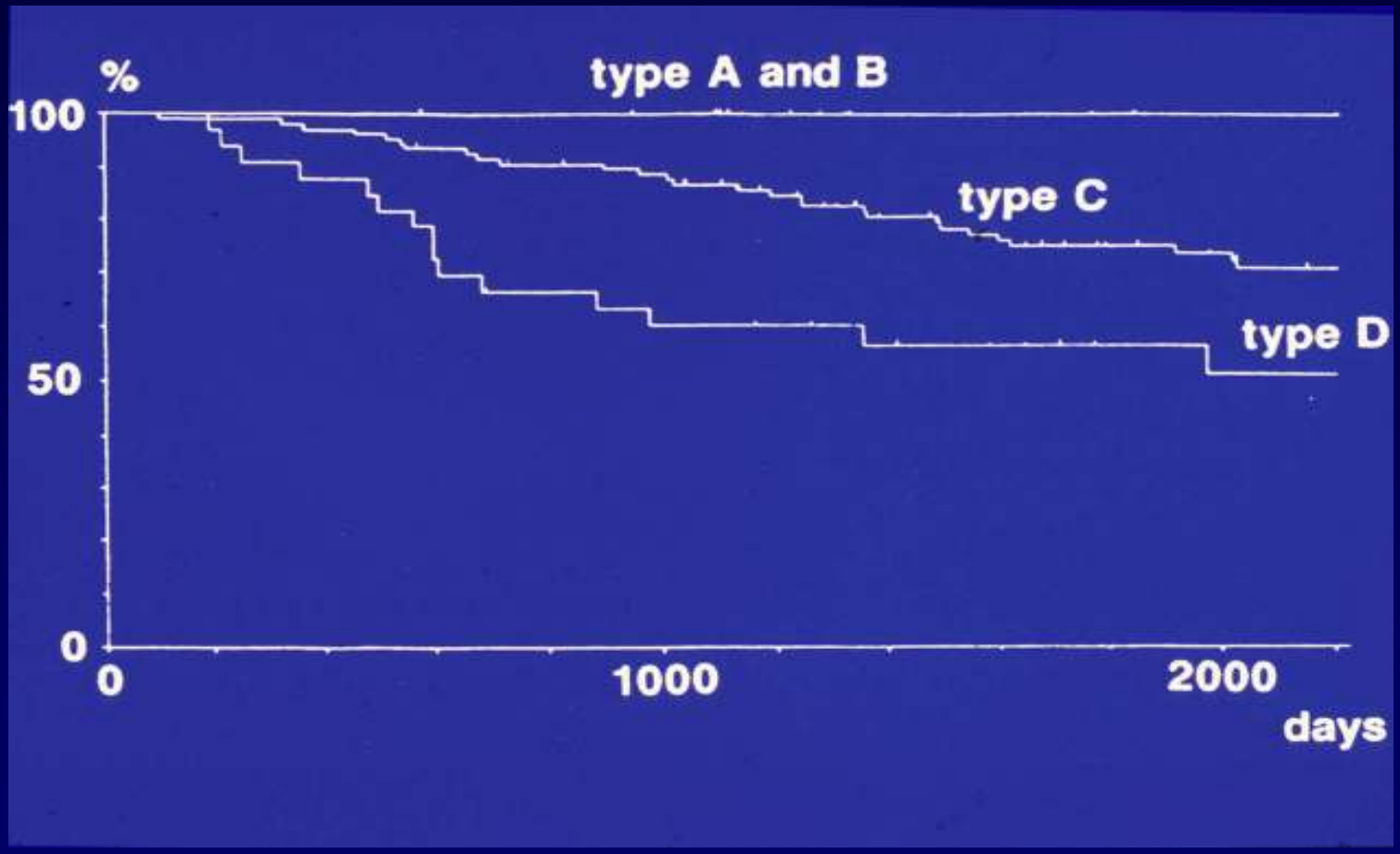
   } With or without mucin formation

2. Bronchiolo-alveolar

1981 WHO

- Acinar
- Papillary
- Bronchioloalveolar carcinoma
- Solid adenocarcinoma

Small Adenocarcinoma 2cm or <
Noguchi M. et al; Cancer 75:2844, 1995



1. EPITHELIAL TUMORS
1.3 Invasive Malignant - 1999

1.3.3 Adenocarcinoma
- 1.3.3.1 Acinar
- 1.3.3.2 Papillary
- 1.3.3.3 Bronchioloalveolar carcinoma
- 1.3.3.4 Solid adenocarcinoma with mucin formation
- 1.3.3.5 Mixed
- 1.3.3.6 Variants

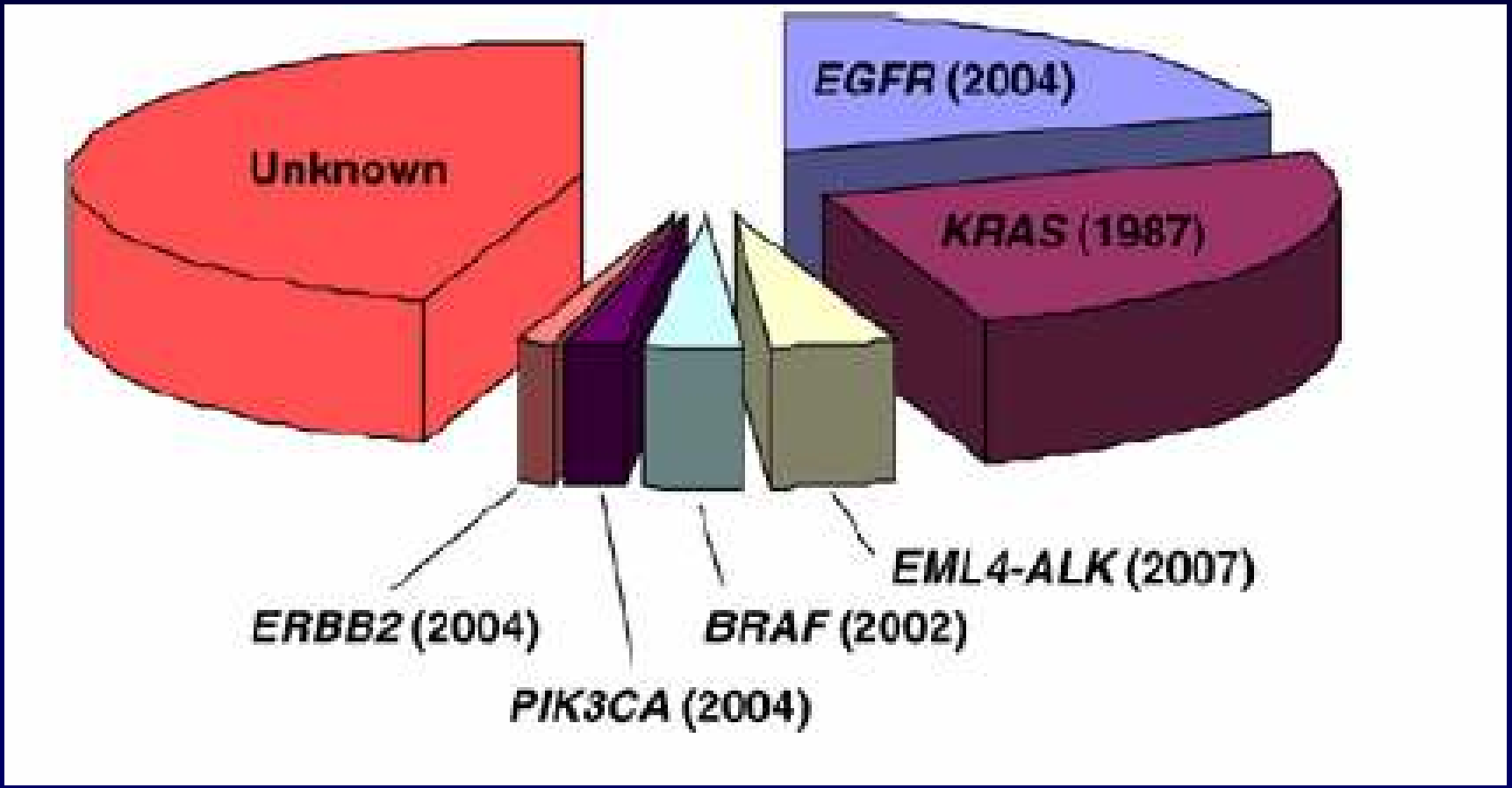
–WHO/IASLC CLASSIFICATION OF LUNG AND PLEURAL TUMORS

EPITHELIAL TUMORS
Invasive Malignant - 2004

Adenocarcinoma
- **Mixed subtype**
- **Acinar**
- **Papillary**
- **Bronchioloalveolar carcinoma**
- **Solid adenocarcinoma with mucin formation**
- **Variants**

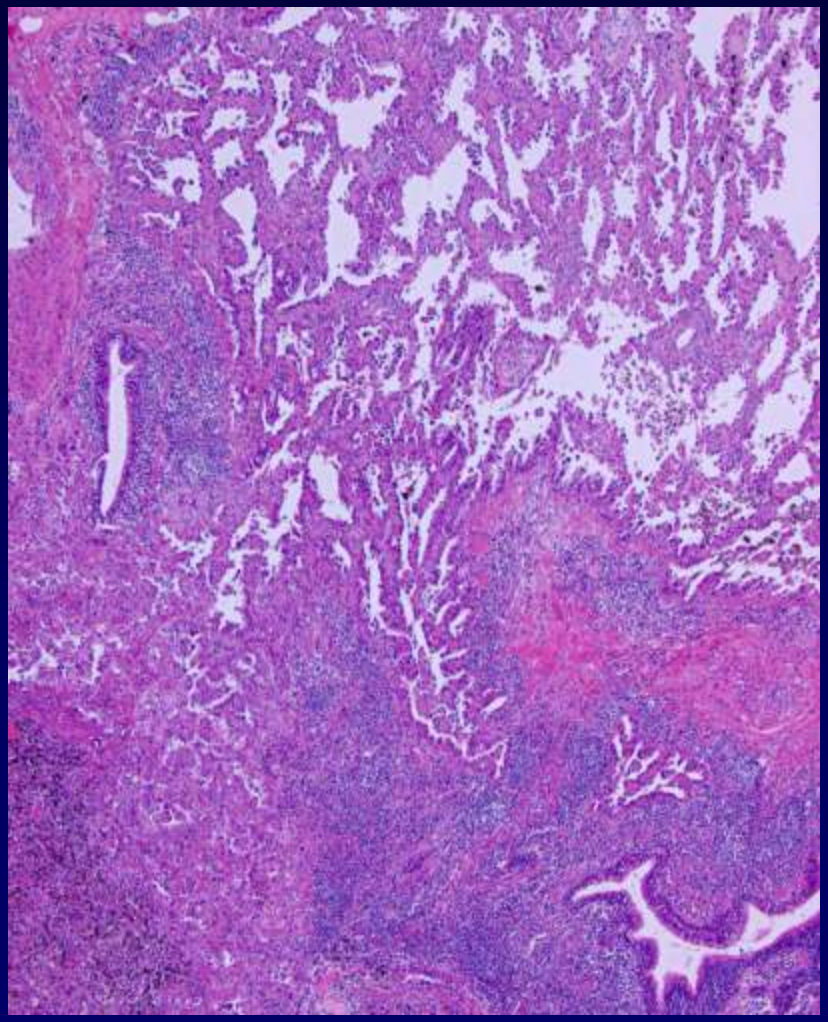
–WHO/IASLC CLASSIFICATION OF LUNG AND PLEURAL TUMORS

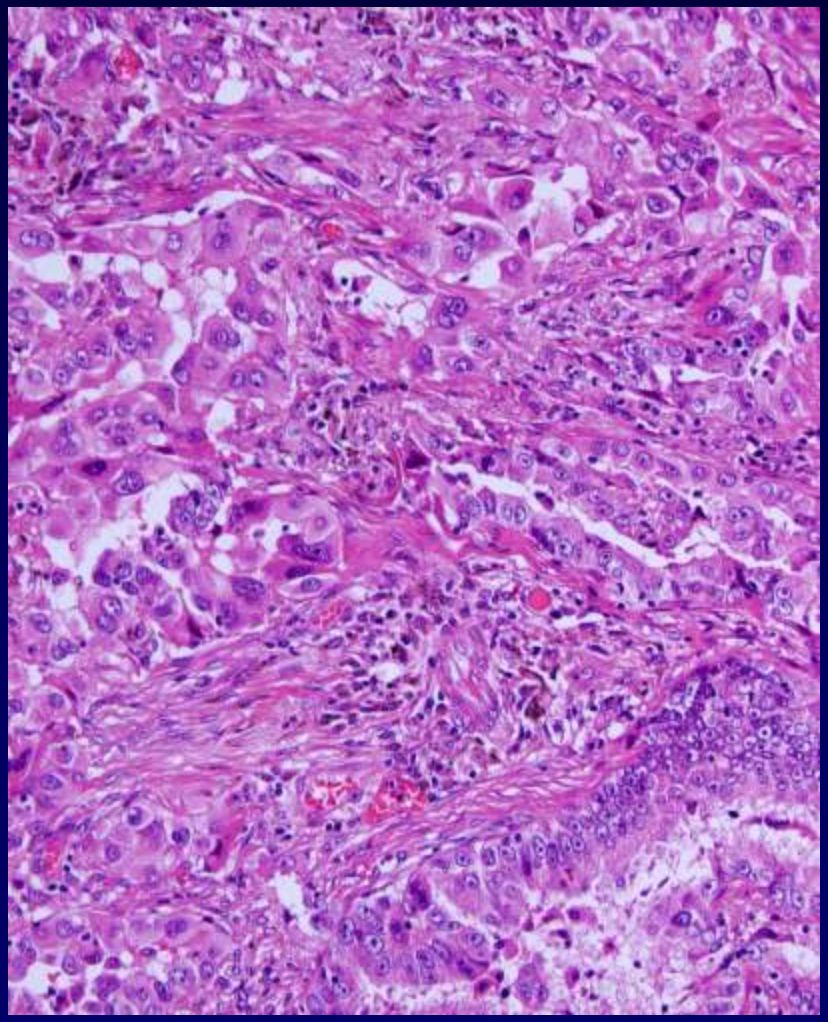
LUNG ADENOCARCINOMA CLASSIFICATION - 2009



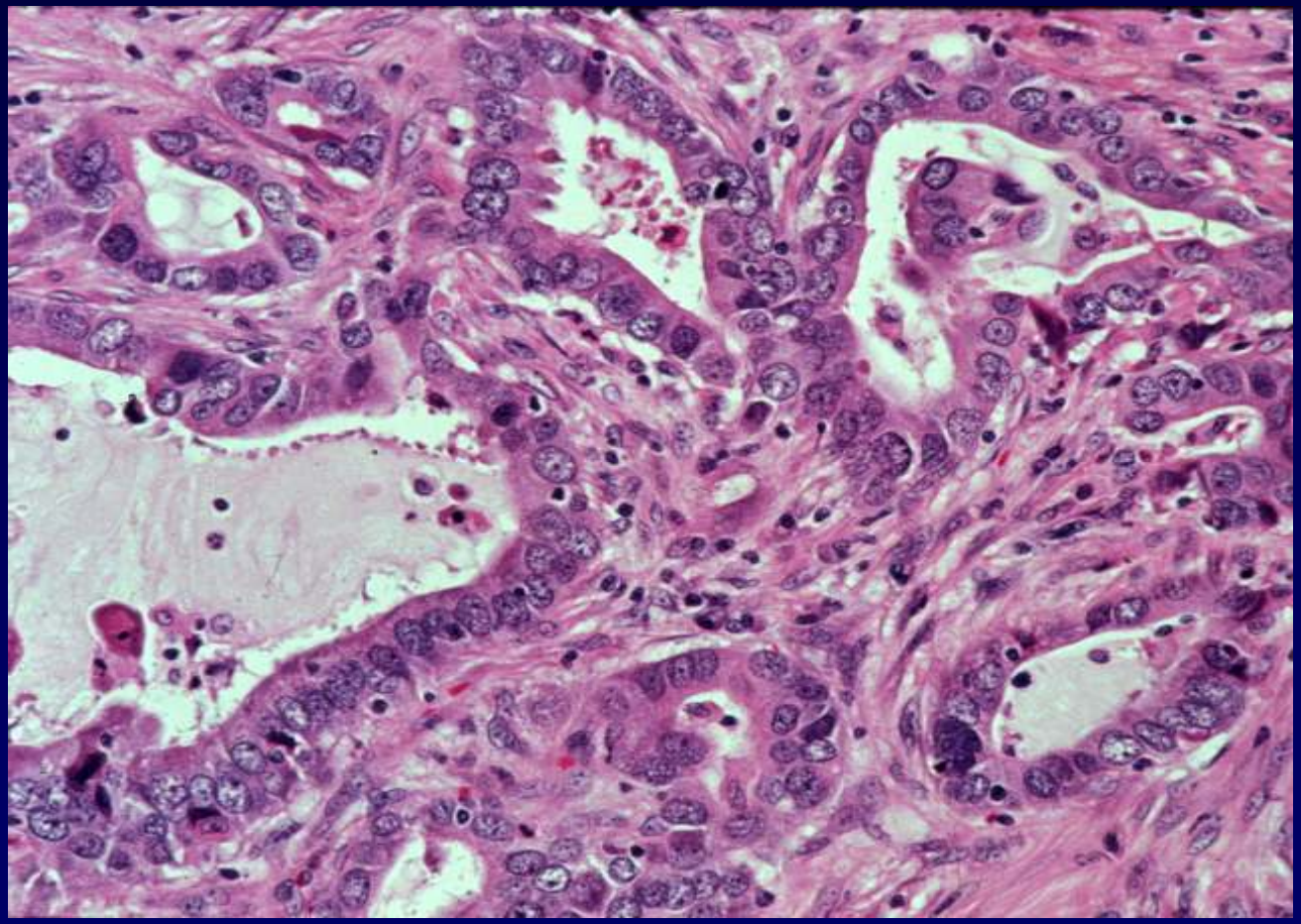
– Ladanyi M and Pao W; Mod Pathol: Suppl 2:S16-22

ADENOCARCINOMA MIXED SUBTYPE

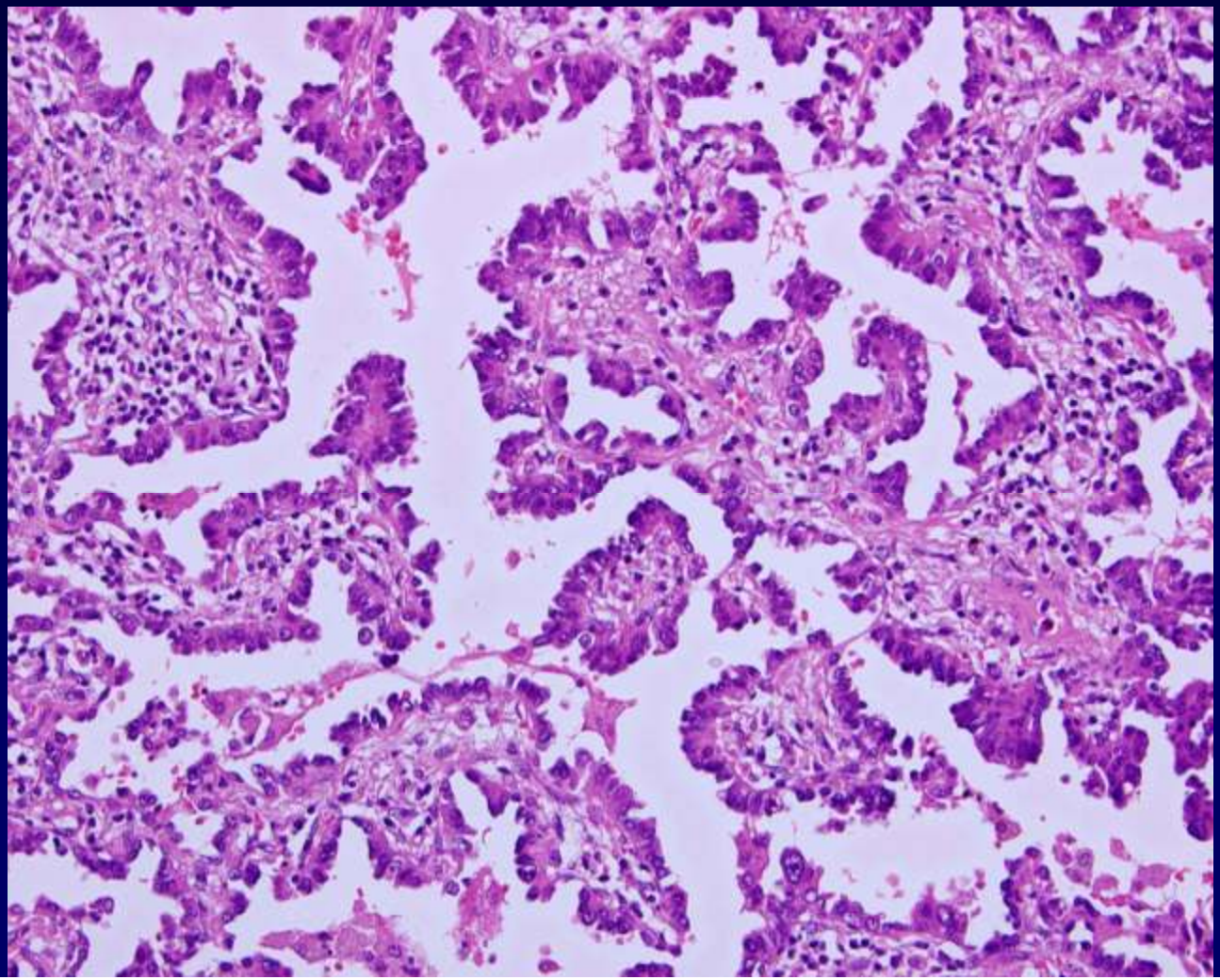




ADENOCARCINOMA ACINAR



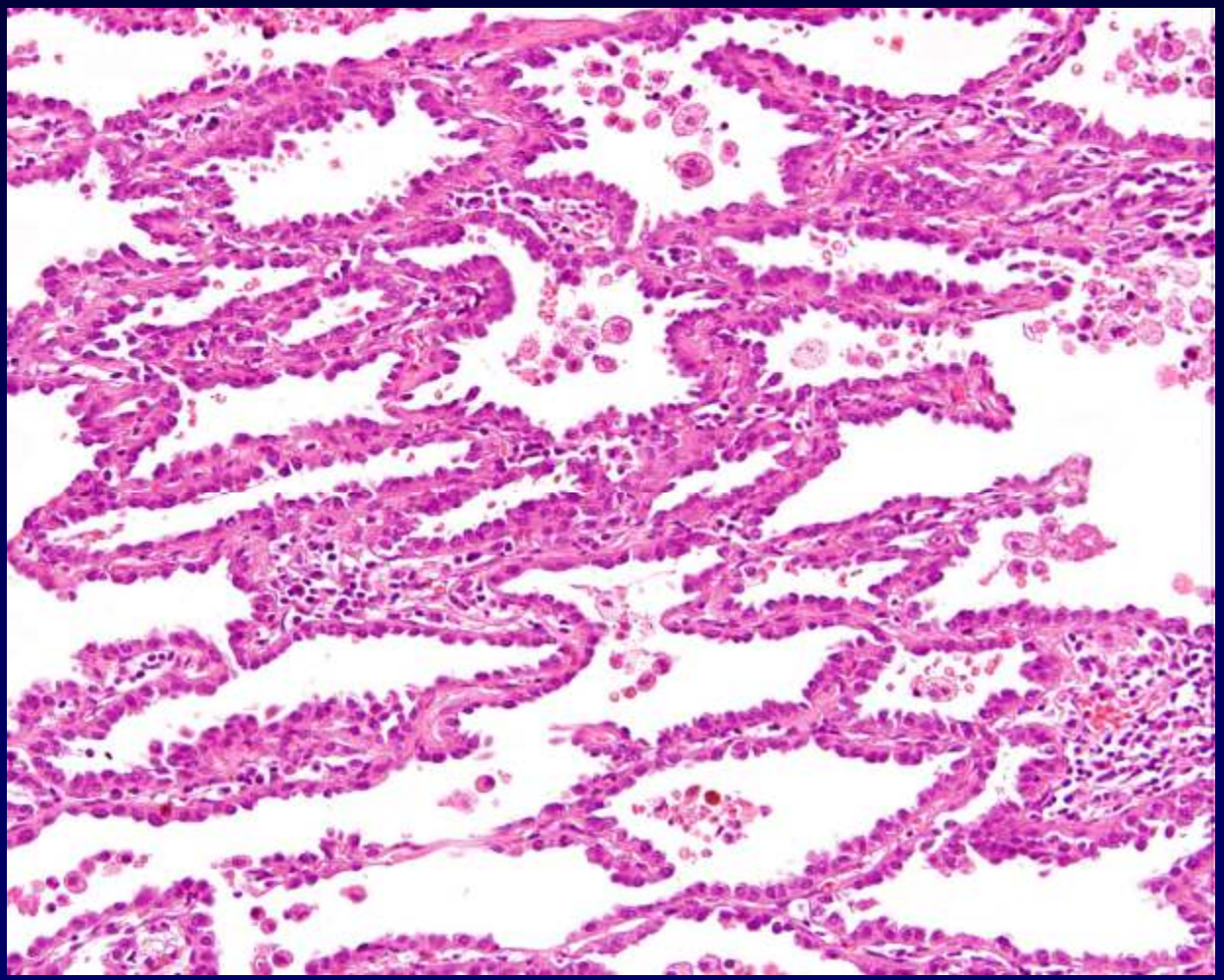
ADENOCARCINOMA PAPILLARY



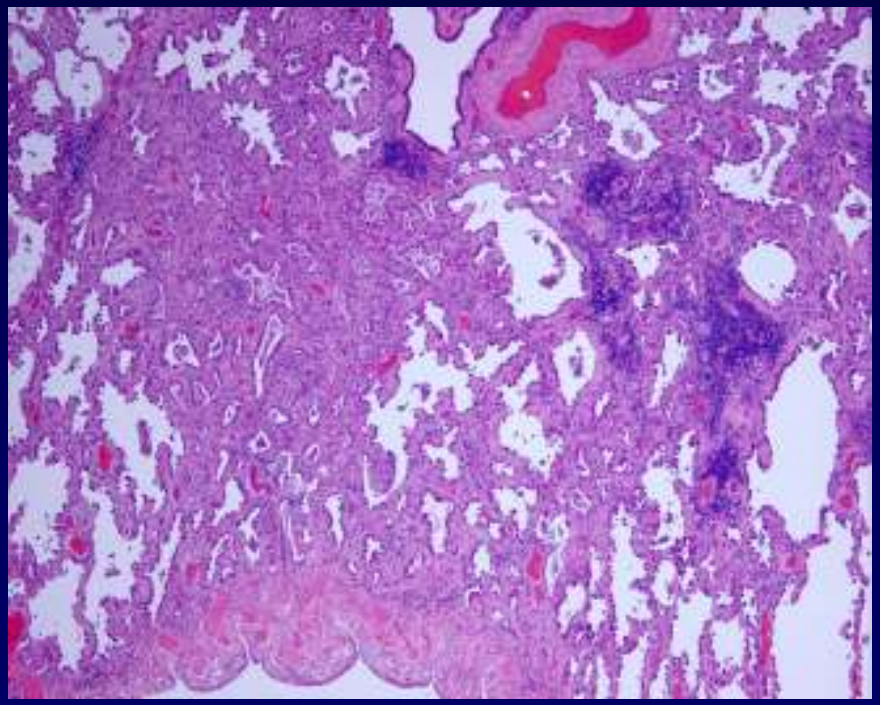
WHO LUNG TUMORS - 2004
Bronchioloalveolar Carcinoma

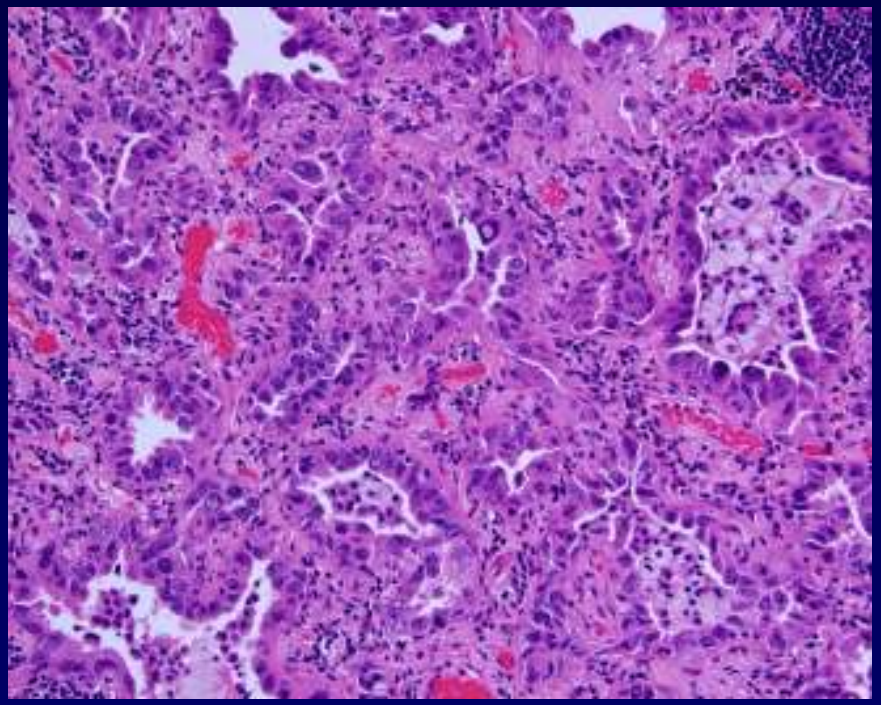
Non-mucinous
Mucinous
Mixed mucinous and non-mucinous

BRONCHIOLOALVEOLAR CARCINOMA, NONMUCINOUS

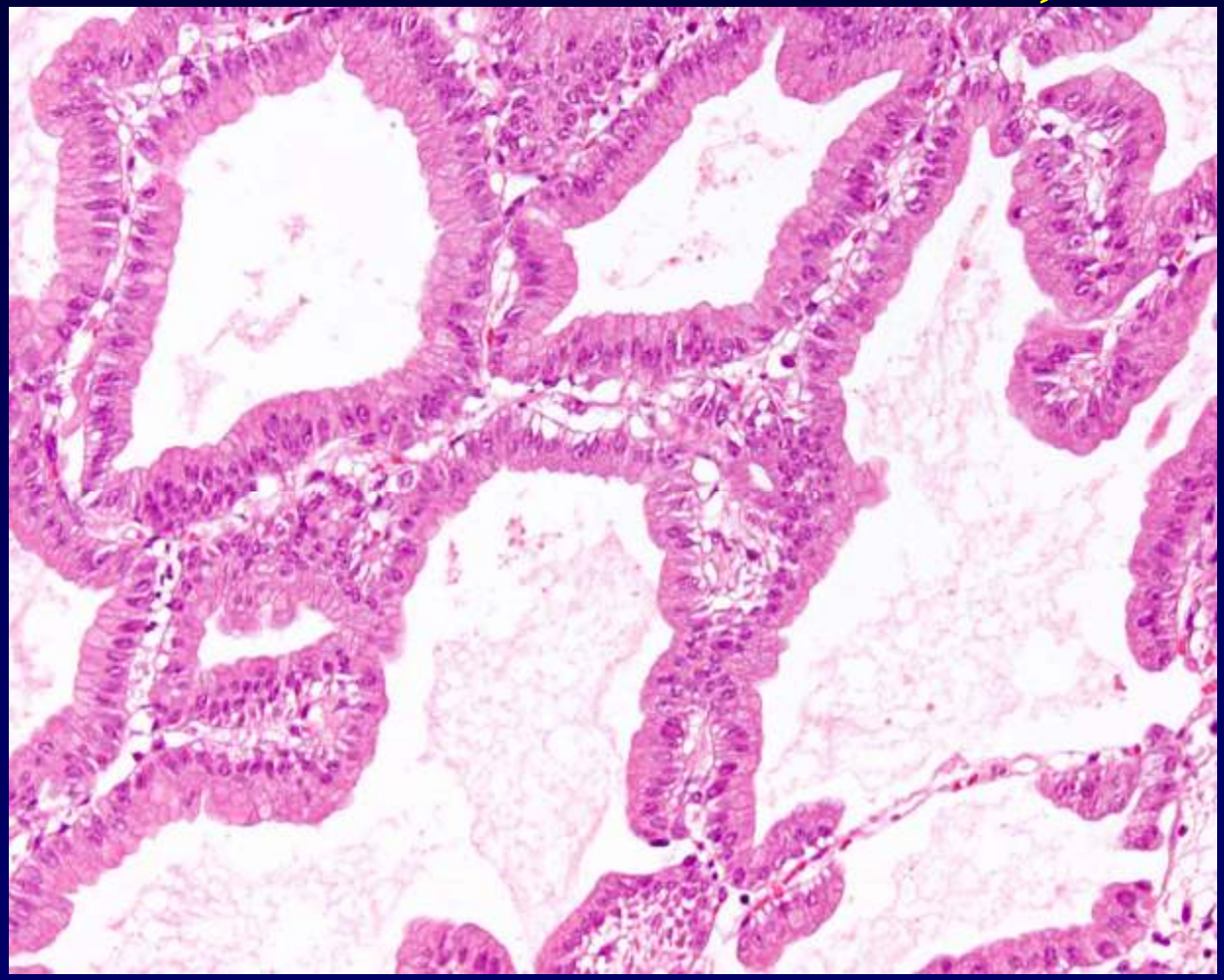


BAC, NON-MUCINOUS WITH NOGUCHI B/"COLLAPSE" VS INVASION





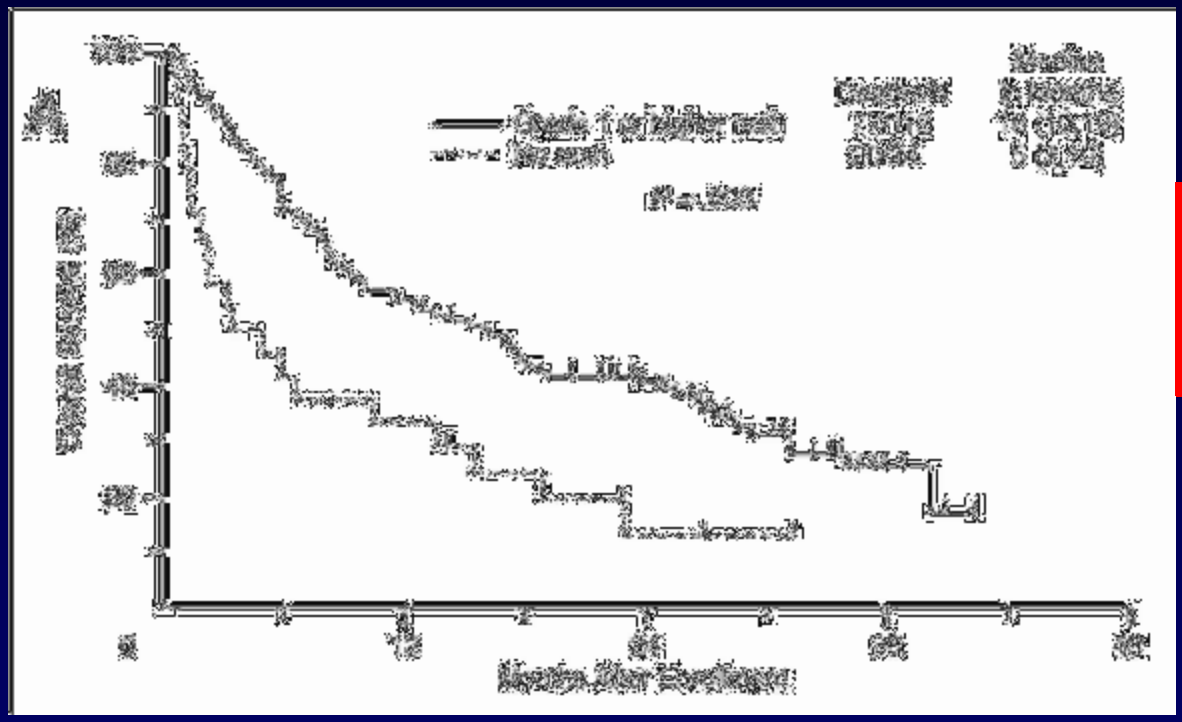
BRONCHIOLOALVEOLAR CARCINOMA, MUCINOUS



COMPARED TO NONMUCINOUS BAC

- **More often Kras mutations**
- **More often multicentric**
- **Overall worse outcome**

TERMINOLOGY PROBLEM: CLINICAL CONCEPT OF ADVANCED BAC: POOR SURVIVAL

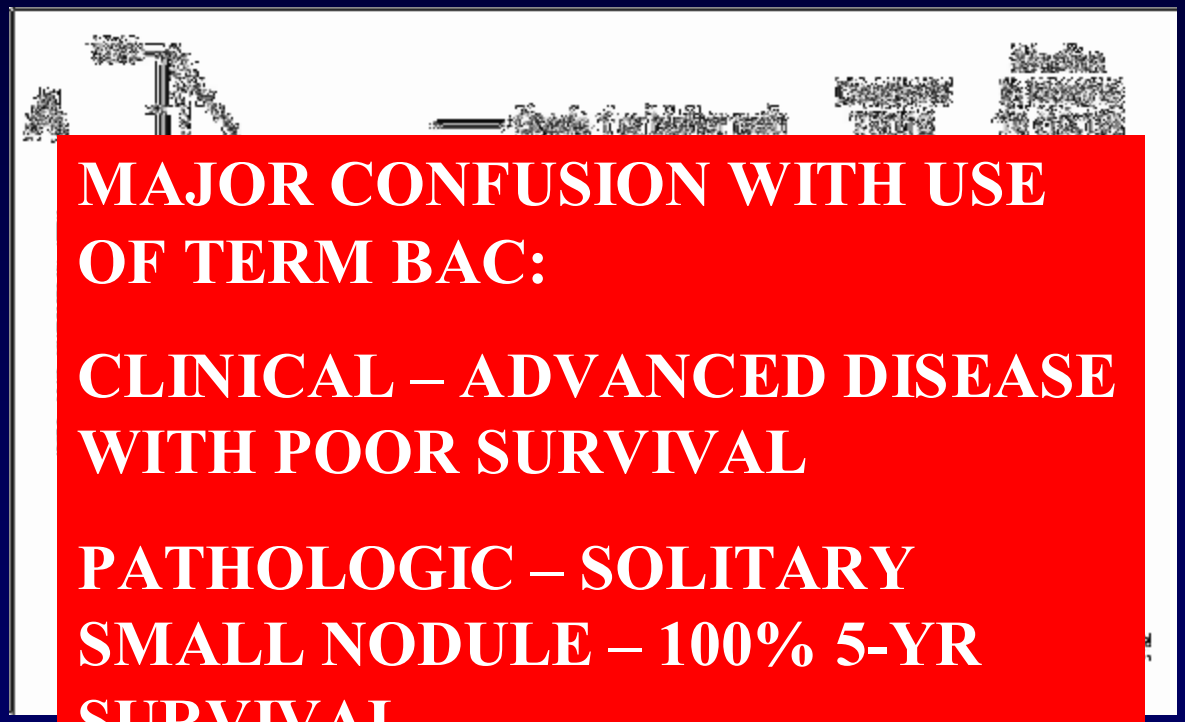


3 YR SURVIVAL

20-30%

West HL, et al: Advanced BAC; SWOG; JCO 24:1807, 2006

TERMINOLOGY PROBLEM: CLINICAL CONCEPT OF ADVANCED BAC: POOR SURVIVAL



MAJOR CONFUSION WITH USE OF TERM BAC:

CLINICAL – ADVANCED DISEASE WITH POOR SURVIVAL

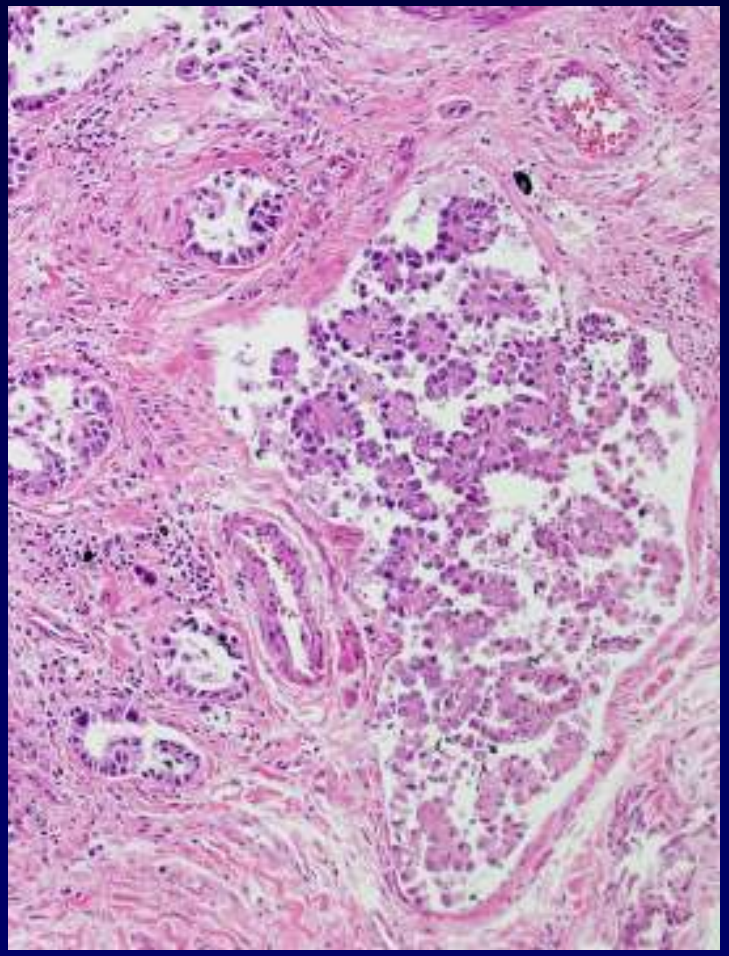
PATHOLOGIC – SOLITARY SMALL NODULE – 100% 5-YR SURVIVAL

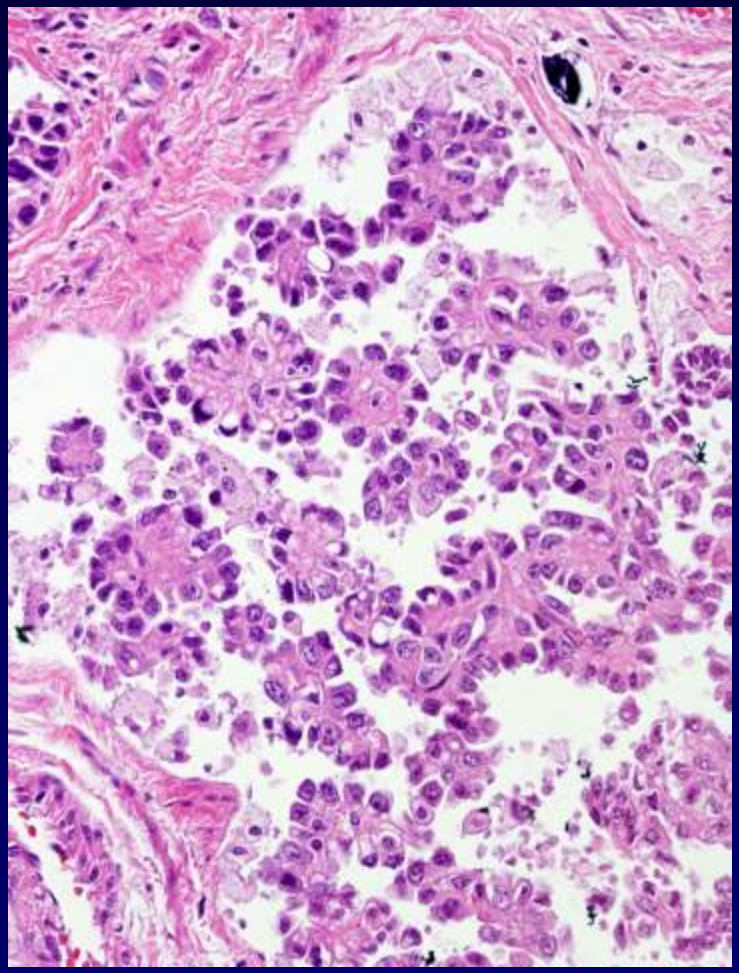
3 YR SURVIVAL

20-30%

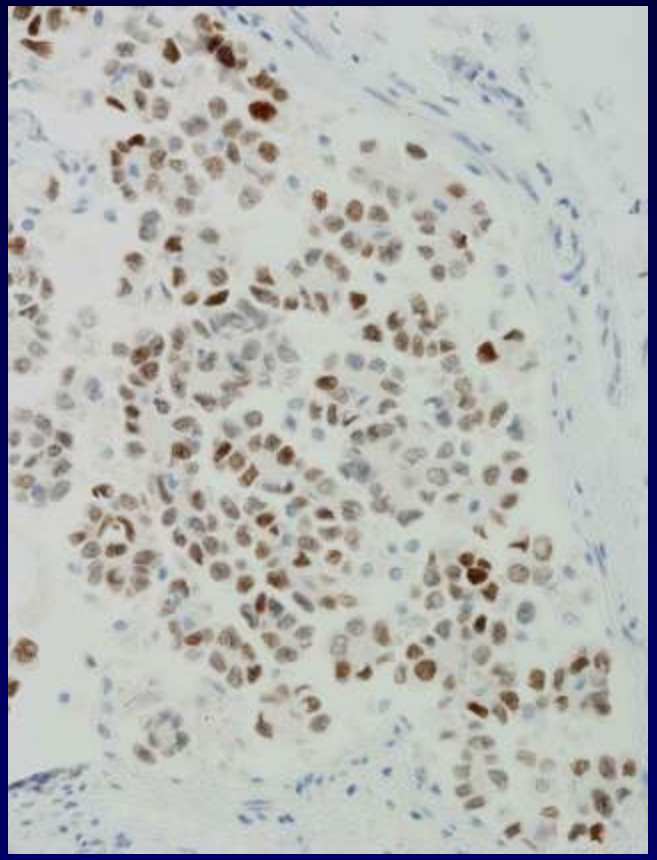
West HL, et al: Advanced BAC; SWOG; JCO 24:1807, 2006

MICROPAPILLARY ADENOCARCINOMA

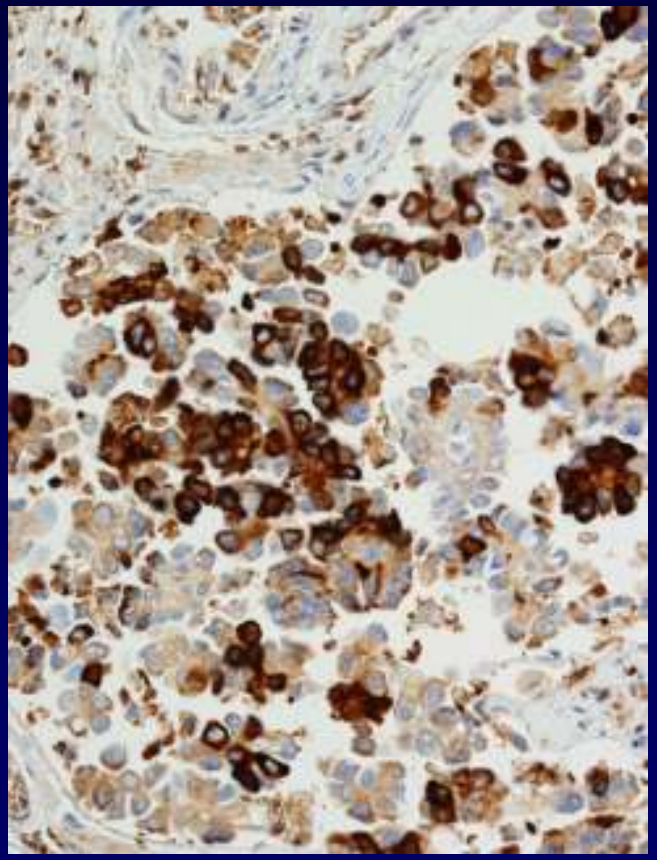




MICROPAPILLARY ADENOCARCINOMA

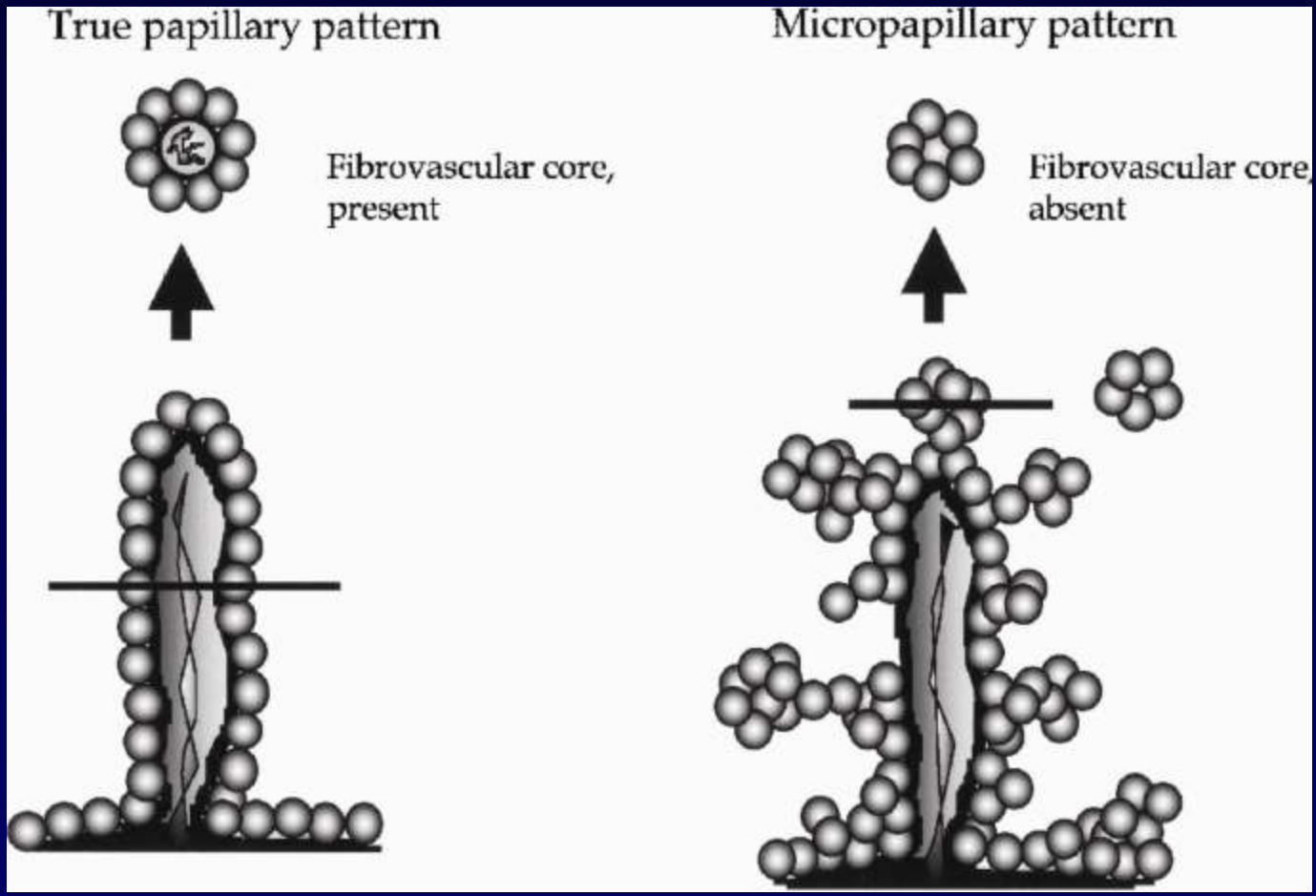


TTF1



PE10

MICROPAPILLARY ADENOCARCINOMA



Miyoshi T, et al: AJSP 27:101, 2003

MICROPAPILLARY (MP) ADENOCARCINOMA

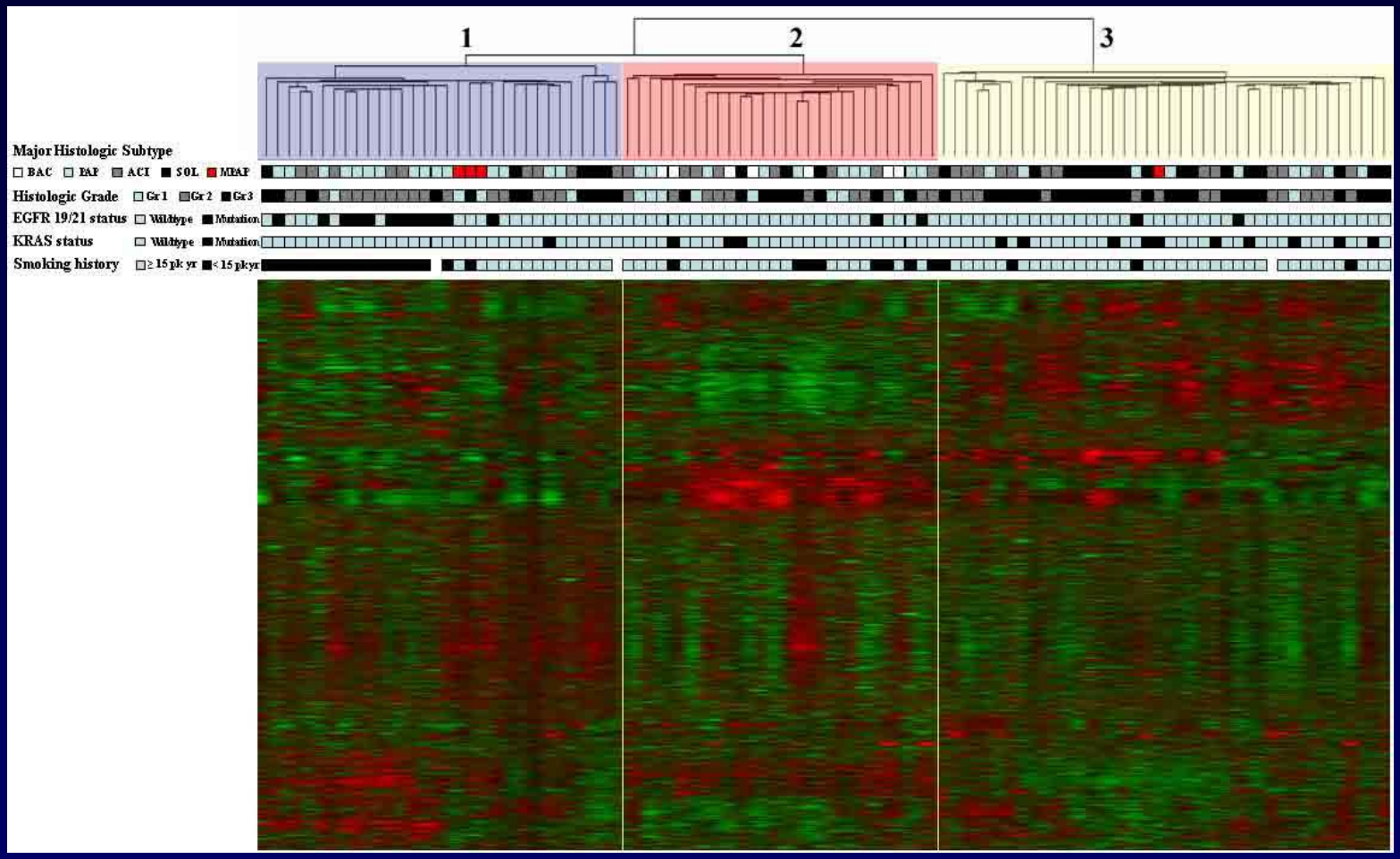
- **Silver SA et al: AJSP 21:43, 1997** 23/31 (74%) of papillary adenocarcinomas had a MP component
- **Amin M et al: AJSP 26:358, 2002**: 35 MP CA; 21% =focal <5%, 58%=moderate 5-30% and 21%=extensive >30%
  - 94% metastasized to LN (74%), lung (49%), brain (26%), bone (26%)
- **Miyoshi T, et al: AJSP 26: 358, 2003:** 40% of 344 adenocarcinomas had a MP pattern. More frequent LN mets ($p<0.001$), pleural invasion ($p=0.02$) intrapulmonary metastases ($p<0.001$), non-smoking status ($p=0.002$).
  - None; 1-5% - focal; 6-50% moderate; 51-100% extensive
  - Survival Stage I: 79% MPP pos (>5%) vs 93% MPP neg ($p=0.004$)

NCI DIRECTOR'S CHALLENGE

- 500 Lung adenocarcinomas: gene expression analysis using HG-U133A Affymetrix chip
- Four institutions: Memorial Sloan Kettering Cancer Center, Univ of Michigan, Univ of Toronto, Moffitt Cancer Center
- N. Motoi, et al peer reviewed the pathology in detail for all 500 cases
- 100 Cases from MSKCC – N. Motoi et al

N. Motoi et al; William Gerald – AJSP 32:810, 2008

MSKCC: 100 ADENOCARCINOMAS



N. Motoi et al; William Gerald – AJSP 32:810, 2008

GENE EXPRESSION VS HISTOLOGIC SUBTYPE

Gene expression profile	BAC vs Other		Papillary vs Other		Acinar vs Other		Solid Vs Other		All Histologic types
Cluster 1 vs	0	16	11	5	5	11	0	16	
									35*
									75
									01

–CLUSTER 1- PAPILLARY; EGFR mut; less smoking; >TTF-1

–CLUSTER 2 – BAC

–CLUSTER 3 – SOLID; KRAS mut; more smoking; <TTF-1

N. Motoi et al; William Gerald – AJSP (in press)

EGFR MUTATION VS PAPILLARY MSKCC: (P<0.001)

	Other Subtype	Papillary	
No EGFR mut	60 (95.2%) (71.4%)	24 (62.2%) (28.6%)	84
EGFR mut	3 (4.8%) (18.7%)	13 (37.8%) (81.3%)	16
	63 (100%)	37 (100%)	100

N. Motoi et al; William Gerald – AJSP 32:810, 2008

ADENOCARCINOMA SUBTYPES AND PERCENTAGES

Histologic Subtype	Pure Histologic Subtype	Major Histologic Component	Any Amount	10% of Subtype present	30% of Subtype present
Mixed subtype	94	NA	NA	NA	NA
Acinar	1	30	88	88	43
Papillary	3	37	78	76	50
Micropapillary†			61	42	10
Bronchioloalveolar	0	7	51	33	10
Nonmucinous		3	44	27	5
Mucinous		3	4	3	3
Mixed		1	3	3	2
Solid with mucin	2	25	54	49	17
Total	100	100	332	288	130

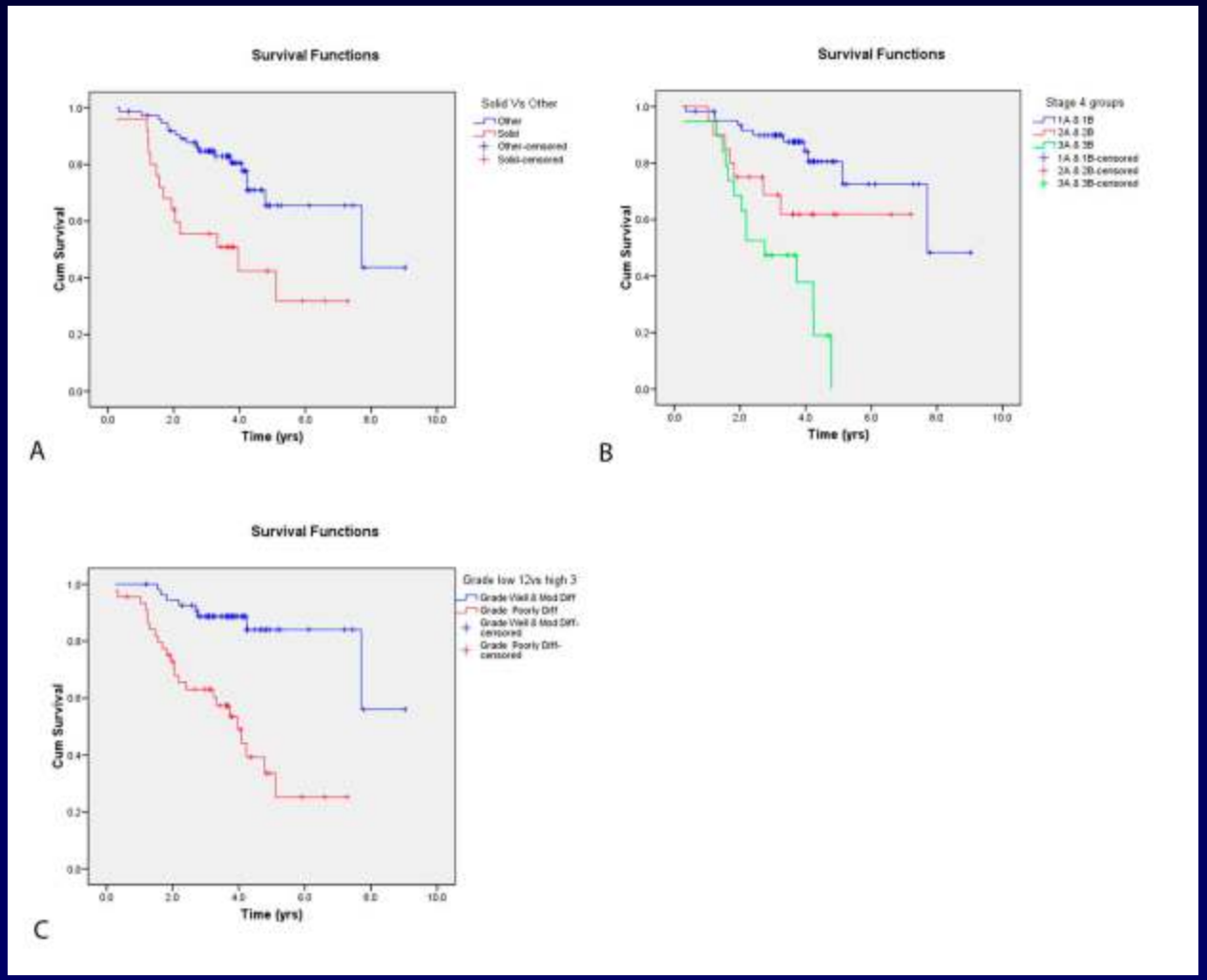
N. Motoi et al; William Gerald – AJSP (in press)

MAJOR HISTOLOGIC SUBTYPE

- Semiquantitative assessment of all histologic subtypes (10% increments) – avoid two equal major subtypes
- Assess – MAJOR subtype
- For Adenocarcinoma, mixed subtype, (further specify the major subtype)
- i.e.: Adenocarcinoma, mixed subtype with major papillary component

N. Motoi et al; William Gerald – AJSP 32:810, 2008

SURVIVAL BY SOLID, STAGE, GRADE



N. Motoi et al; William Gerald – AJSP 32:810, 2008

ADVANTAGES OF SEMIQUANTITATION

- EVERY MIXED SUBTYPE ADENOCA IS DIFFERENT – WAY TO DOCUMENT THIS
- PAPERS THAT FOCUS ON SINGLE SUBTYPE – DO NOT CONTROL FOR IMPACT OF OTHER SUBTYPES
- FORCES OBSERVER TO ADDRESS ALL TYPES: IF FOCUS ONLY ON BAC VS OTHER – DON'T REALLY ADDRESS ISSUES LIKE BAC VS PAPILLARY OR ACINAR

ADVANTAGES OF SEMIQUANTITATION

- REPRODUCIBILITY – NOT THAT BAD
- REALLY NOT TIME CONSUMING (LESS THAN LOOKING FOR VASCULAR INVASION)
- PROVIDES A QUANTITATIVE WAY TO COMPARE MULTIPLE TUMORS (SYNCHRONOUS, METACHRONOUS)
- RESEARCH: CAN ANALYZE DATA AS CONTINUOUS VARIABLE

PROGNOSTIC SIGNIFICANCE OF COMPREHENSIVE HISTOLOGIC SUBTYPING (CHS) AS BASIS FOR GRADING

- **GRADE 1 – BAC**
- **GRADE 2 – Papillary and acinar**
- **GRADE 3 – Solid and micropapillary**

– Sica G, Yoshizawa A, Moreira A, et al

PROGNOSTIC SIGNIFICANCE OF COMPREHENSIVE HISTOLOGIC SUBTYPING (CHS) AS BASIS FOR GRADING

- **Example: adenocarcinoma with 40% acinar, 25% papillary,15% micropapillary, 10% BAC, 10% solid.**
- **Predominant grades (two most abundant grades):**

  - sum of two most abundant patterns –

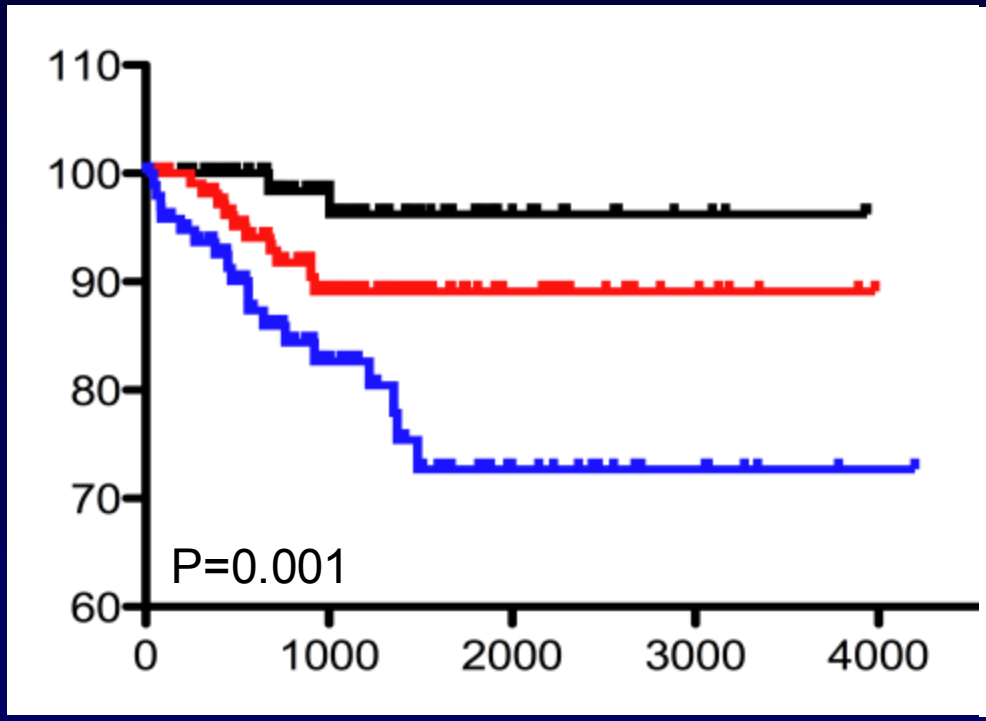
  score 2+2=4.
- **Worst grades (two highest grades):**

  - sum of two highest grades - score 3+3 = 6

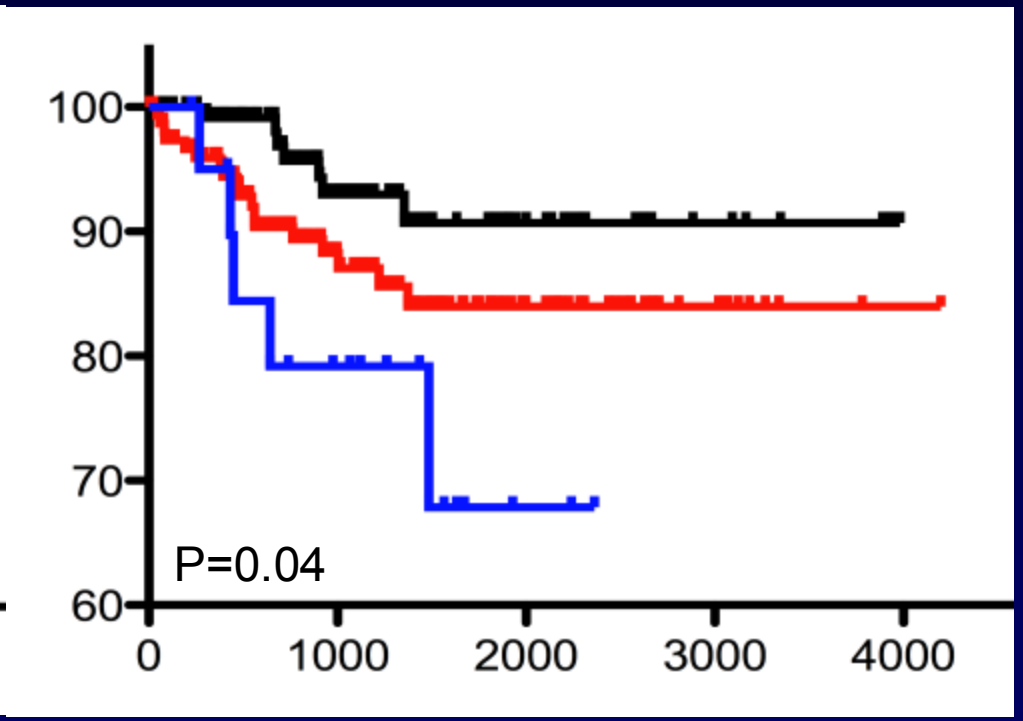
– Sica G, Yoshizawa A, Moreira A, et al

Stage IA Lung Adenocarcinoma, disease free interval

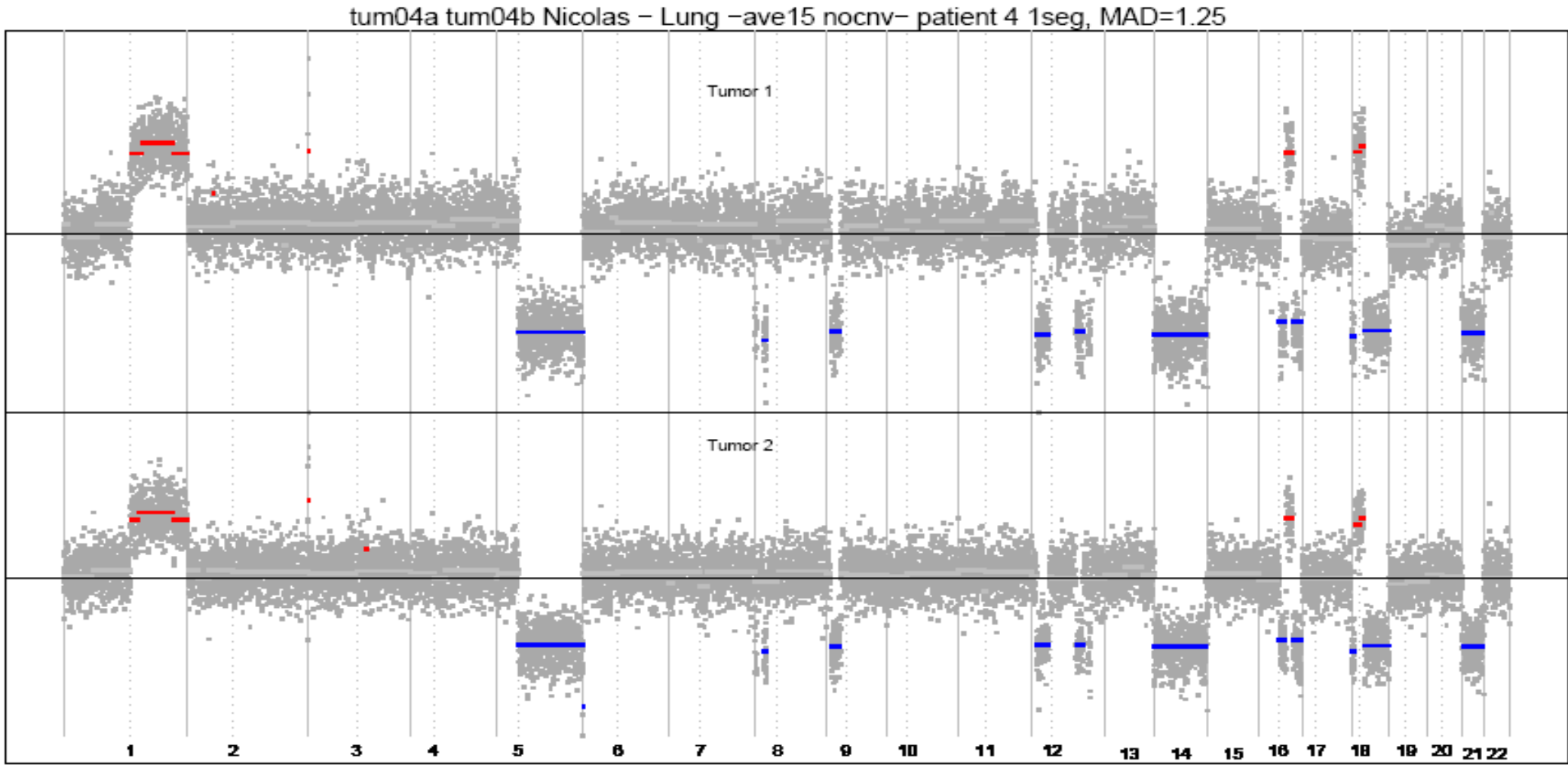
Predominant Histologies



Worst Grades

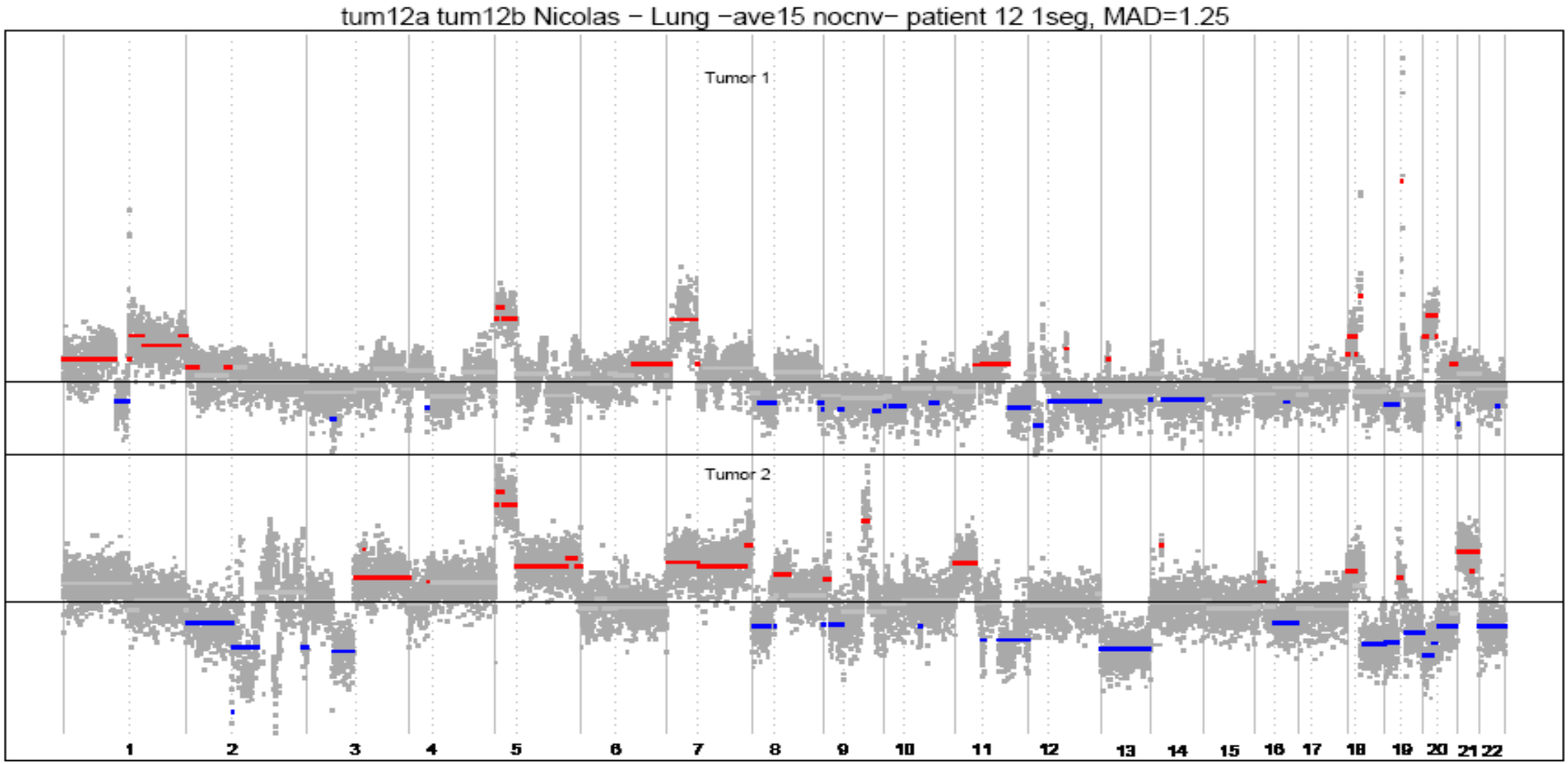


Genomic profiling: different profile = metastases



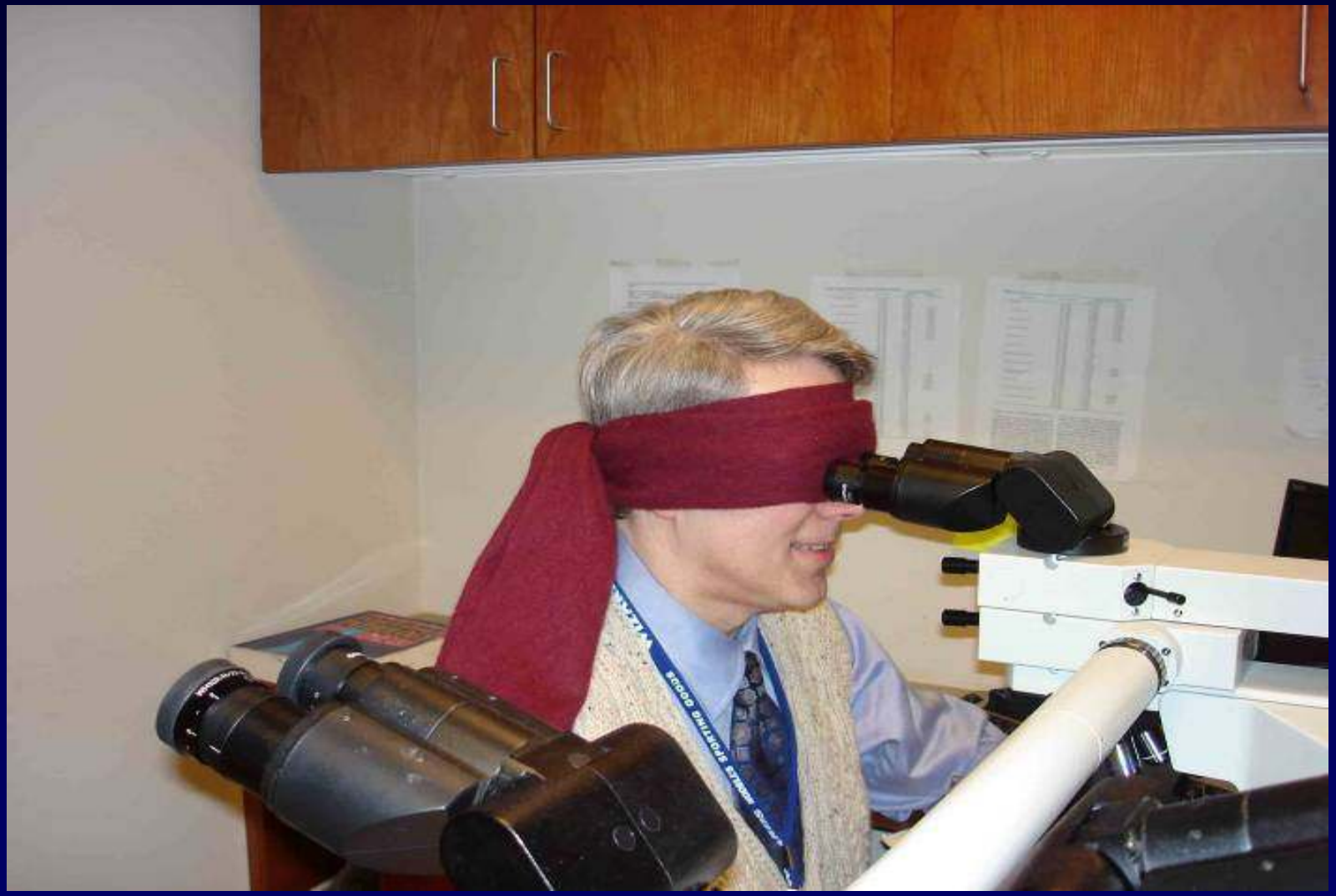
–Girard, N, Pao, W, Begg C et al

Genomic profiling: different profile = multiple primary



–Girard, N, Pao, W, Begg C et al

« Blinded » pathology review



DISTINGUISHING MULTIPLE PRIMARY LUNG TUMORS FROM METASTASES

- Genomic and mutational profiling were feasible to assess clonal relationships between multiple lung tumors
- Martini Melamed clinical criteria were inaccurate in 32% of cases
- Comprehensive histologic subtyping accuracy rate was
  - 91% on surgical pathology specimens
  - 64% on frozen specimens

–Girard, N, Pao, W, Begg C et al

ADENOCARCINOMA MSKCC EXAMPLE OF DIAGNOSIS

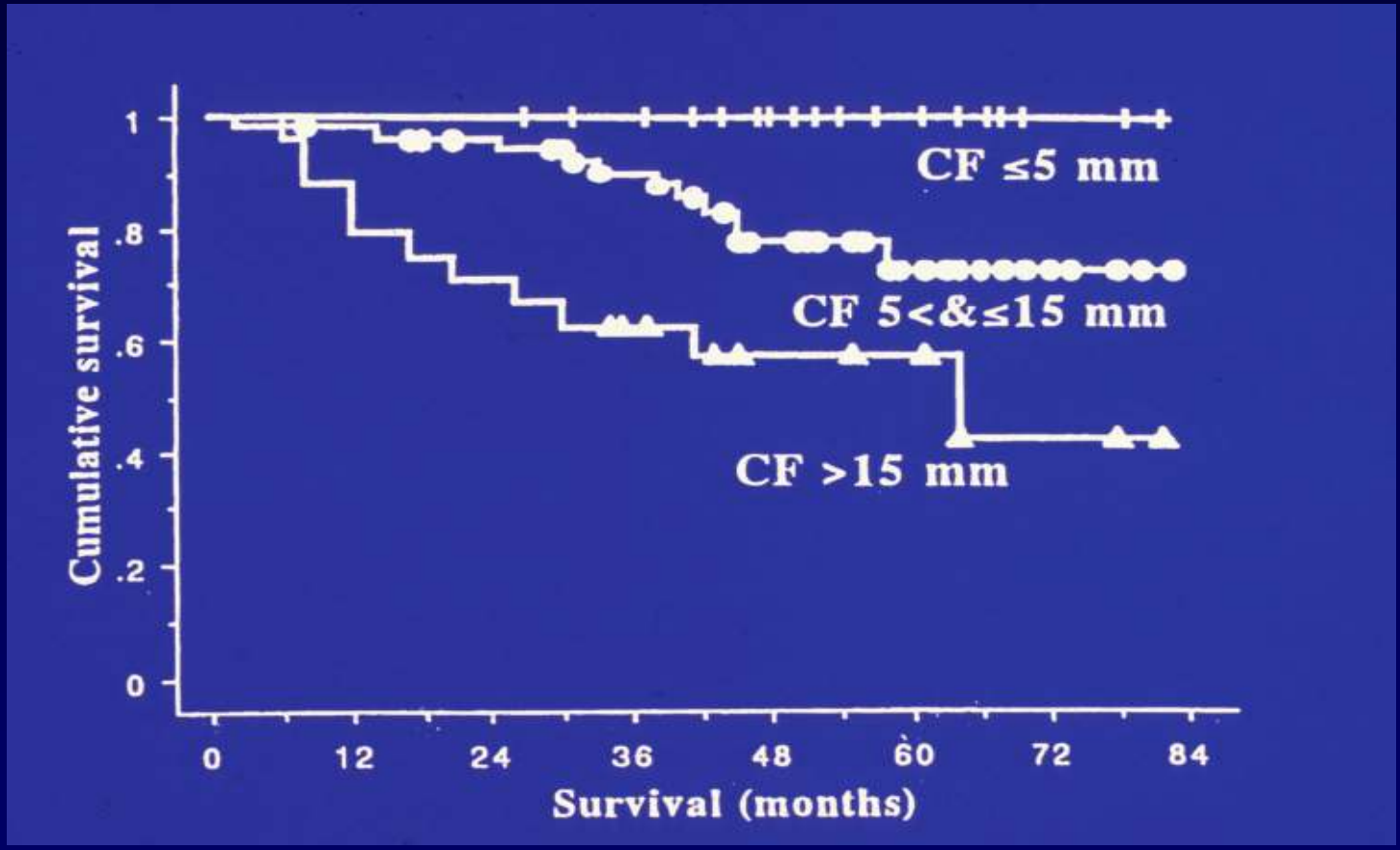
- LUNG, LEFT LOWER LOBE, WEDGE RESECTION: ADENOCARCINOMA, MIXED SUBTYPE, WITH ACINAR (50%), PAPILLARY (30%) AND BRONCHIOLOALVEOLAR (20%) PATTERNS

THE QUEST FOR "MINIMALLY INVASIVE" BAC CRITERIA

- Suzuki et al; ATS 69:893, 2000: Scar Size: 0-5mm, 5-15mm, >15mm. Less than 5mm has 100% survival
- Yokose et al. Lung Ca 29:179, 2000: MV analysis, unfavourable-vascular invasion and > 25% papillary
- Terasaki et al. AJSP 27: 937, 2003; Gr 1: pure BAC; 2a: </=5mm invasive area 2b >5mm. No survival data
- Sakurai et al. AJSP 28:198, 2004: Pattern invasion:
  - 0: none; 1 – invasion in BAC area; 2 - periphery of scar; 3 – within scar
  - 1 or 2 = excellent survival; 3: poor survival

Travis WD et al: JCO 23:3279, 2005

SMALL ADENOCARCINOMA 3 CM OR < SURVIVAL BY SIZE OF SCAR



–Suzuki K et al; Ann Thorac Surg 69:893, 2000

CASE FOR MINIMALLY INVASIVE LUNG ADENOCARCINOMA: N=141 Stage 1 or 2

- Group 1- BAC
- Group 2- mixed subtype with BAC and < 5mm invasion
- Group 3- mixed subtype with BAC and >5 mm invasion
- Group 4- mixed subtype without BAC

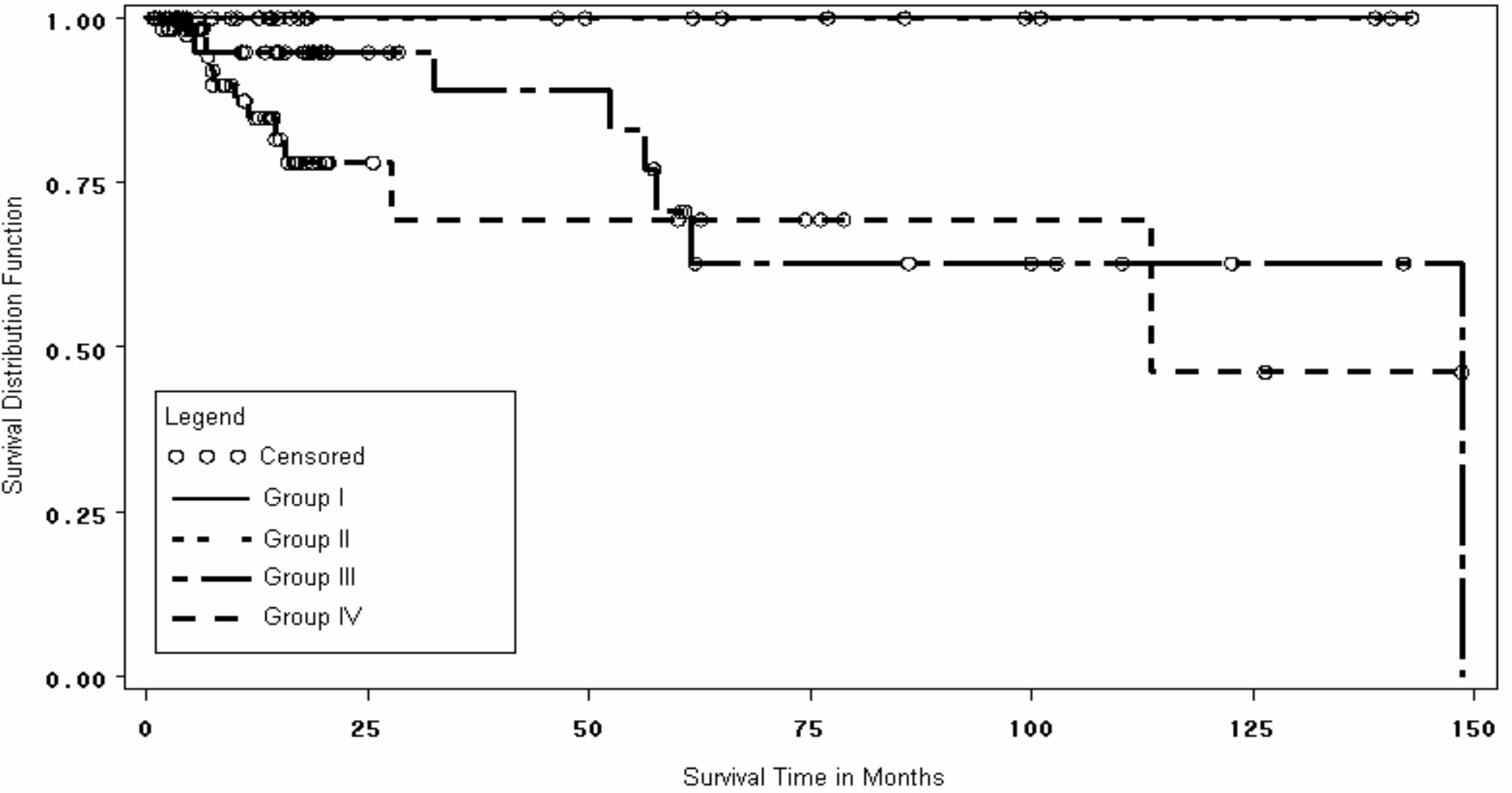
Yim J et al. Modern Pathology. 2007, 20:233-41

CASE FOR MINIMALLY INVASIVE LUNG ADENOCARCINOMA: N=141 Stage 1 or 2

- Group 1- BAC
- Group 2- mixed subtype with BAC and < 5mm invasion
- Group 3- mixed sub
  invasion
- Group 4- mixed subtype without BAC

MINIMALLY INVASIVE ADENOCARCINOMA

Yim J et al. Modern Pathology. 2007, 20:233-41



Yim J et al. Modern Pathology. 2007, 20:233-41

INTERNATIONAL MULTIDISCIPLINARY LUNG ADENOCARCINOMA CLASSIFICATION

- **GOALS:**
  - **Develop a multidisciplinary classification of lung adenocarcinoma**
  - **For this classification to become an international standard.**
- **SPONSORED: IASLC, ATS, ERS**
- **CORE PANEL – attend meetings, direct systematic review, write document**
- **REVIEWER PANEL – offer written comments, help with systematic review, edit/comment document**

SQUAMOUS VS ADENOCARCINOMA/LARGE CELL THERAPY ISSUES

- **Predictive of Toxicity:**
  - **Squamous cell carcinoma: Bevacizumab – contraindicated due to life threatening hemorrhage**
- **Predictive of Response:**
  - **Non-squamous histology: better survival with pemetrexed?**

ADENOCARCINOMA CLASSIFICATION (Biopsy and Cytology)

- Majority of lung cancers (about 70%) do not undergo resection – dx'd by biopsy/cytology
- Not covered in WHO/IASLC 1999 and 2004
- Requirement for more than just NSCLC vs SCLC
- This classification will address this topic for the first time – incorporating immunohistochemistry

TENTATIVE PROPOSAL IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION NYC/MSKCC; March 12/13, 2009

- **PREINVASIVE LESIONS**
  - **ATYPICAL ADENOMATOUS HYPERPLASIA**
  - **ADENOCARCINOMA IN SITU (formerly BAC pattern) †**
    - **non-mucinous**
    - **mucinous**
- **MINIMALLY INVASIVE ADENOCARCINOMA (a lepidic predominant tumor with <=5mm or <10% invasion – definition being refined)**
- **INVASIVE ADENOCARCINOMA**

† Size should be specified. In well sampled tumors adenocarcinoma in situ is independent of size; extensive sampling is needed to exclude invasion, particularly in larger tumors

TENTATIVE PROPOSAL IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION MEETING AT MSKCC, NY: March 12-15, 2009

INVASIVE ADENOCARCINOMA

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

(In explanatory notes, recommend semiquantitative assessment of patterns in 5-10% increments)

TENTATIVE PROPOSAL IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION MEETING AT MSKCC, NY: March 12-15, 2009

VARIANTS

- Mucinous adenocarcinoma with lepidic pattern (formerly mucinous BAC pattern)
- Mucinous cystadenocarcinoma
- Colloid adenocarcinoma
- Fetal adenocarcinoma (low and high grade)
- Enteric adenocarcinoma