Updates on Lung Cancer

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Concentrate in adenocarcinoma

* Review current concepts in
  * Definition of invasion in adenocarcinoma
  * Non-traditional patterns
  * Grading system

Rationale for new adenocarcinoma classification

* Adenocarcinoma: the most common histologic subtype
* Widely divergent clinical, radiologic, molecular & pathologic spectrum
* Rapidly evolving molecular advances

Jemal A, Travis WD, Tarone RE, et al. Int J Cancer 2003; 105: 101-107.

W.H.O. Classification 2014

Pre-invasive lesions

-Atypical adenomatous hyperplasia

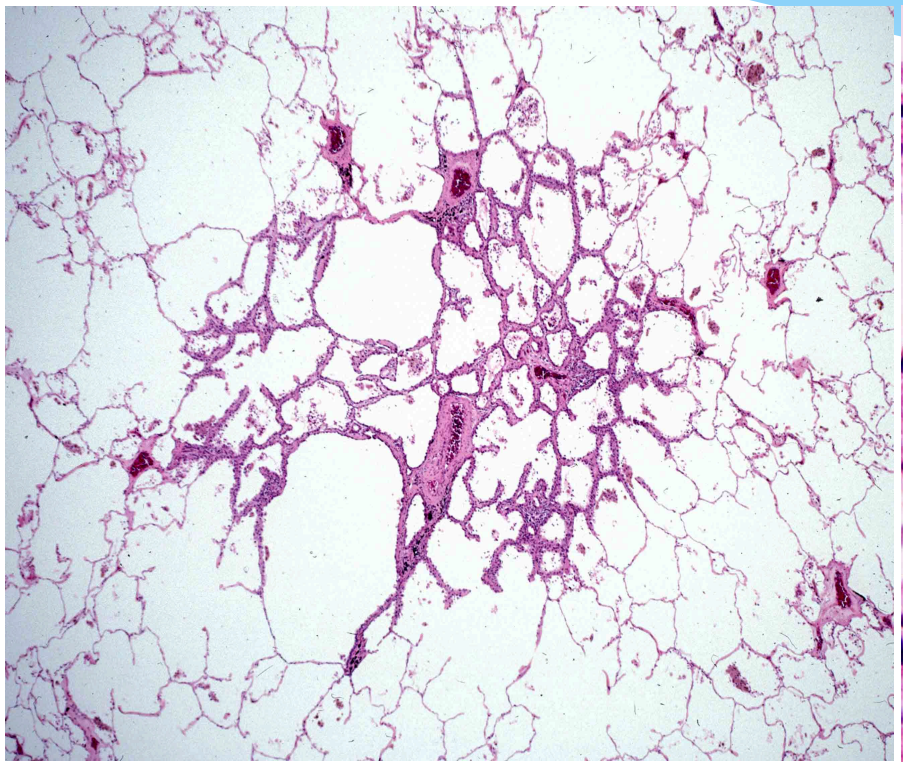
-Adenocarcinoma *in situ* (≤3 cm, formerly BAC pattern)

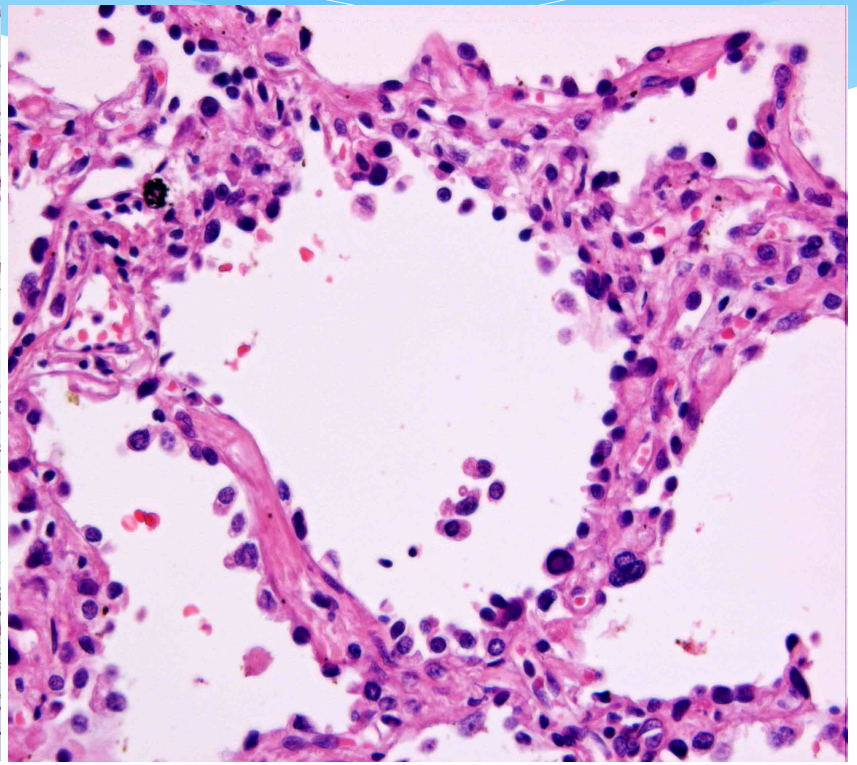
Minimally-invasive adenocarcinoma (≤3 cm, a lepidic predominant tumor with ≤5mm invasion)

Invasive adenocarcinoma

Travis WD, Brambilla E, Riely GJ. J Clin Oncol 2013; 31: 992-1001.

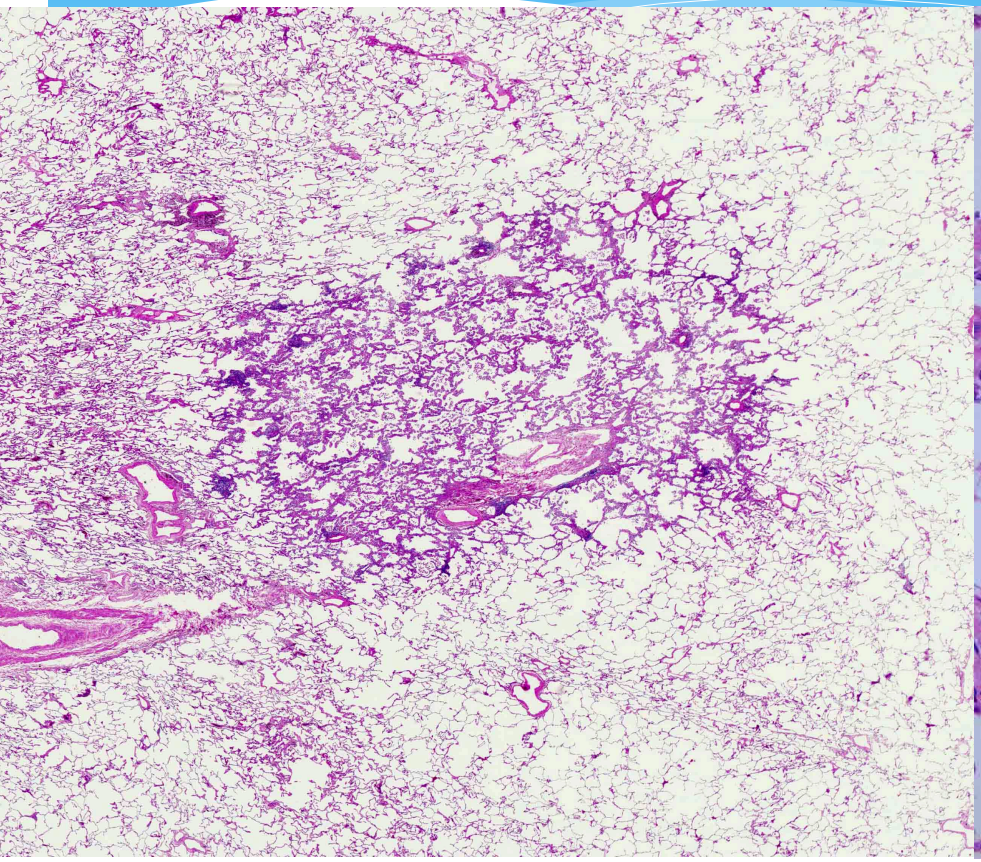
Atypical adenomatous hyperplasia

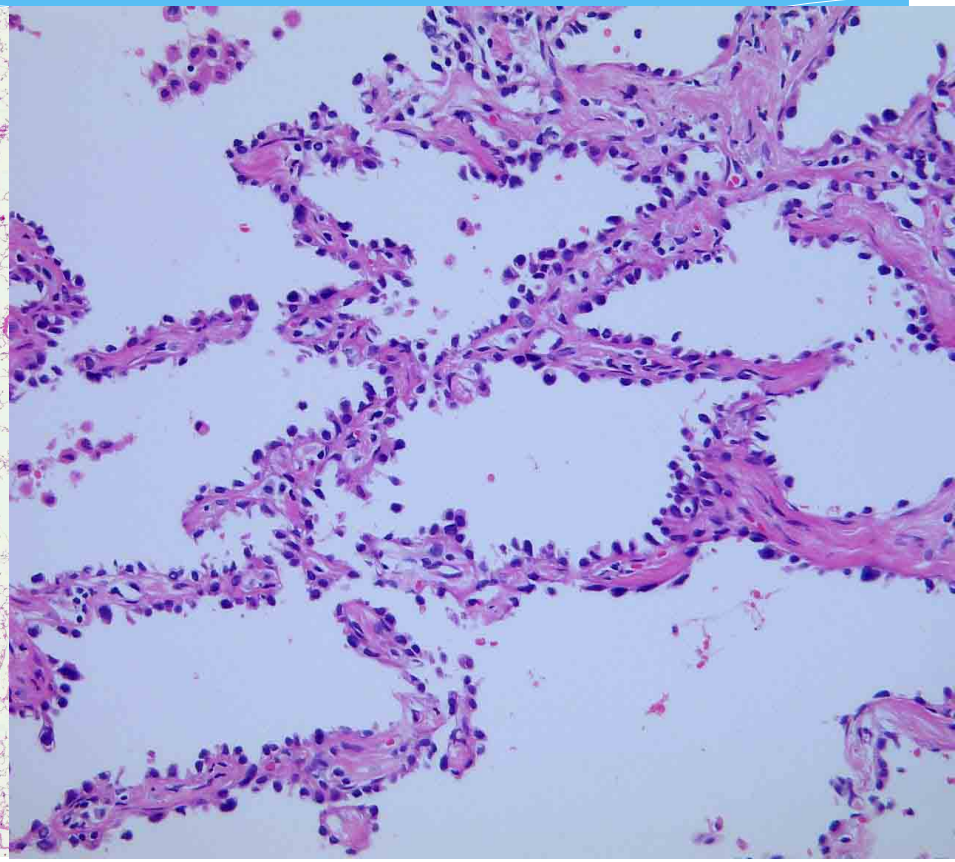




Less than 3mm in greatest dimension, discontinuous proliferation of atypical pneumocytes, Absence of inflammation

Adenocarcinoma *in situ*





Pure lepidic pattern without stromal, lymphatic or pleural invasion

Adenocarcinoma *in situ*

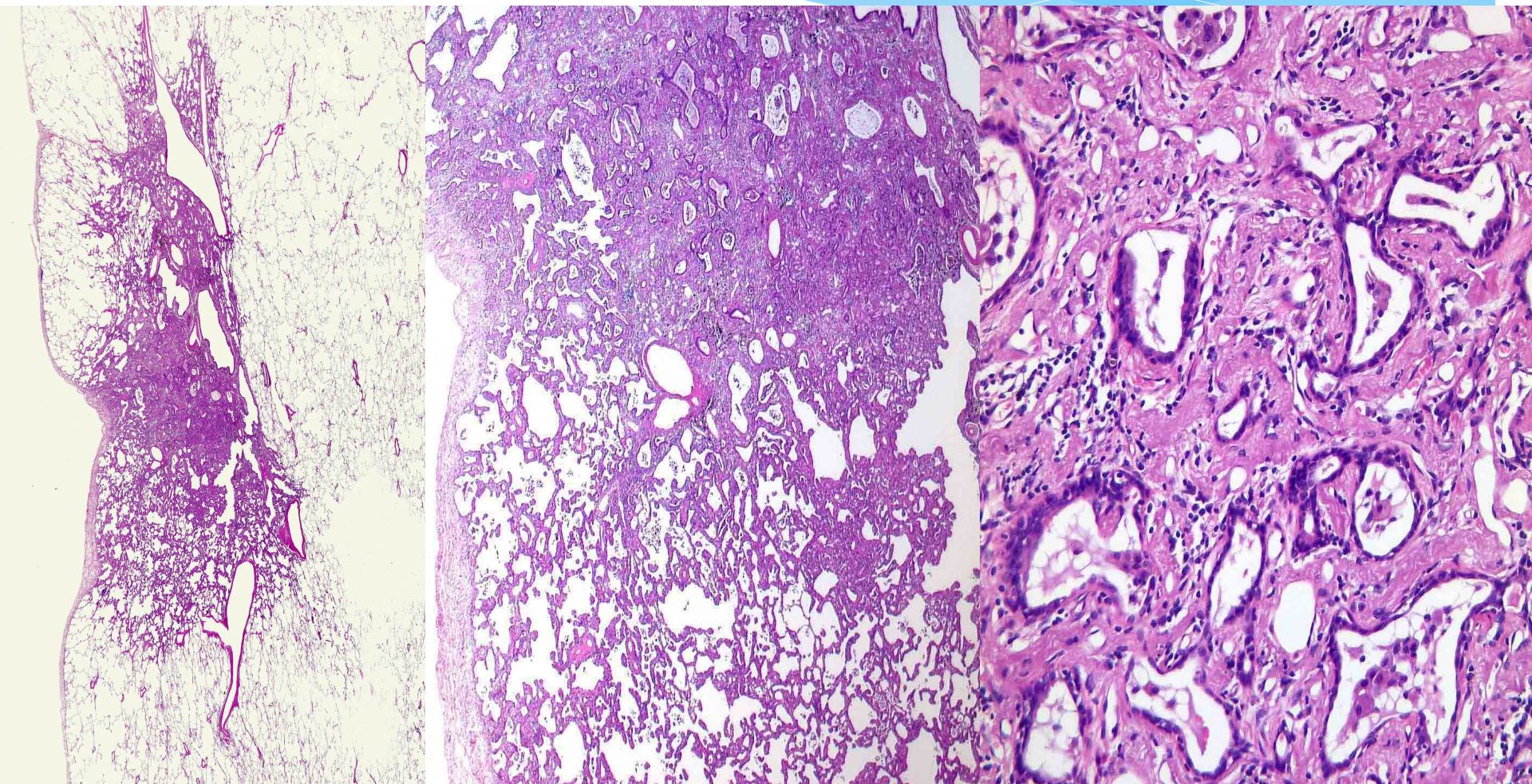
* Ground-glass opacity (GGO)
* In general less than 3 cm

Minimally-invasive adenocarcinoma (MIA)

* New concept!
* Predominant lepidic adenocarcinoma with an area of invasion that is equal or less than 0.5 cm
* Has an excellent prognosis similar to Adenocarcinoma *in situ*: 100% disease free survival in 5 years.

Travis WD, Brambilla E, Riely GJ. J Clin Oncol 2013; 31: 992-1001.

Minimally-invasive adenocarcinoma nonmucinous



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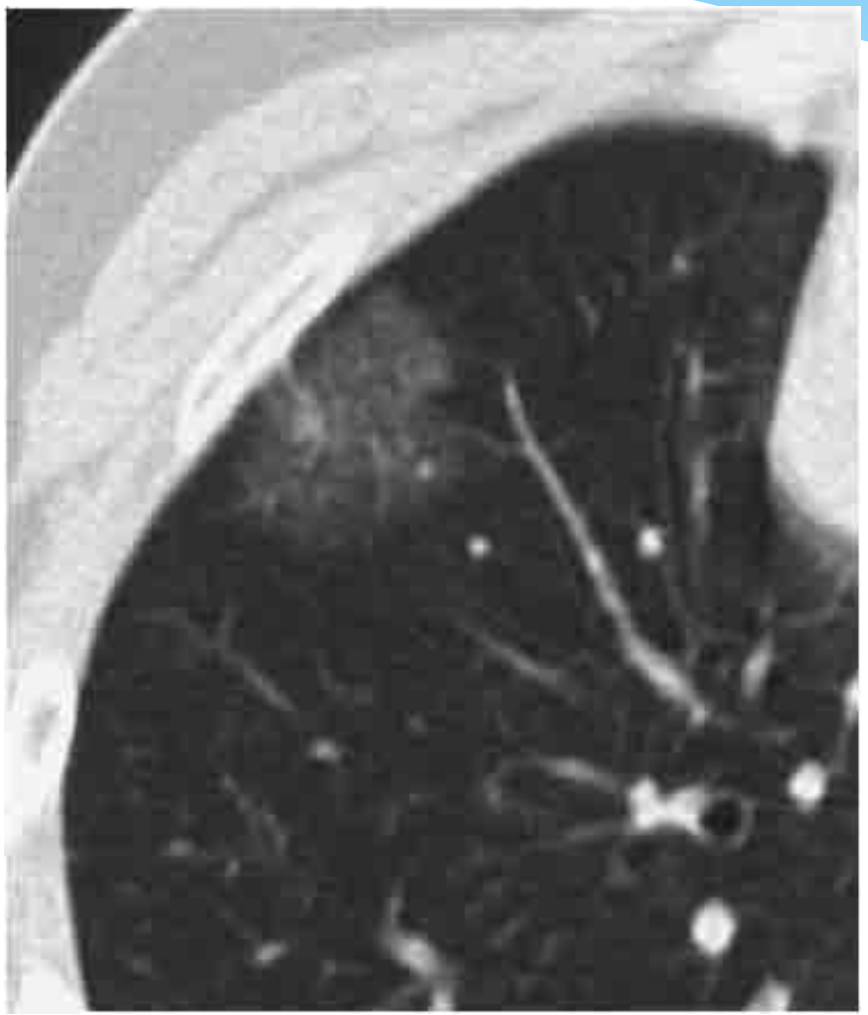


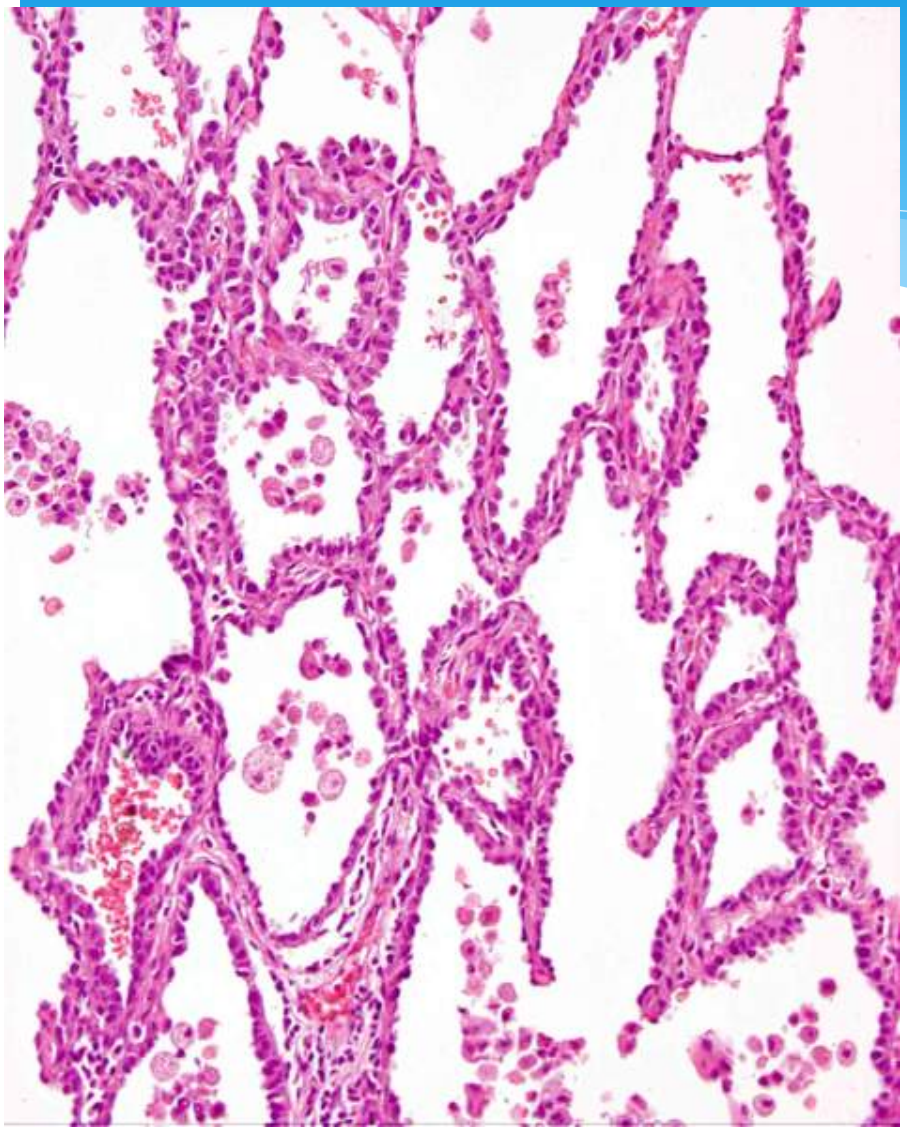
* Often a mixture of GGO and solid component
* Less than 3 cm

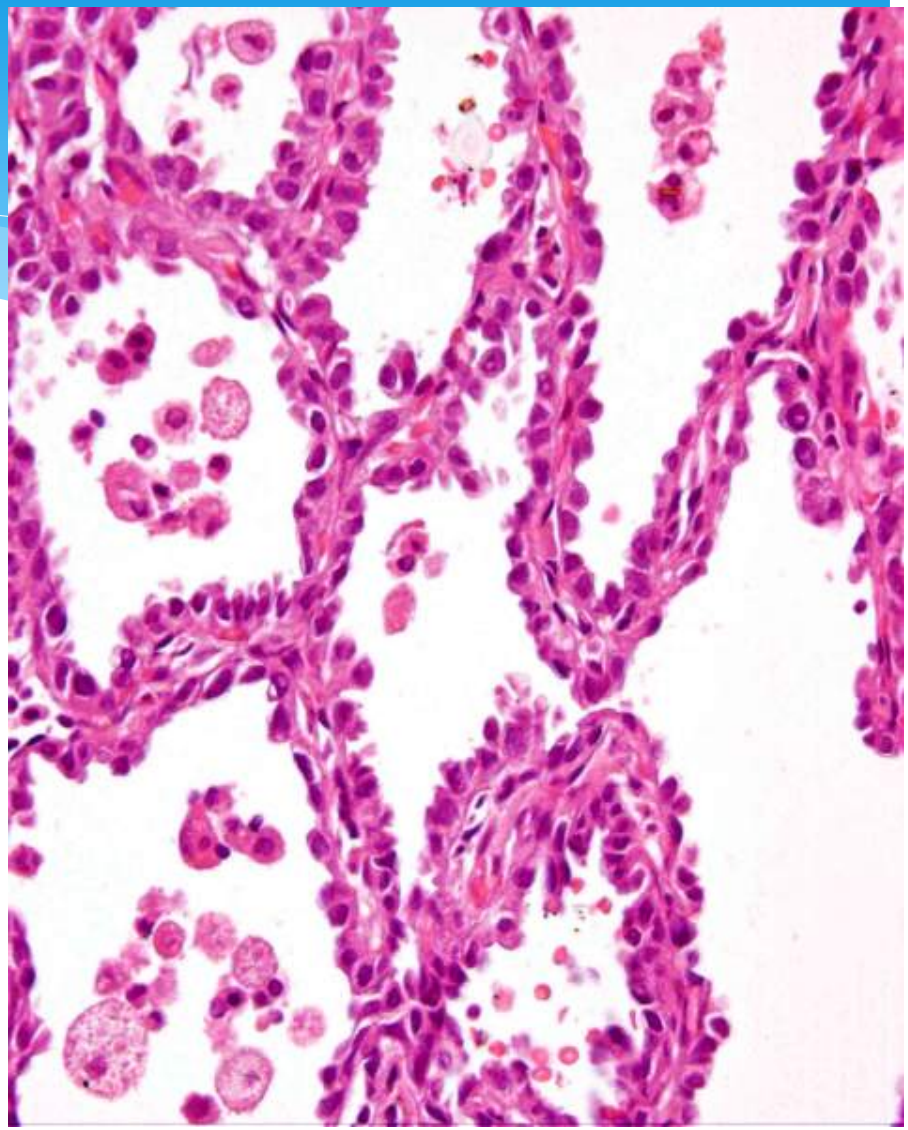
How can I measure invasion?

* Problems :
* - invasive patterns versus lepidic
* - collapse alveoli versus invasion versus needle track, do I need elastic stains?
* -fibrosis due to invasion versus scar
* - multiple foci of invasion

Invasive patterns versus lepidic

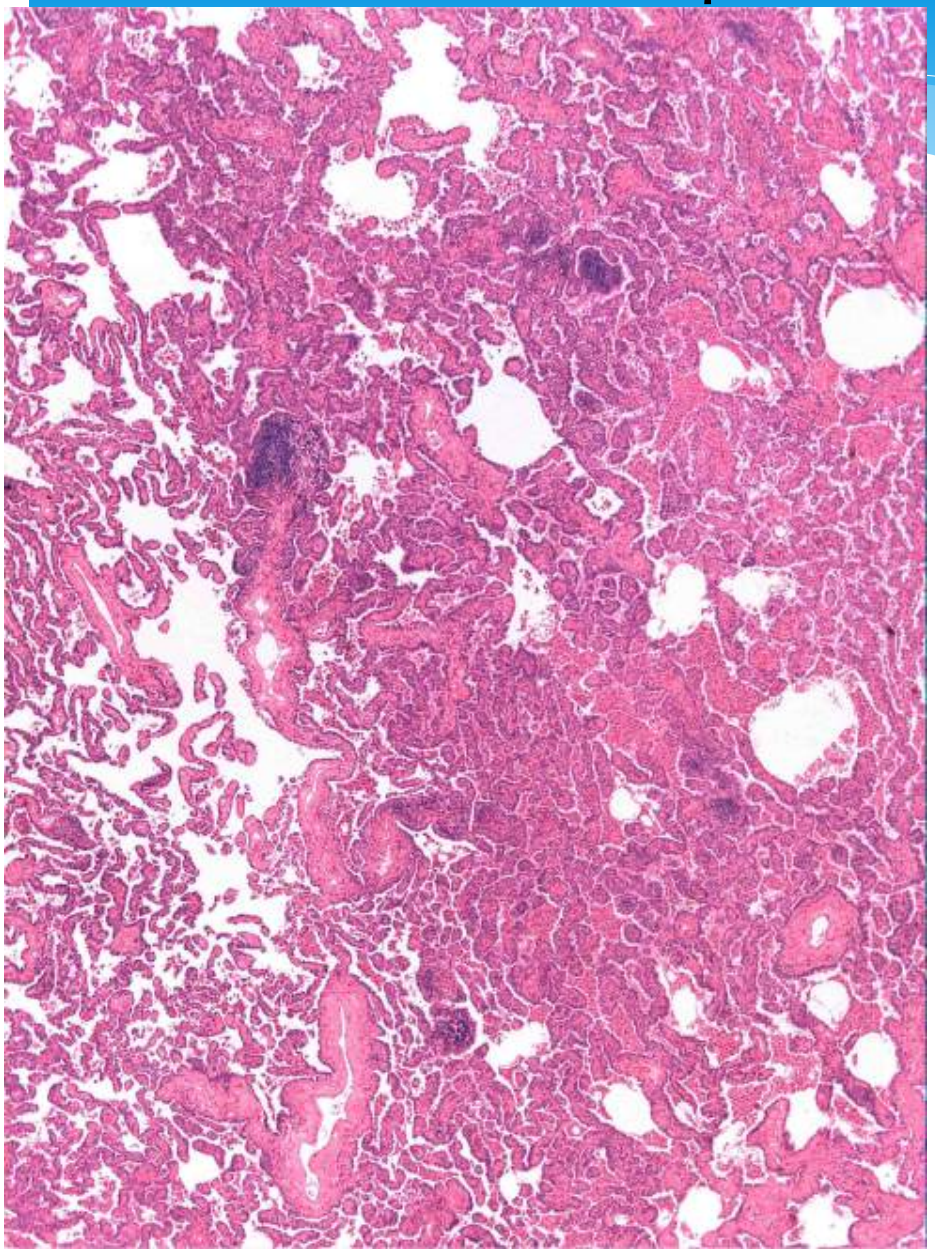
* Several articles showed that the reproducibility for determination of invasion is poor among experts!
* Thunnissen E et al Modern Path.2012
* Shih AR et al Histopathology. 2019 (epub ahead of print)

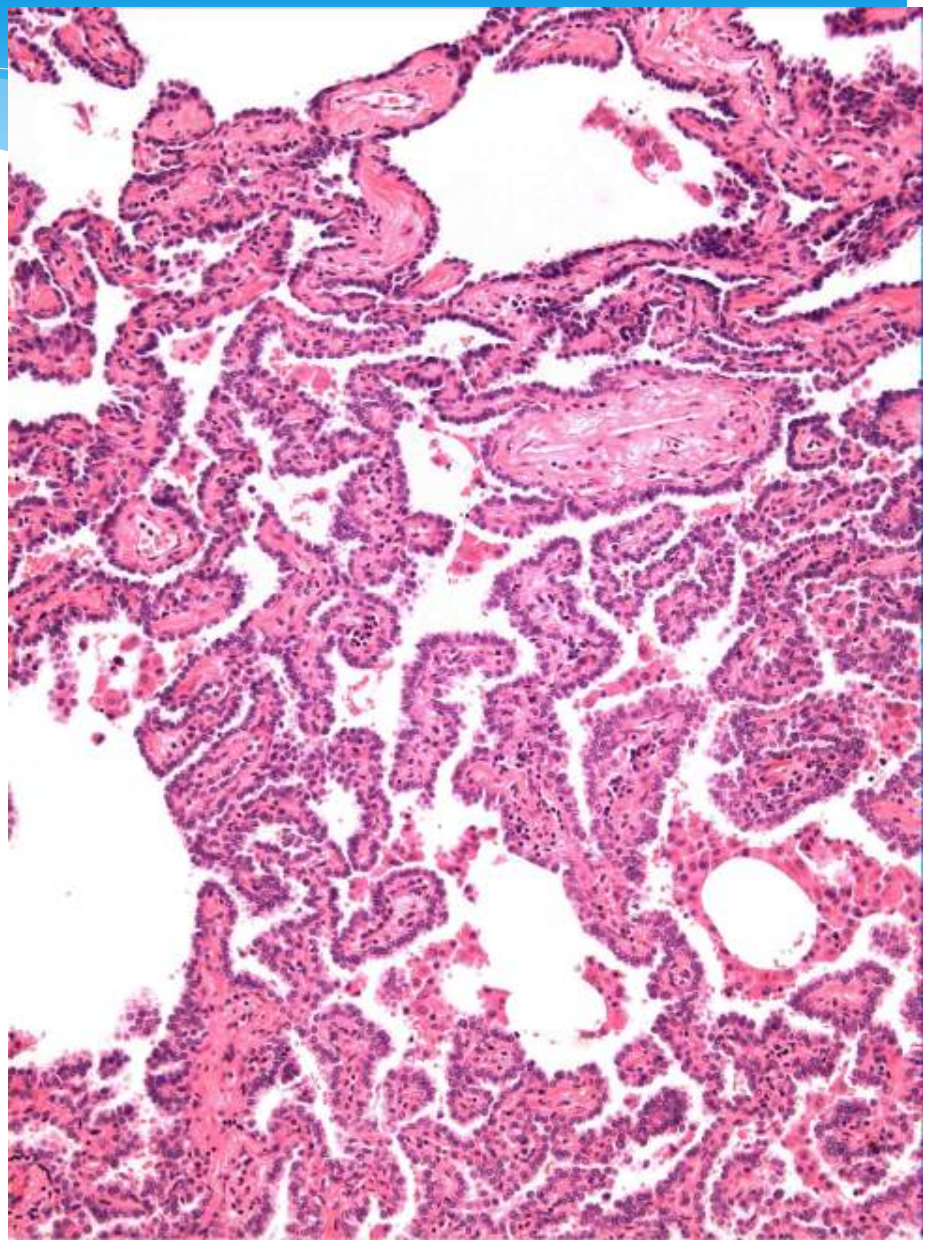




Thunnissen e et al. Modern Path 2012

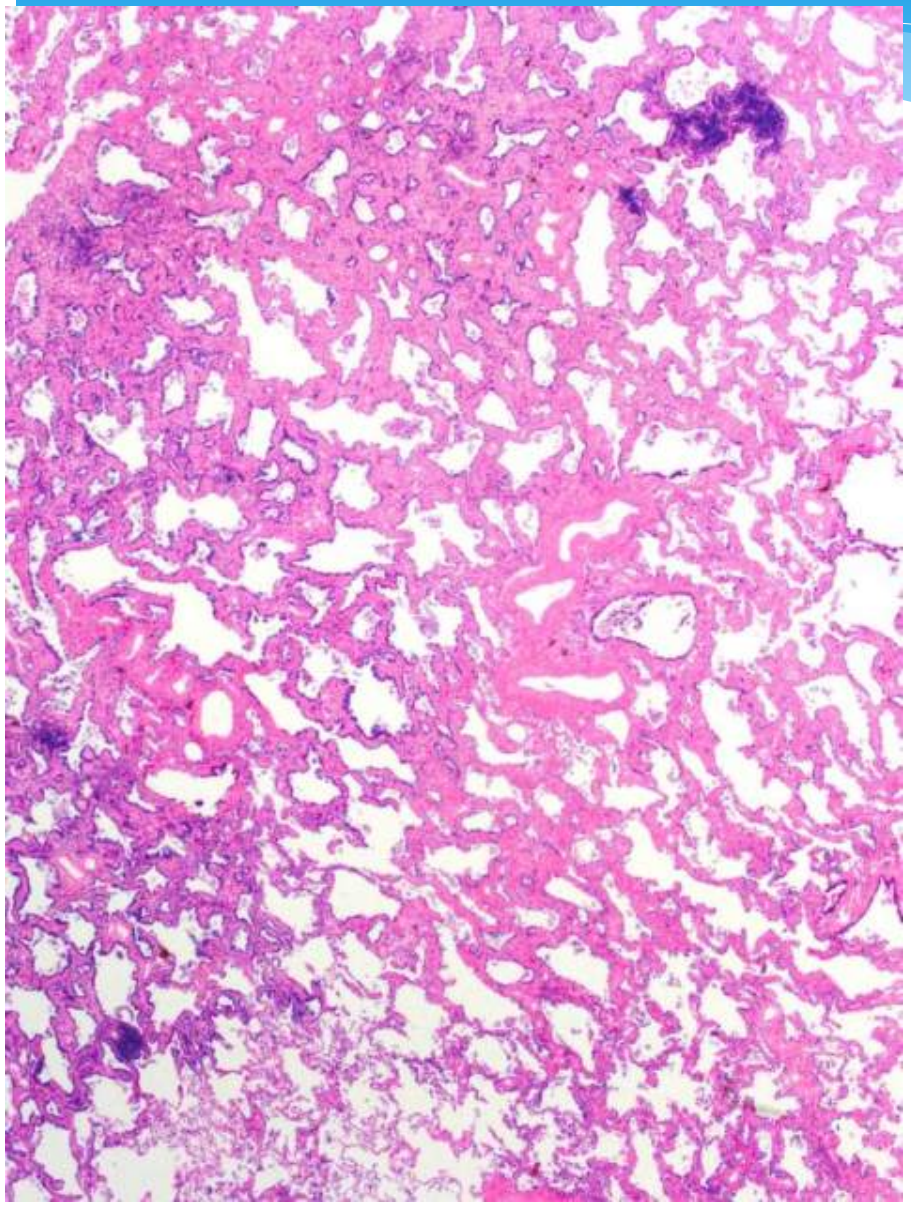
Lepidic or papillary?

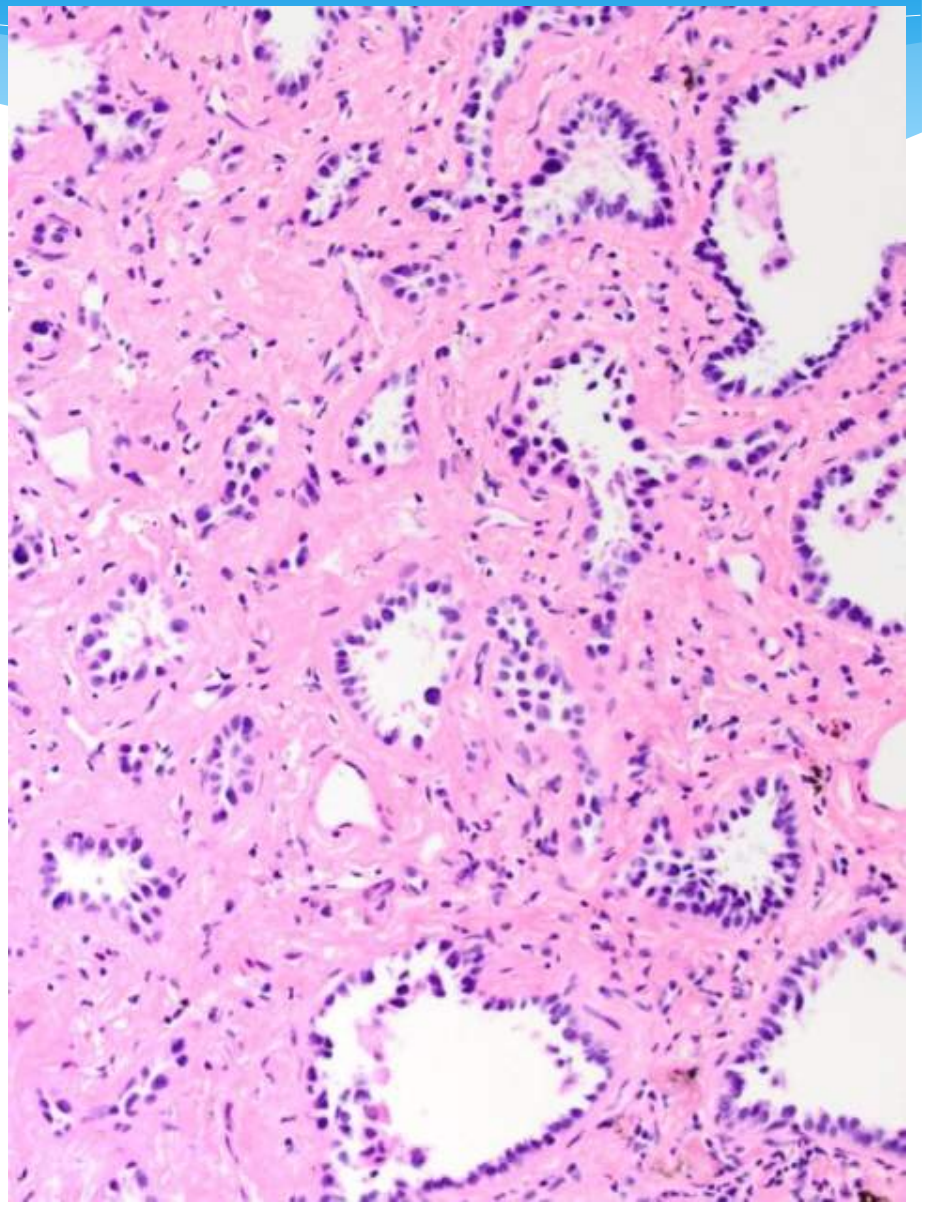




Thunnissen e et al. Modern Path 2012

Lepidic or acinar?

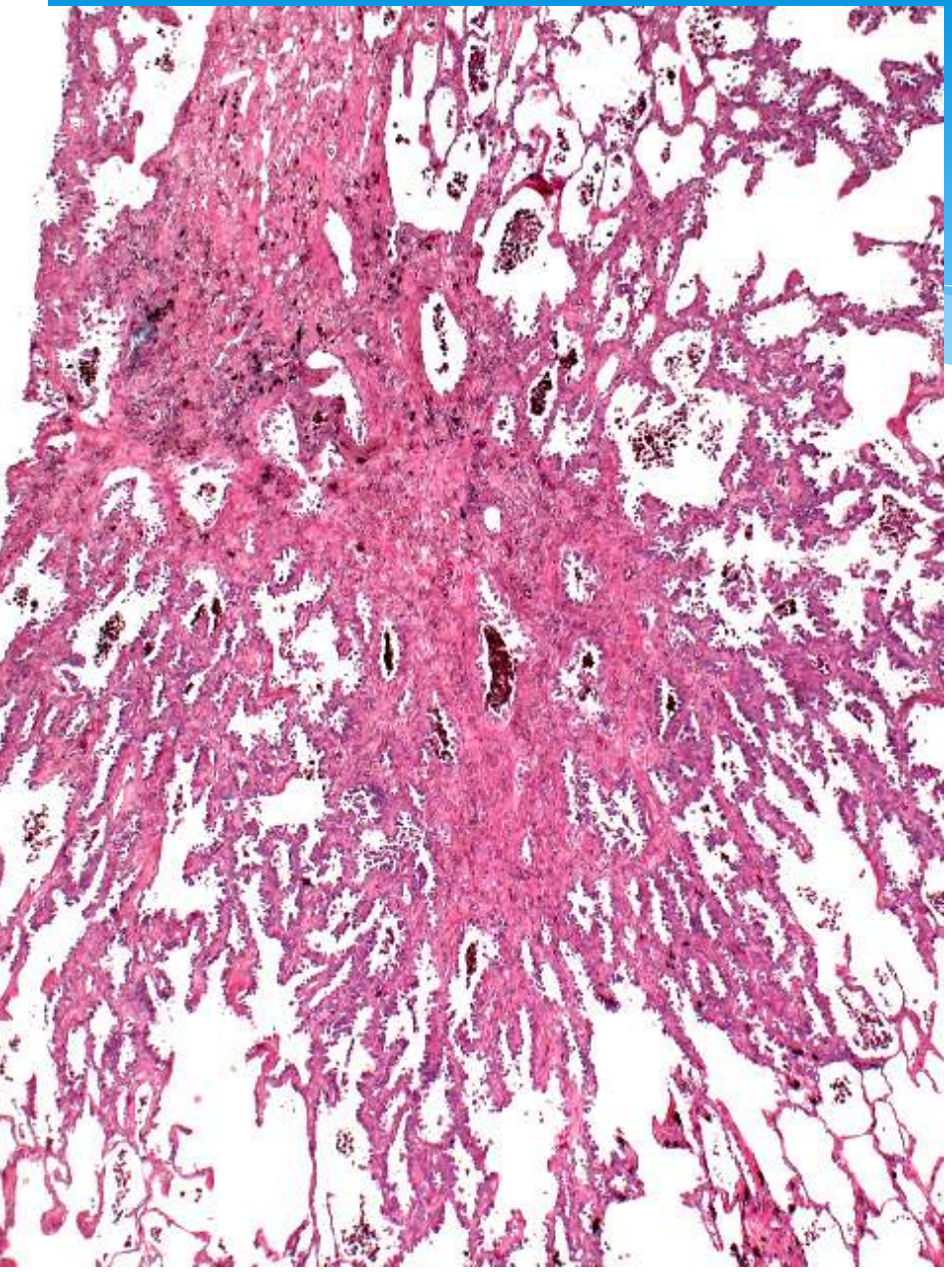


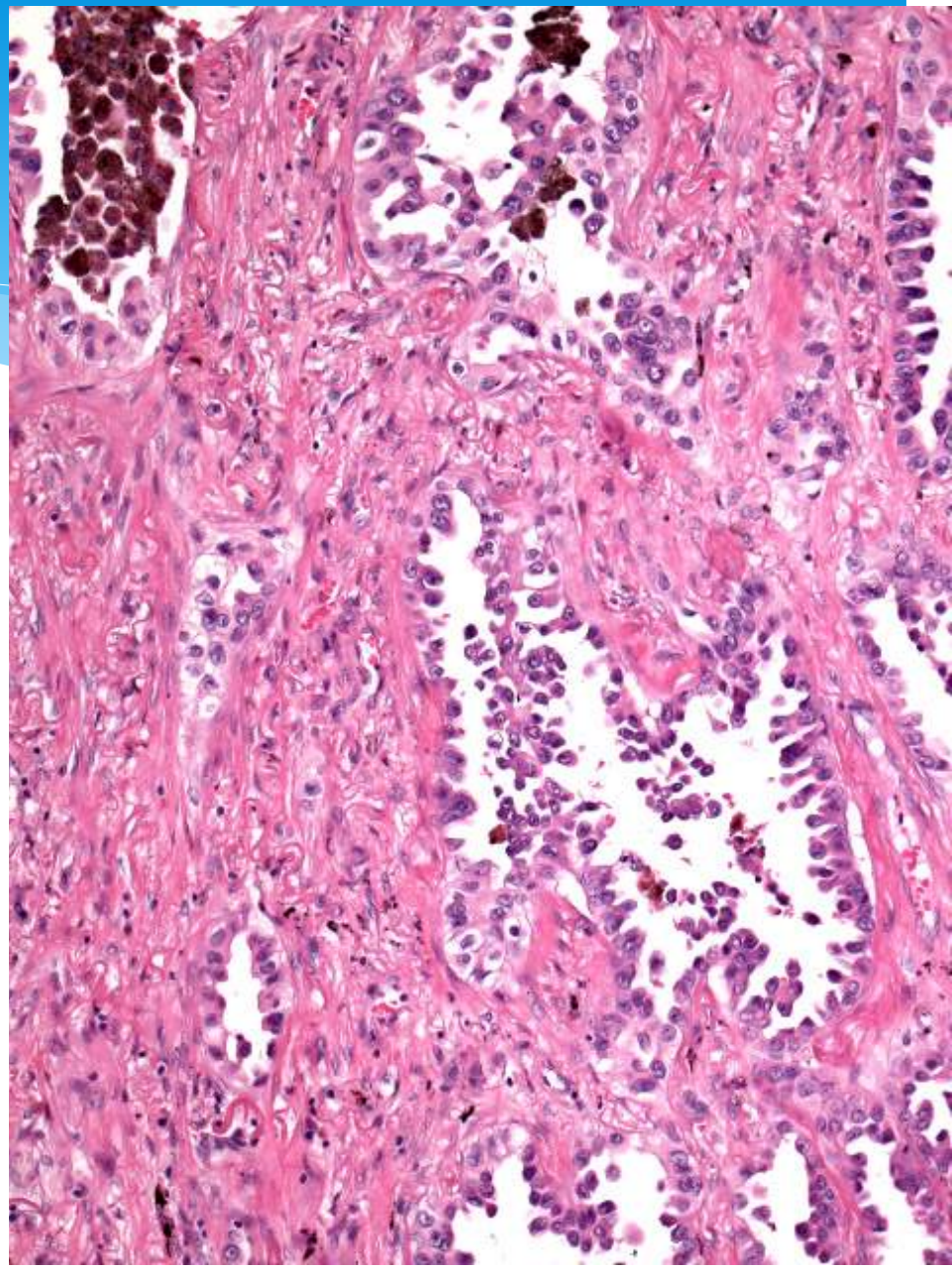


Thunnissen E et al. 2102. Modern Path

Collapse alveoli versus invasion

* The reproducibility of the diagnosis of invasion is poor!
* The classification allows for thickening of the alveolar septae in the diagnosis of AIS, but not desmoplasia.
* The determination of desmoplasia is not clear.
* Emerging concept of “ collapsed alveoli”





Thunnissen E et al. 2102. Modern Path

Elastic stain anyone?

* There are suggestions that an elastic stain can distinguish between collapse (preserved) and desmoplasia (disrupted).
* Elastic stain is difficult to perform and to interpret.
* There are suggestions that elastic frame is retained in papillary pattern.
* **There is no consensus on what represents invasion in lepidic predominant adenocarcinoma**

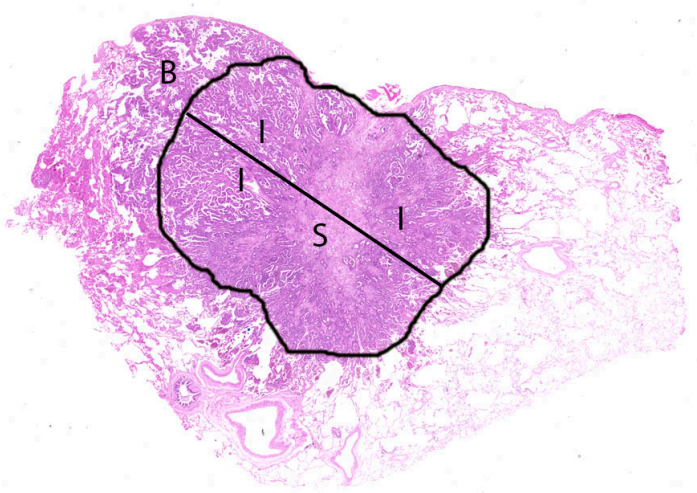
Fibrosis due to invasion versus scar

* How to measure the area of invasion, once you are confident that you have invasion?
* Do I include the area of scar or not?
* There are no clear recommendations in the IASLC/ERS/ATS document.
* Some authors have included the area of scar within the measurement in their definition of MIA.

Multiple foci of invasion

* measure the largest focus of invasion instead of “ adding up” all measurements of smaller foci.
* Determine the percentage of the invasive component and calculate the measurement

Case B, Multiple areas of invasion



B

* Direct measurement:
* total size 1.2 cm, Invasive 0.8 cm (with scar)- lepidic predominant (LPP)adenocarcinoma

* Percentage:
* 30% invasion = 0.36 cm (MIA)

* 40% invasion = 0.48 cm (MIA)
* 50% invasion = 0.6 cm (LPP)
* 60% invasion = 0.72 cm LPP)

Summary

* Difficult to diagnosis lepidic predominant tumors because the criteria are new, which can generate a lot of confusion!!
* Rare cases!
* Does it really matter?
* There is no difference in prognostic significance between an AIS and MIA
* If the area of doubt is larger than 5 mm, best call it a lepidic predominant adenocarcinoma (personal opinion!!)

IASLC/ATS/ERS Adenocarcinoma classification

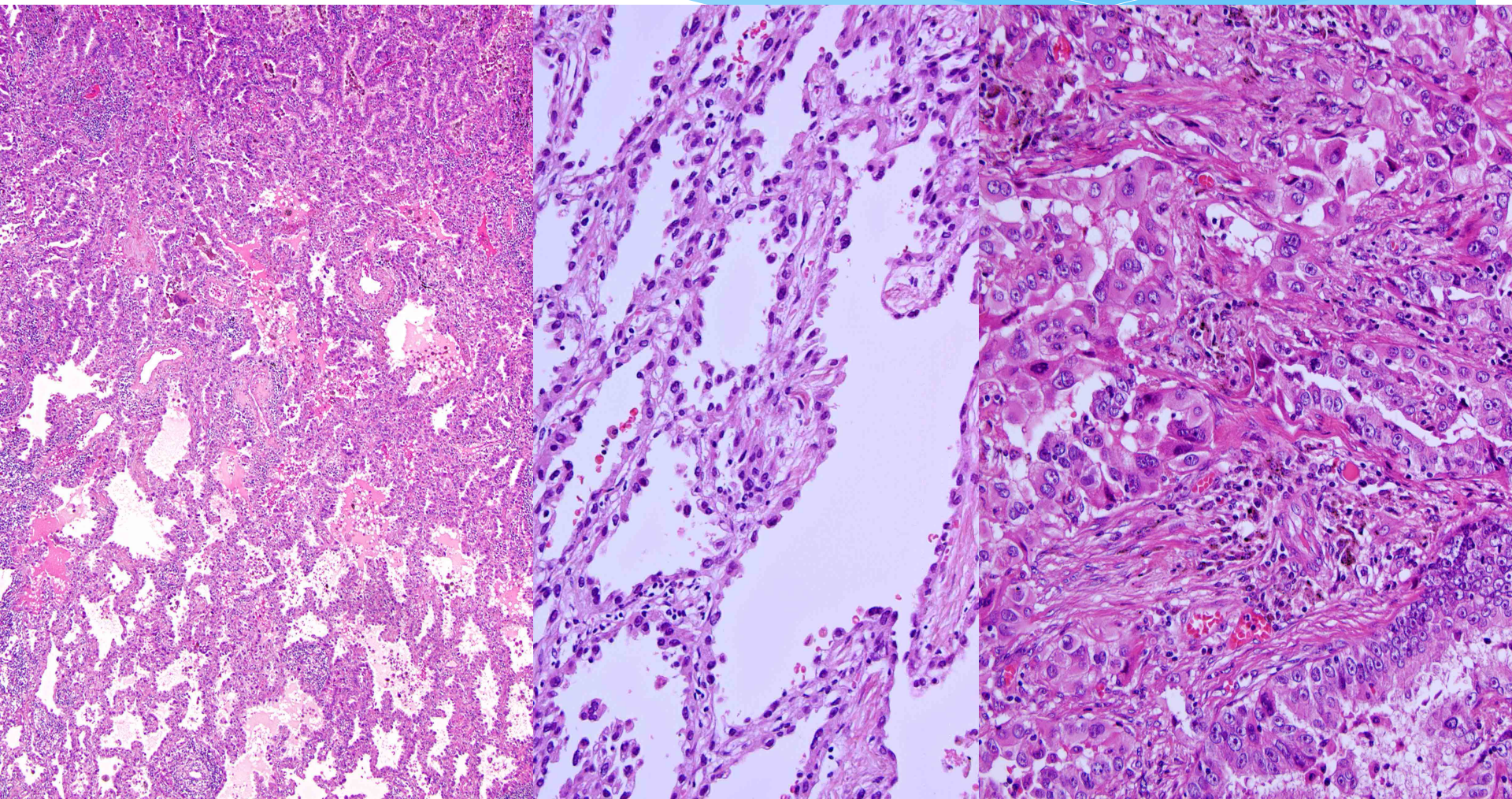
Invasive adenocarcinoma (invasive component is > 0.5 cm)

- Lepidic pattern predominant
- Acinar pattern predominant
- Papillary pattern predominant
- Micropapillary pattern, predominant
- Solid pattern predominant

New problems: other non-traditional patterns (cribriform, fused glands, etc.)

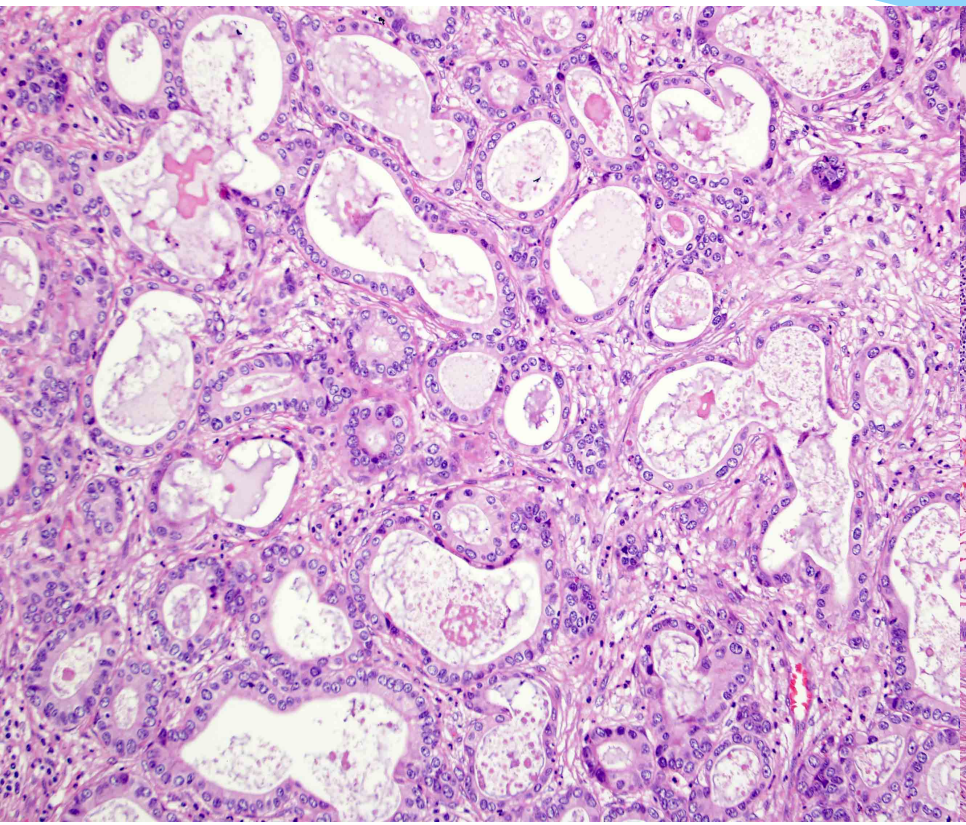
Older problems: Reproducibility

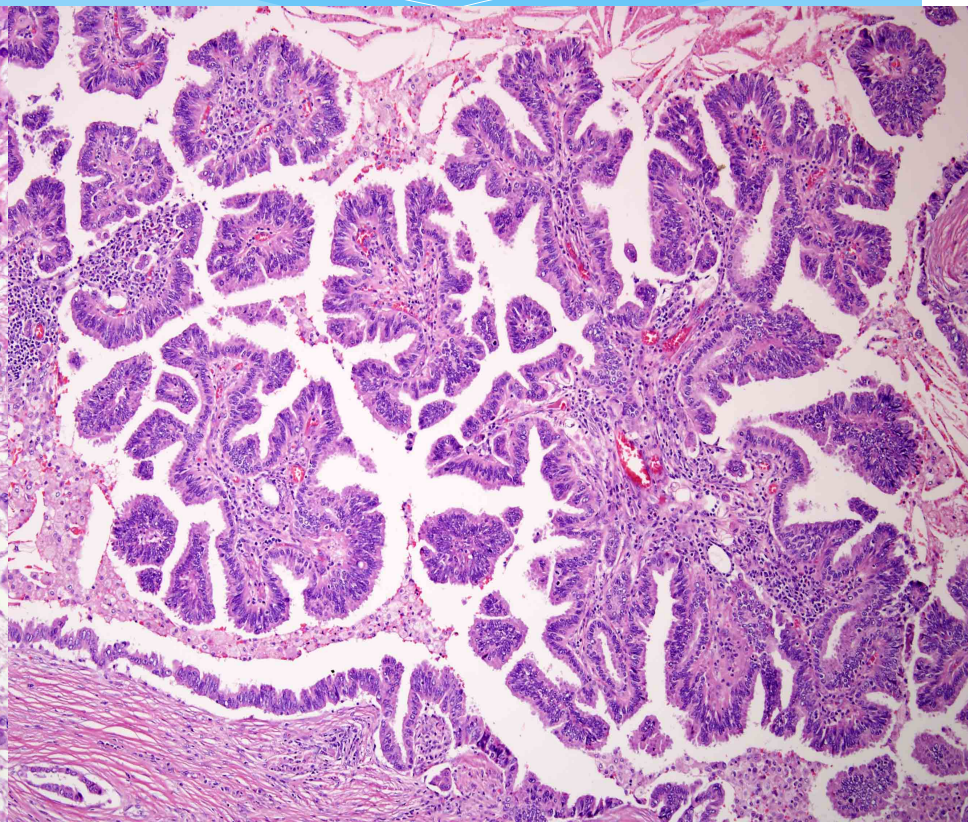
Lepidic predominant



Acinar

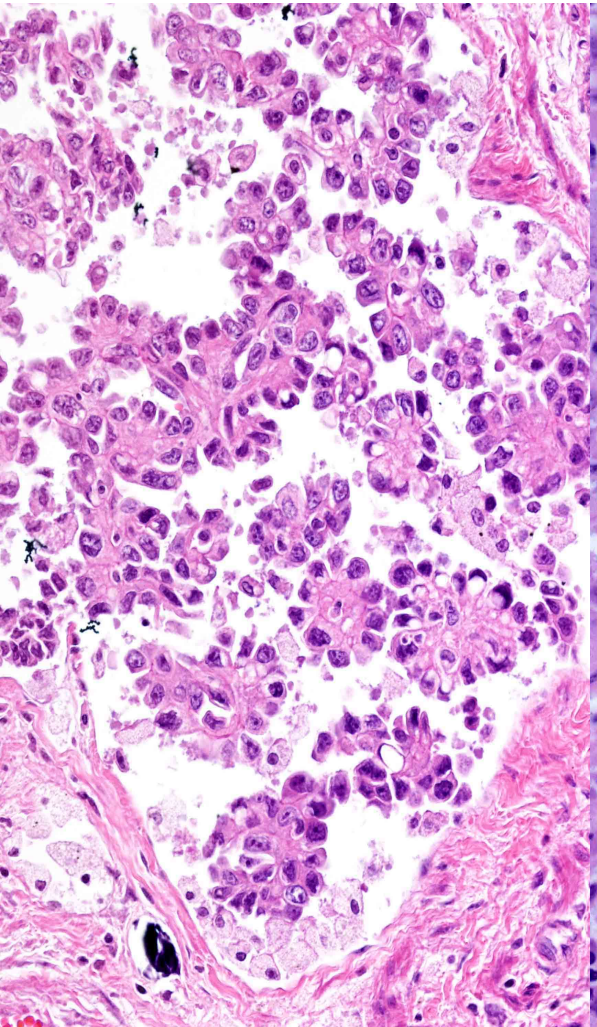
Papillary

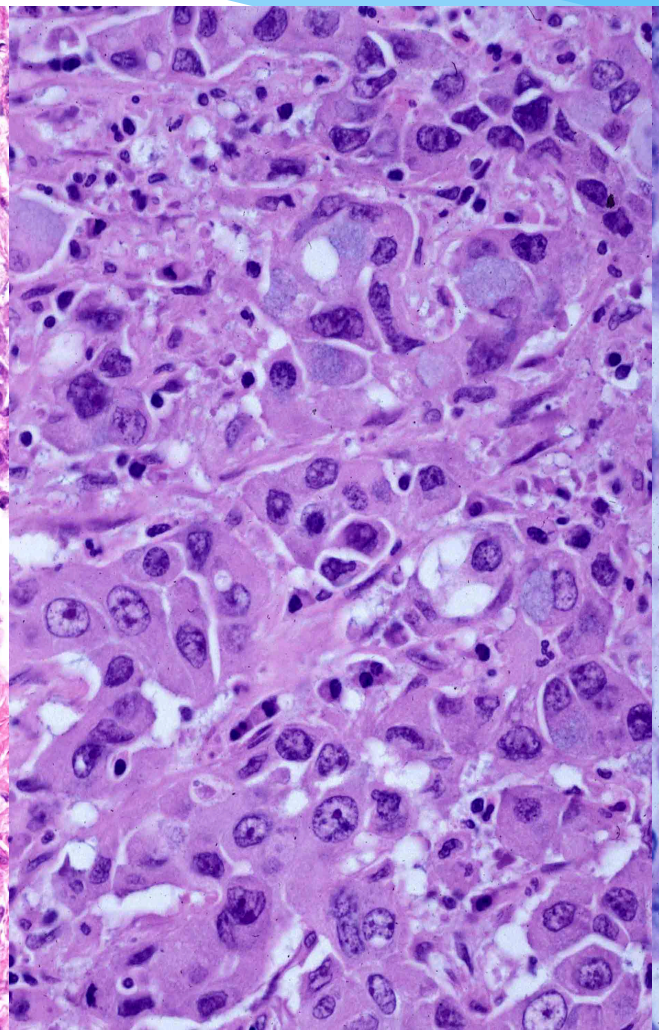


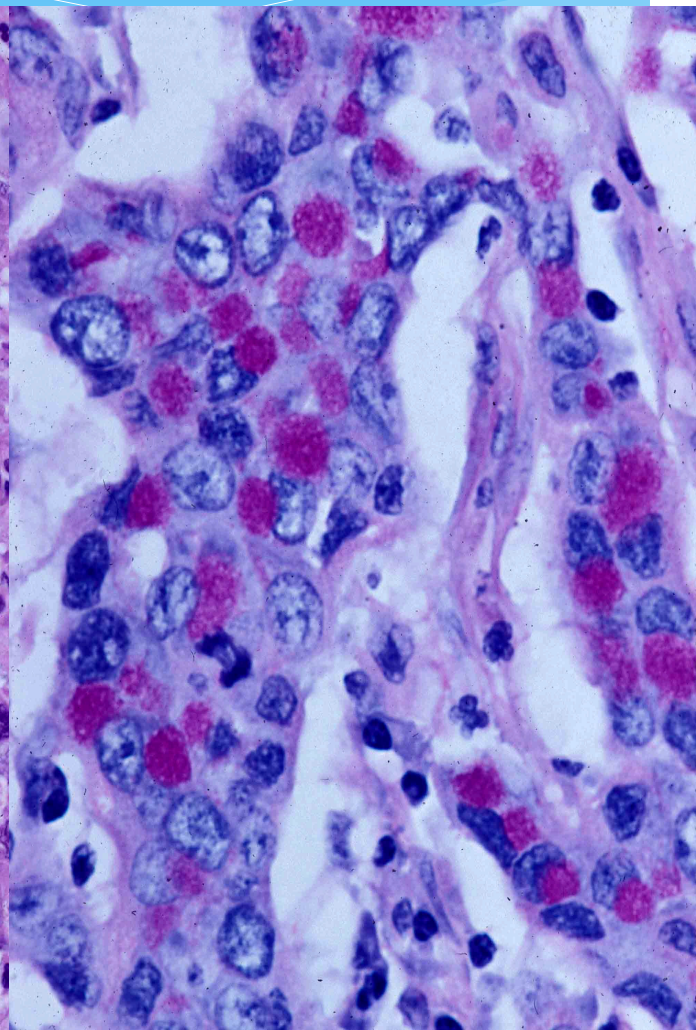


Micropapillary

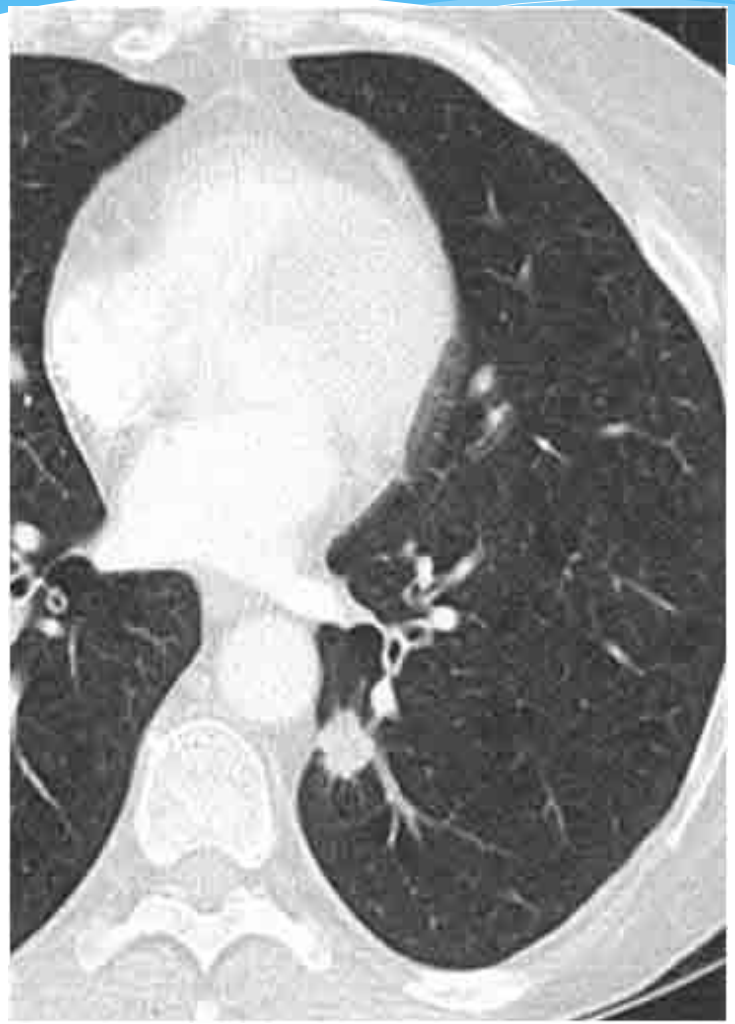
Solid





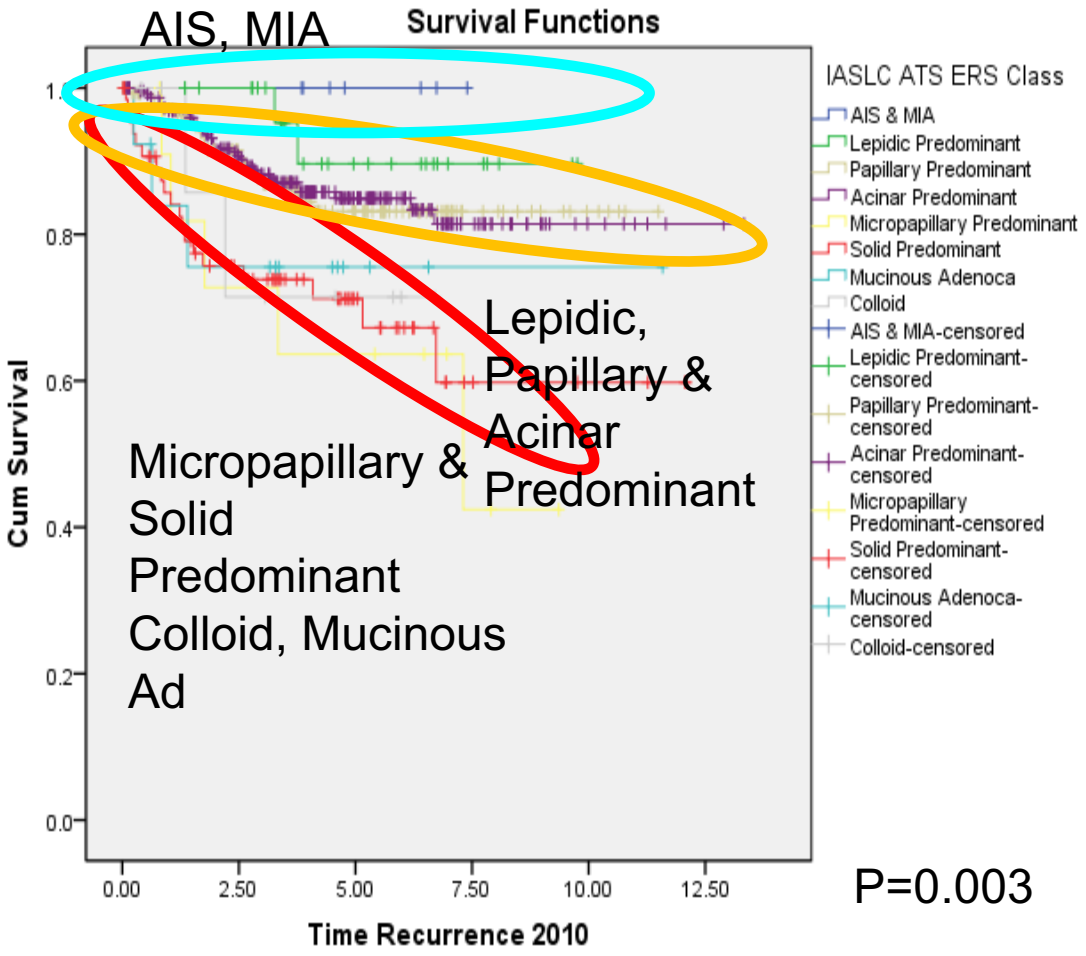


Invasive adenocarcinoma



Stage I adenocarcinoma (N=514)

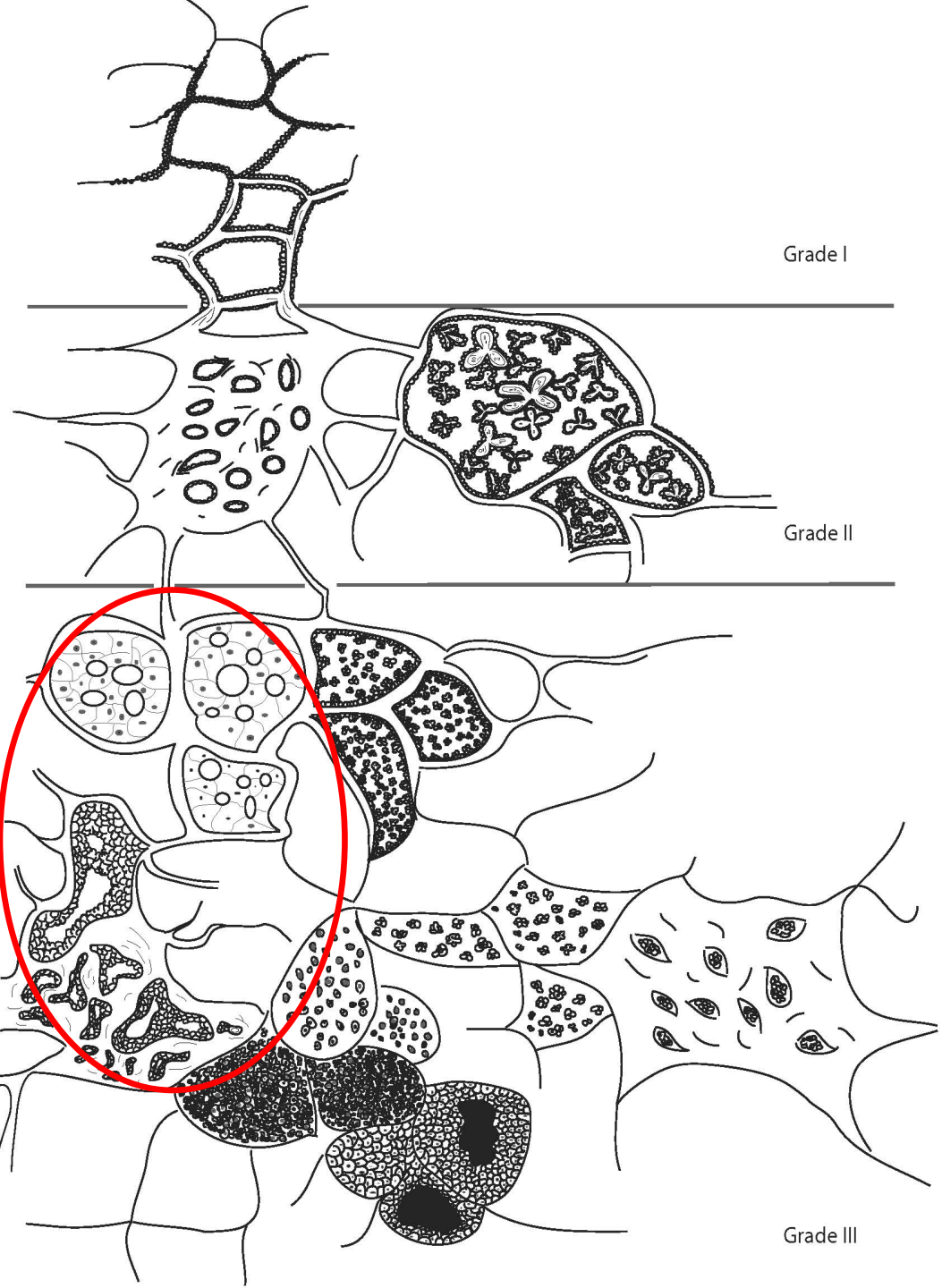
Recurrence-free survival(RFS) by IASLC histologic type



P=0.003

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

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



- **Lepidic**

- **Acinar**
- **Papillary**

Solid

- **Micropapillary**

Complex glandular patterns

Sica G, Moreira AL *et al*. A Grading System of Lung Adenocarcinomas Based on Histologic Pattern is Predictive of Disease Recurrence in Stage I Tumors. American Journal of Surgical Pathology. 34(8):1155-1162, August 2010.

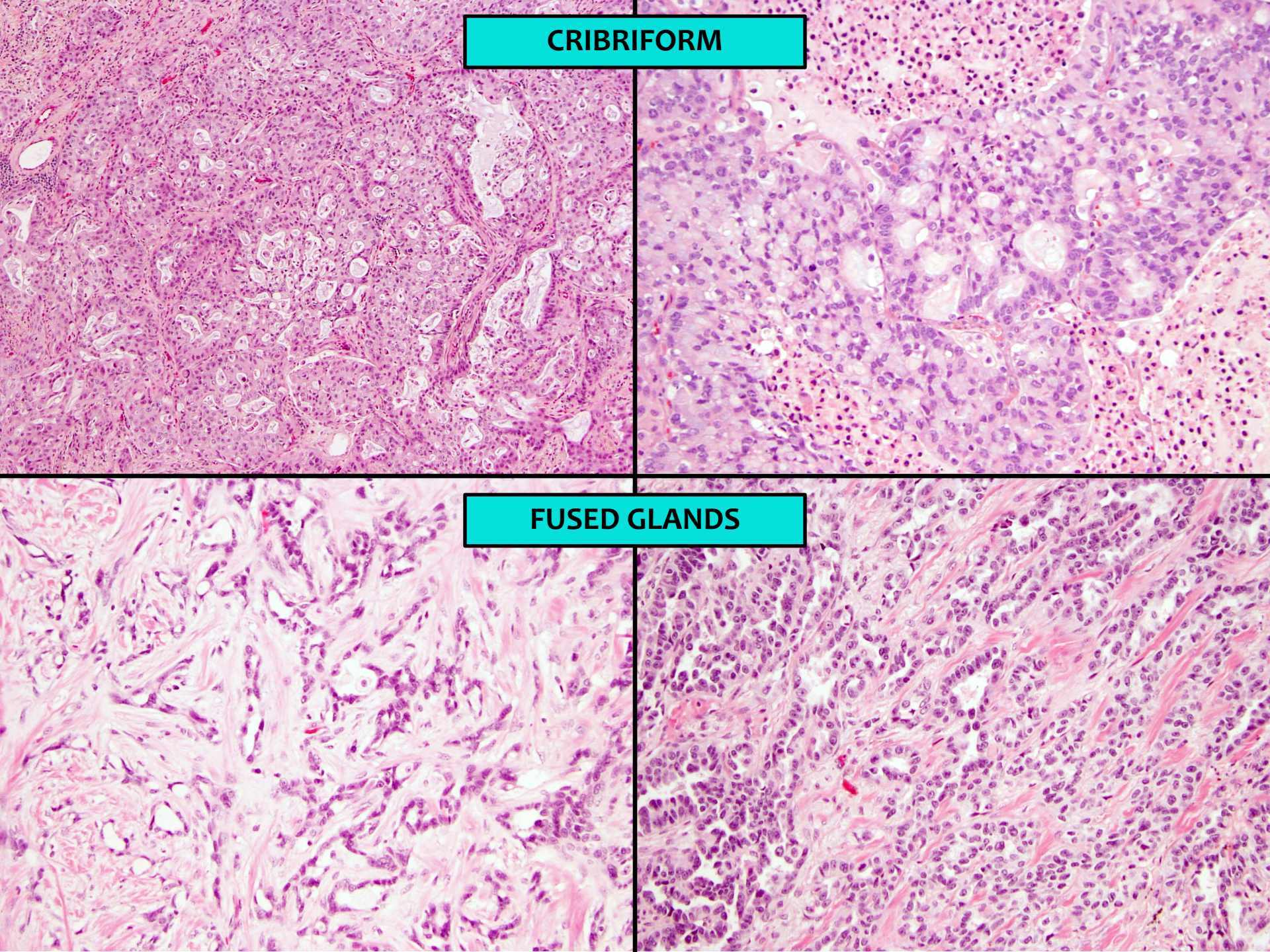
DEFINITION OF COMPLEX GLANDULAR PATTERNS (CGP):

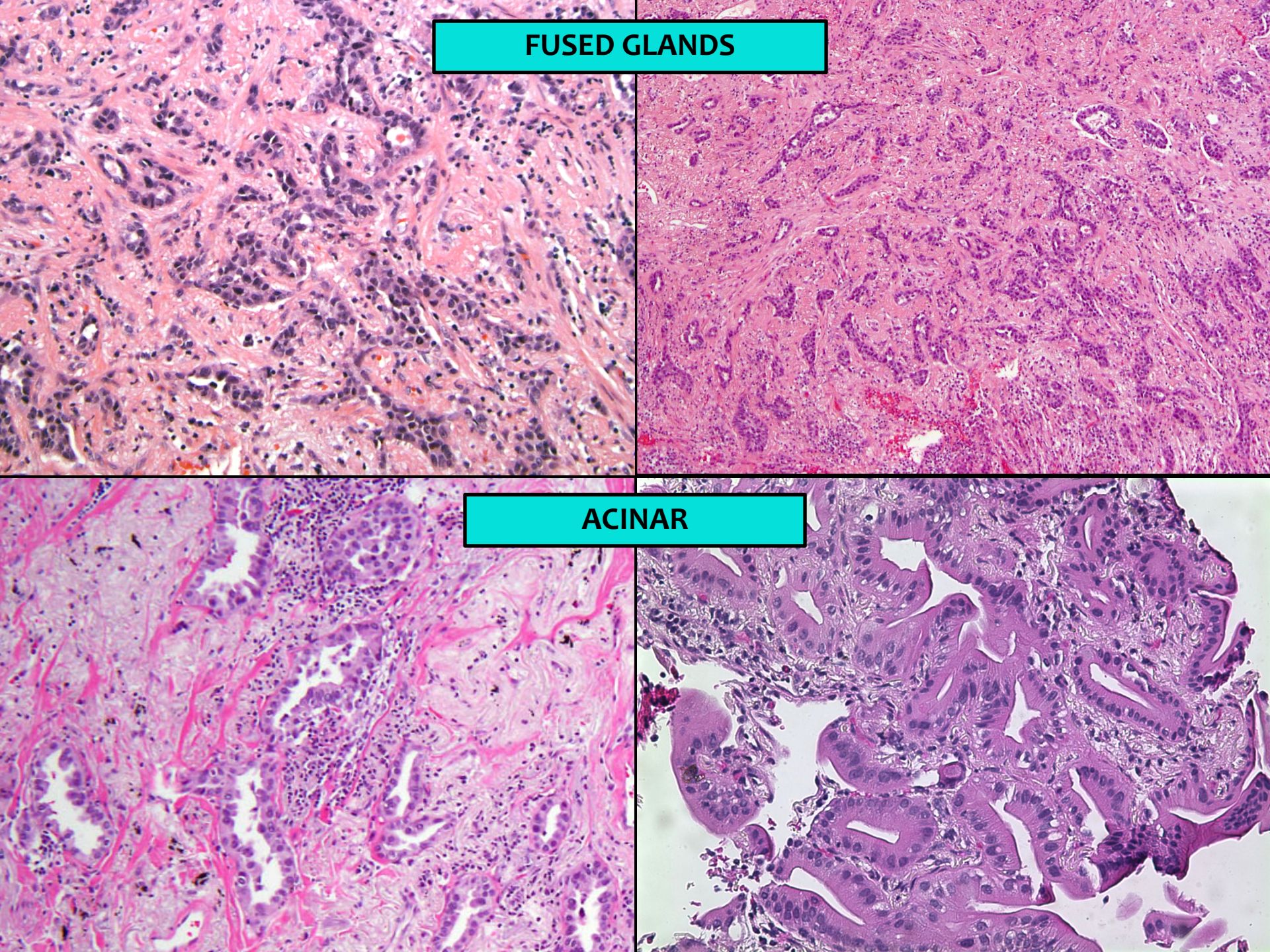
* CRIBRIFORM:
  * Solid nests of tumor cells with sieve-like perforations

* FUSED-GLANDS:
  * Fused glands and back-to-back glands with irregular borders or ribbon-like formation

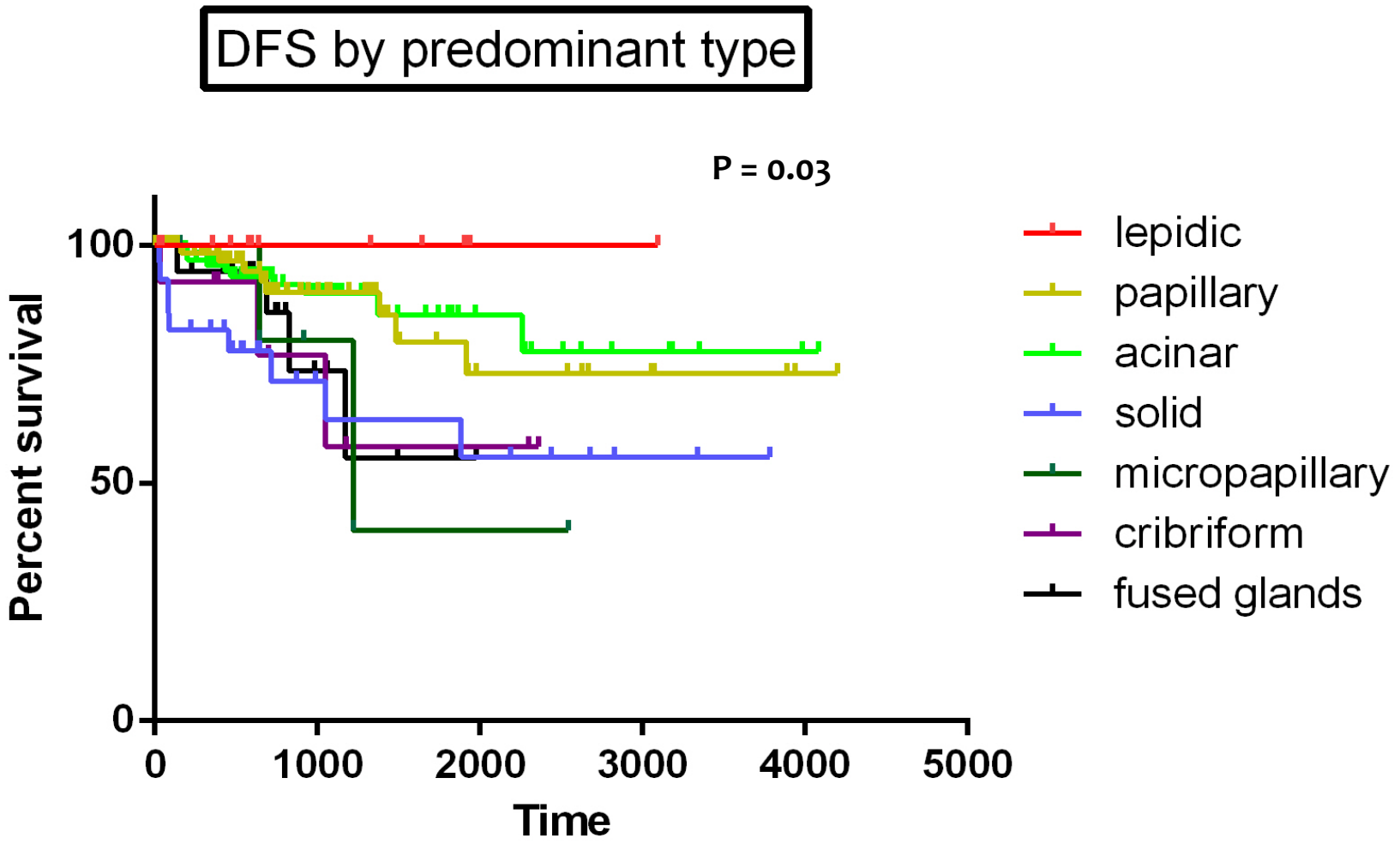
* Complex glandular patterns include:
  * Cribriform pattern
  * Fused glands

* Patterns not recognized in the last IASLC/ATS/ERS classification, therefore, difficult to classify


CRIBRIFORM
FUSED GLANDS

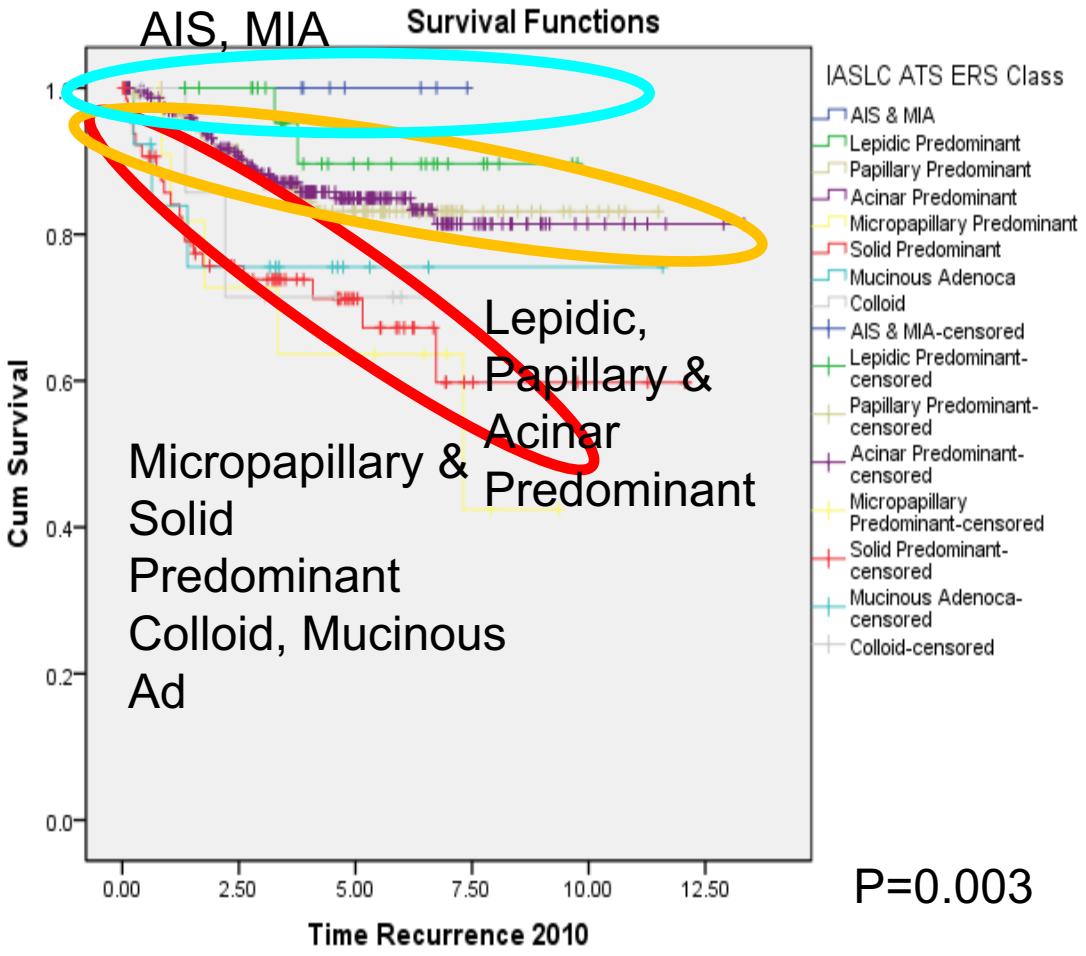

FUSED GLANDS
ACINAR

PROGNOSIS VALUE OF CGP



Moreira Al et al Hum Pathol, 2014, 45:213-20

The current classification hints at a grading system



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Problems with one pattern

- What to do with the intermediate grade group?
  - >50 % of all adenocarcinoma
  - Very heterogenous group

Proposals to help in grading- modifiers

- Nuclear grade
- Mitotic count
- Cytology grade
- STAS (spread through alveolar space)
- Secondary patterns

Grading system

* **Evaluate and create an objective grading system for invasive adenocarcinoma**
* Evaluate the best model to predict outcome (RFS and OS)
  - Evaluate pattern combinations
  - Significance of modifiers (STAS, Nuclear grade, cytology grade, etc)
  - Establish if there is a Cut-off of high grade pattern that is associated with recurrence/death of disease
  - Reproducibility assay

Experimental model

* **Evaluate 5 independent dataset provided by IASLC pathology committee**
* **Training set n= 284 (Stage 1)-** evaluate multiple histological parameters role of modifiers and devise the model
* What is the best and practical model
* **Validation N= 212 (Stage 1) - 2 combined data sets**
* **Test set stage 1 N= 303 (Stages 1 and 2) - 2 combined datasets**

Histological pattern- Training set

Patient Characteristics Statistics (N = 284)					
		Total	**Recurrence = Yes (N = 66)**	**Recurrence = No (N = 218)**	**P-value**
Predominant Histologic Pattern	Acinar	129(45%)	21(32%)	108(50%)	
	Cribriform	3(1%)	0(0%)	3(1%)	
	Fused glands	16(6%)	10(15%)	6(3%)	
	Lepidic	20(7%)	0(0%)	20(9%)	<0.0001
	Micropapillary	21(7%)	10(15%)	11(5%)	
	Papillary	55(19%)	10(15%)	45(21%)	
	Solid	40(14%)	15(23%)	25(11%)	

Histological modifiers

Patient Characteristics Statistics (N = 284)					
		Total	Recurrence = Yes (N = 66)	Recurrence = No (N = 218)	P-value
Mitotic count	1 (0-1/10 hpf)	201(71%)	36(55%)	165(76%)	0.0003
	2 (2-4/10 hpf)	48(17%)	13(20%)	35(16%)	
	3 (>5/10 hpf)	35(12%)	17(26%)	18(8%)	
Nuclear Grade	1	126(44%)	16(24%)	110(50%)	0.0001
	2	98(35%)	26(39%)	72(33%)	
	3	60(21%)	24(36%)	36(17%)	
Cytologic grade	High	87(31%)	34(52%)	53(24%)	<0.0001
	Low	197(69%)	32(48%)	165(76%)	
STAS	Absent	264(93%)	55(83%)	209(96%)	0.001
	Present	20(7%)	11(17%)	9(4%)	

Variables in the model	Recurrence		Variables in the model	Death	
	C-index	AUC		C-index	AUC
Baseline	0.595	0.611	**Baseline**	0.627	0.620
Baseline + Dominant	0.684	0.691	**Baseline + Dominant**	0.702	0.700
Baseline + Dominant + Secondary	0.728	0.740	**Baseline + Dominant + Secondary**	0.763	0.755
Baseline + Dominant + Worst	0.727	0.725	**Baseline + Dominant + Worst**	0.747	0.726

Role of modifiers

Variables in the model	Recurrence		Variables in the model	Death	
Baseline + Dominant + Secondary + Mitotic count + Nuclear grade + Cytologic grade + STAS	**0.741**	**0.746**	**Baseline + Dominant + Secondary + Mitotic count + Nuclear grade + Cytologic grade + STAS**	**0.775**	**0.761**
-Mitotic count, cytology grade, and STAS	0.743	0.748	**-Nuclear grade, Cytology Grade, STAS**	0.787	0.769
-Cytology Grade and STAS	0.741	0.752	**-Nuclear grade and STAS**	0.785	0.768
STAS	0.740	0.752	**STAS**	0.785	0.765

Summary

Model#1

* Baseline = 0.611
* Best predictor of recurrence (predominant + secondary pattern)= 0.740 and OS 0.755
* STAS was the best modifier = 0.752
* Modifiers have different weights between RFS and OS
* Modifiers = do not add significantly to the model, improvement is not statistical significant

Model#2

* Predominant plus worse pattern
* Easier for pathologists

* Recurrence = 0.725, OS= 0.726
* Modifiers did not add significantly to the model
* There is no significant difference between model#1 and #2

Model for grading

* Similar performance in a 4 different data sets from different institutions and countries

Predominant + worse

* **Well-differentiated (grade 1)**
* Lepidic predominant + Acinar/papillary
* **Moderately Differentiated (grade 2)**
* Acinar/Papillary predominant + no high grade or less than 20%
* **Poorly-Differentiated (grade 3)**
* High grade pattern + any other pattern
* AC/PA/LP = high grade pattern >20%

• Take home message

- Objective grading for adenocarcinoma is possible
- Could help in future studies to determine influence of therapy in adenocarcinomas as a common language to evaluate tumor heterogeneity
- Strength of this study: the model had a consistent performance in difference data sets which prevents institutional biases!