The new WHO classification of Lung tumours

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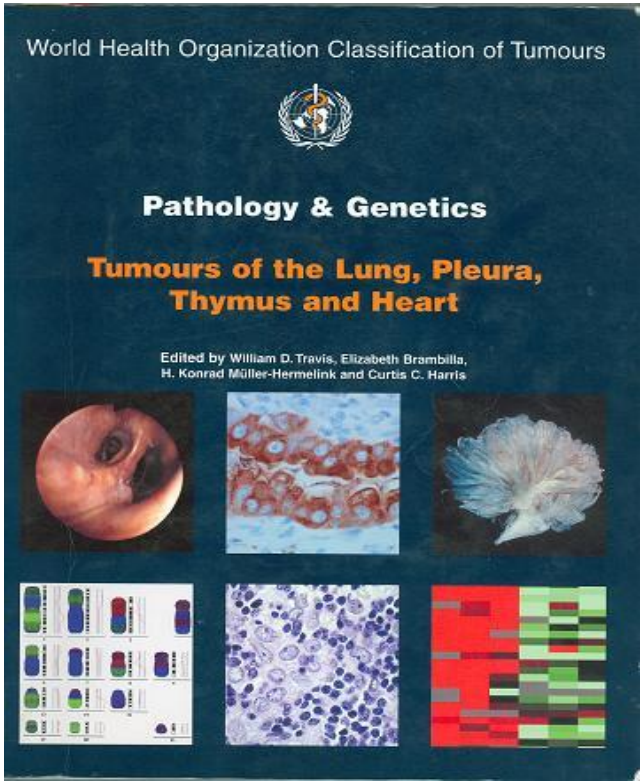
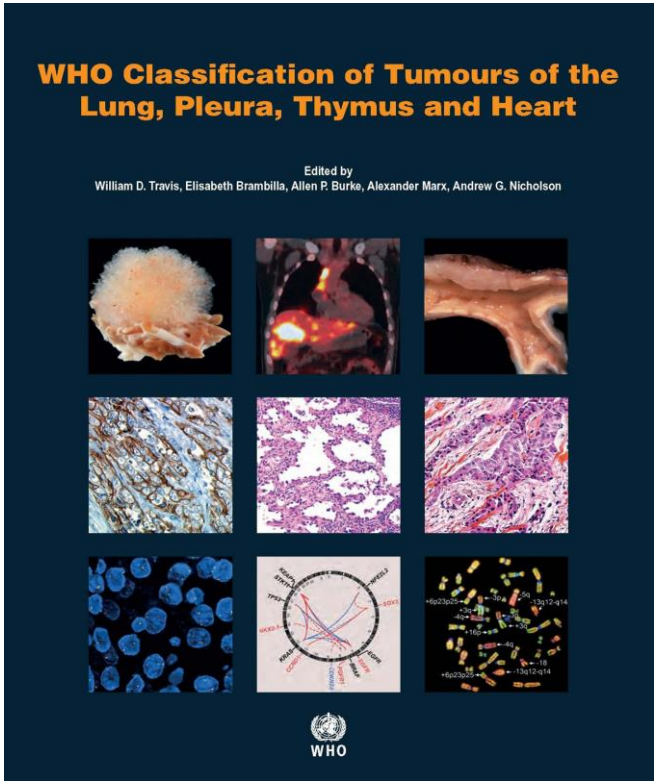
WHO 2004 WHO 2015/2021

Pathologists' view	⟹	Multidisciplinary
Resected specimen	⟹	Small biopsy/Resection
HE stain	⟹	IHC, MB, Genetics, Biomarkers





Updates in 2021 WHO classification of the Lung Tumours

- Histopathological definitions remain largely the same
- Grading system of Adenocarcinoma
- Structural changes for more consistency
- Significant advances in molecular subgroupings for NENs

Changes in 2021 WHO classification of the Lung Tumours

- Newly included entities
  - SMARCA4-deficient undifferentiated tumour
  - Bronchiolar adenoma / ciliated muconodular papillary tumour
- Changes of terminology
  - Lymphoepithelioma-like carcinoma → “lymphoepithelial carcinoma”
  - Enteric adenocarcinoma” → “enteric-type adenocarcinoma”
- Essential and desirable criteria as well as definition in each diagnosis

1.3: Epithelial tumours

- 1.3.1: Papillomas
  - 1.3.1.1: Bronchial papillomas
- 1.3.2: Adenomas
  - 1.3.2.1: Sclerosing pneumocytoma
  - 1.3.2.2: Alveolar adenoma
  - 1.3.2.3: Papillary adenoma of the lung
  - 1.3.2.4: Bronchiolar adenoma / ciliated muconodular papillary tumour
  - 1.3.2.5: Mucinous cystadenoma of the lung
  - 1.3.2.6: Mucous gland adenoma of the lung
- 1.3.3: Precursor glandular lesions
  - 1.3.3.1: Atypical adenomatous hyperplasia of the lung
  - 1.3.3.2: Adenocarcinoma in situ of the lung
- 1.3.4: Adenocarcinomas
  - 1.3.4.1: Minimally invasive adenocarcinoma of the lung
  - 1.3.4.2: Invasive non-mucinous adenocarcinoma of the lung
  - 1.3.4.3: Invasive mucinous adenocarcinoma of the lung
  - 1.3.4.4: Colloid adenocarcinoma of the lung
  - 1.3.4.5: Fetal adenocarcinoma of the lung
  - 1.3.4.6: Enteric-type adenocarcinoma of the lung
- 1.3.5: Squamous precursor lesions
  - 1.3.5.1: Squamous dysplasia and carcinoma in situ of the lung
- 1.3.6: Squamous cell carcinomas
  - 1.3.6.1: Squamous cell carcinoma of the lung
  - 1.3.6.2: Lymphoepithelial carcinoma of the lung
- 1.3.7: Large cell carcinomas
  - 1.3.7.1: Large cell carcinoma of the lung
- 1.3.11: Adenosquamous carcinoma
  - 1.3.4.7: Adenosquamous carcinoma of the lung
- 1.3.8: Sarcomatoid carcinomas
  - 1.3.8.1: Pleomorphic carcinoma of the lung
  - 1.3.8.2: Pulmonary blastoma
  - 1.3.8.3: Carcinosarcoma of the lung
- 1.3.9: Other epithelial tumours
  - 1.3.9.1: NUT carcinoma of the lung (see NUT carcinoma of the thorax)
  - 1.3.9.2: Thoracic SMARCA4-deficient undifferentiated tumour
- 1.3.10: Salivary gland-type tumours

1.4: Lung neuroendocrine neoplasms

- 1.4.1: Lung neuroendocrine neoplasms: Introduction
- 1.4.2: Precursor lesion
  - 1.4.2.1: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- 1.4.3: Neuroendocrine tumours
  - 1.4.3.1: Carcinoid/neuroendocrine tumour of the lung
- 1.4.4: Neuroendocrine carcinomas
  - 1.4.4.1: Small cell lung carcinoma
  - 1.4.4.2: Large cell neuroendocrine carcinoma of the lung

1.5: Tumours of ectopic tissues

- 1.5.0.1: Melanoma of the lung
- 1.5.0.2: Meningioma of the lung

1.6: Mesenchymal tumours specific to the lung

- 1.6.0.1: Pulmonary hamartoma
- 1.6.0.2: Pulmonary chondroma
- 1.6.1.4: Diffuse pulmonary lymphangiomatosis
- 1.6.1.1: Pleuropulmonary blastoma
- 1.6.1.2: Pulmonary artery intimal sarcoma
- 1.6.1.5: Congenital peribronchial myofibroblastic tumour
- 1.6.1.3: Primary pulmonary myxoid sarcoma with EWSR1-CREB1 fusion
- 1.6.2: PEComatous tumours
  - 1.6.2.1: Lymphangioleiomyomatosis of the lung
  - 1.6.2.2: PEComa of the lung

1.7: Haematolymphoid tumours

Bronchiolar adenoma/ciliated mucociliary papillary tumour (BA/CMPT)

➢ **Definition**

- a benign peripheral lung tumour composed of bilayered bronchiolar-type epithelium containing a continuous basal cell layer.

➢ ***Histopathologic features***

- nodular proliferations involving peribronchiolar lung parenchyma
- papillary and/or flat (glandular) architecture
- bilayered cellular elements with luminal epithelial cells and basal cells
- micropapillary tufts of ciliated cells and a minor degree of discontinuous spread are common and should not be regarded as features of malignancy
- Nuclear atypia is absent and mitoses are rare.
- The diagnosis is difficult to make on a small biopsy, although it may be suspected.

Bronchiolar adenoma/ciliated mucociliary papillary tumour (BA/CMPT)

- **Gross feature**

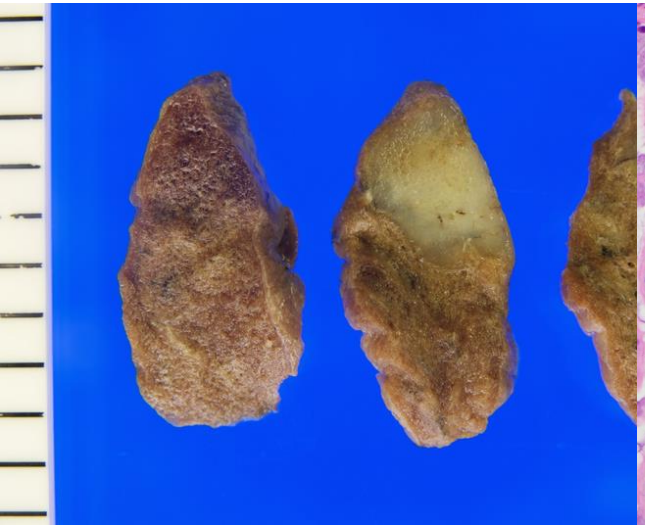
  well circumscribed nodular lesion, gray tan cut surface

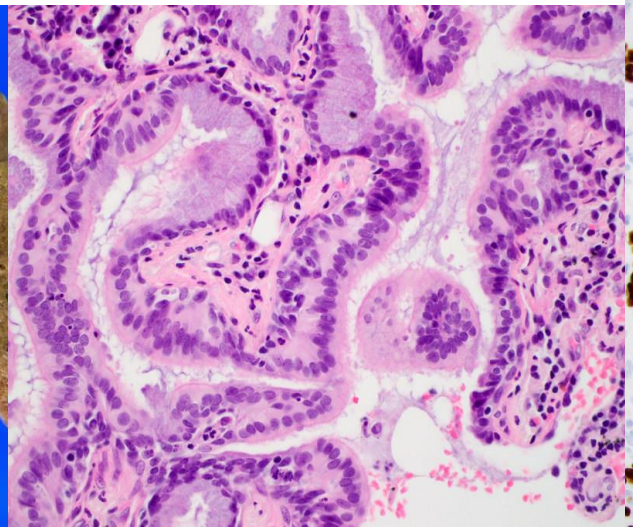
- ***Immunohistochemical features***

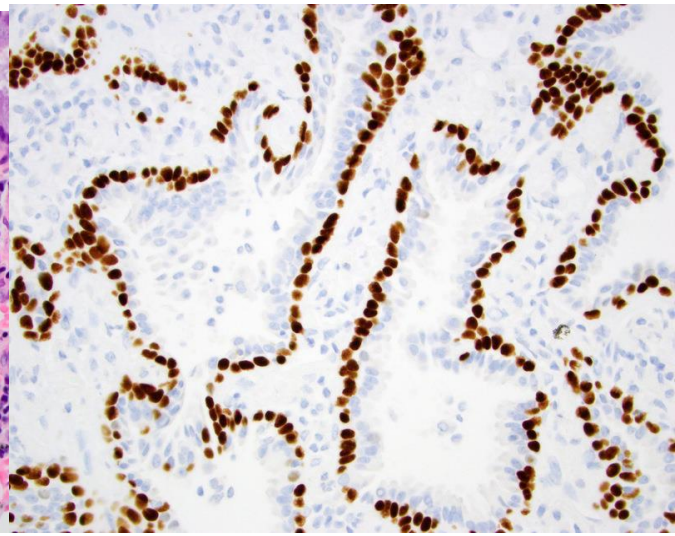
  basal cells: p40 (+), luminal cells : TTF-1 (+)/(-)

- **Differential diagnoses**

  adenocarcinoma, mucinous adenocarcinoma, glandular papilloma







SMARCA4-deficient undifferentiated tumour

➢ **Gross feature**

large, white-grey, and soft,
with massive necrosis

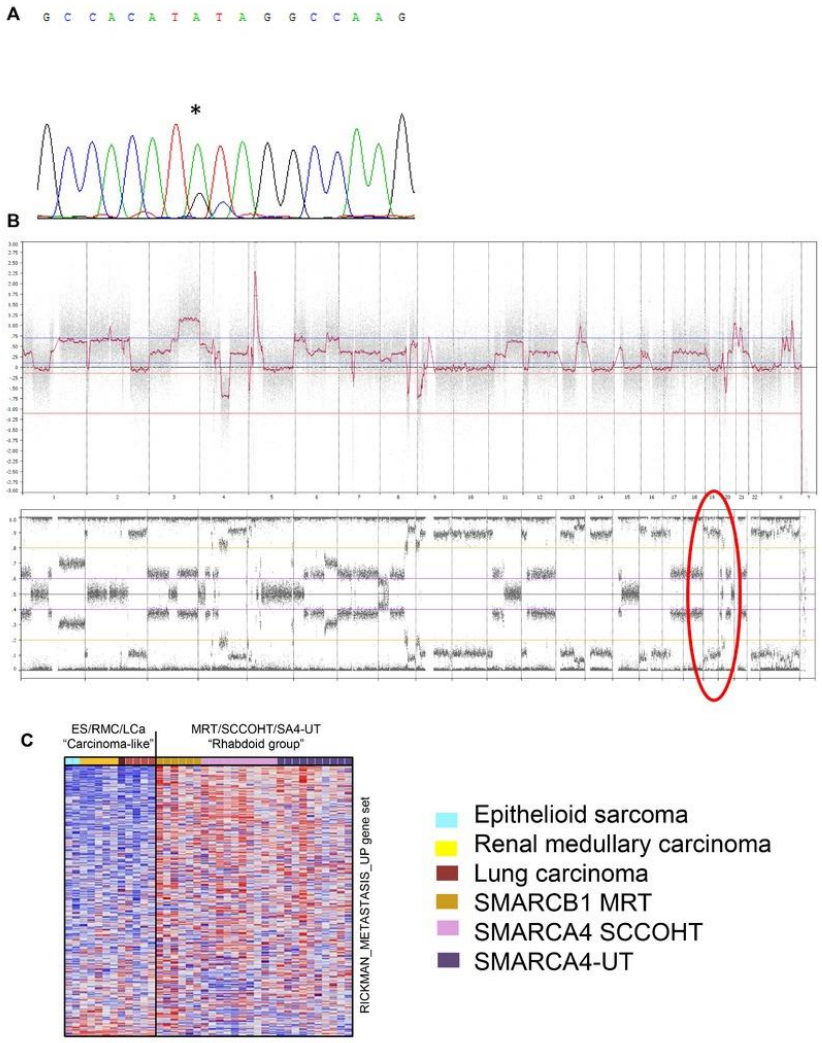
➢ ***Pathogenesis***

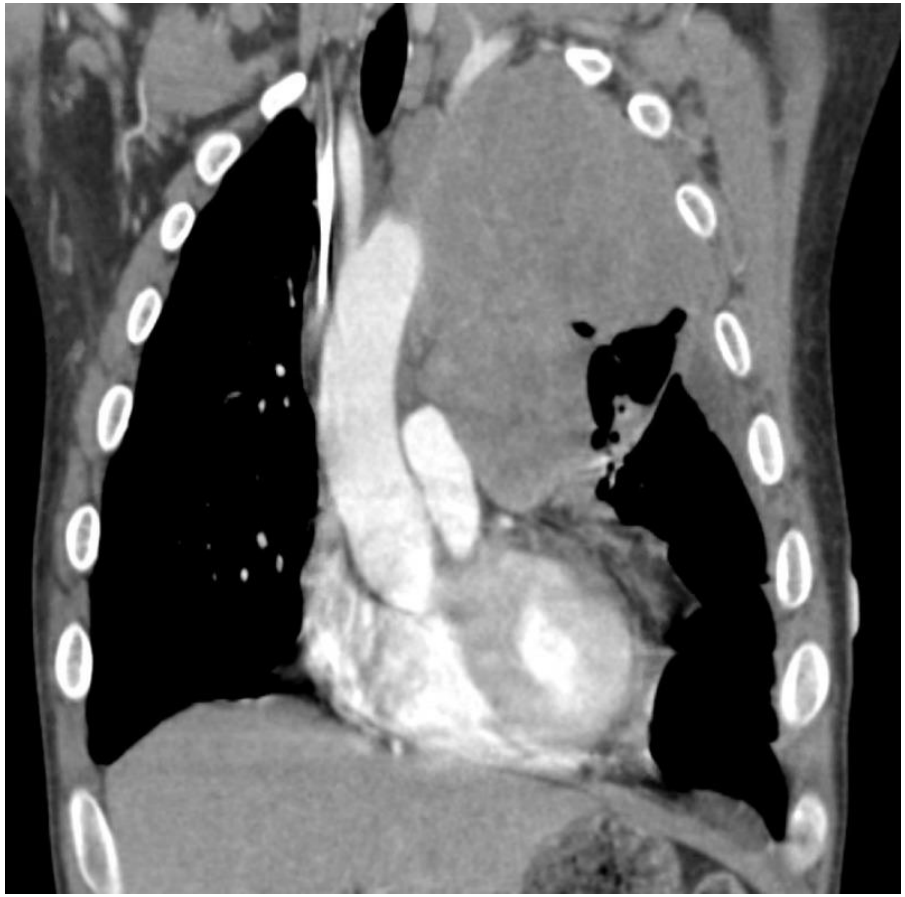
- biallelic inactivation of *SMARCA4*→ loss of SMARCA4 (BRG1) expression
- genomic smoking mutation signatures

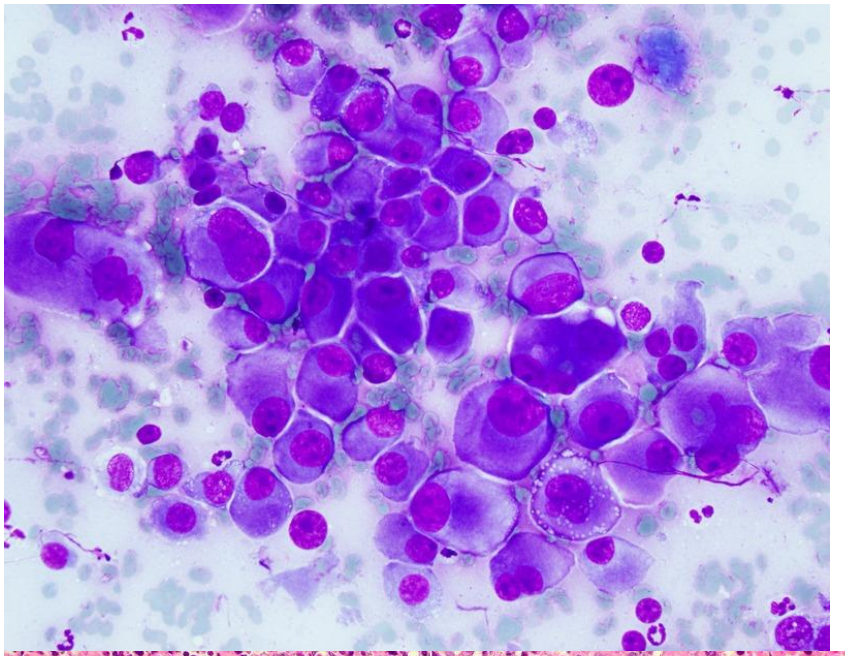
CK expression, focal

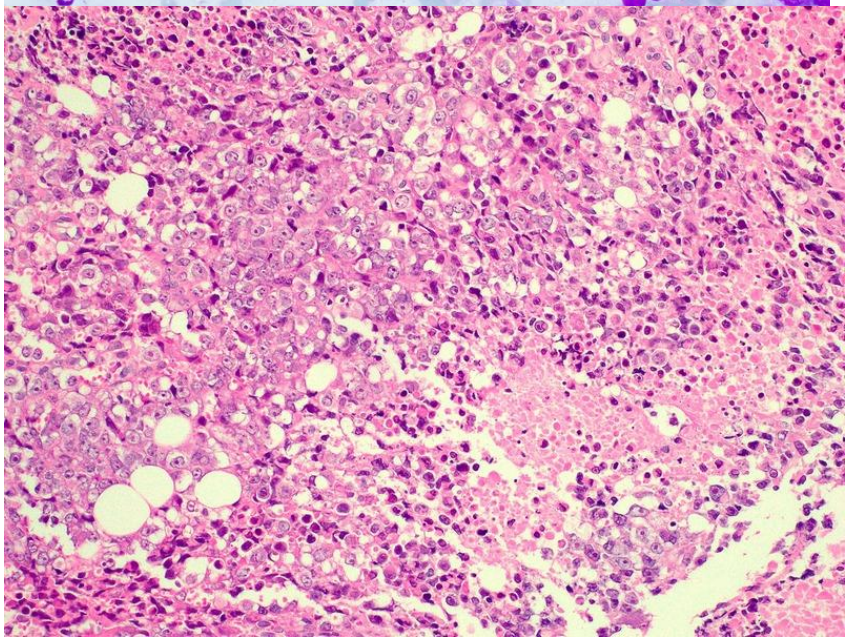
➢ **Differential diagnoses**

NUT carcinoma, lymphoma, melanoma sarcomas









SMARCA4-deficient undifferentiated tumour

➢ ***Essential***

• Tumour in adults, with significant thoracic involvement
• Diffuse sheets of variably discohesive, round to epithelioid, monotonous cells with vesicular nuclei and prominent nucleoli
• No clear evidence of epithelial differentiation
• SMARCA4 (BRG1) deficiency by immunohistochemistry

➢ ***Desirable:***

•SMARCA2 (BRM) deficiency by immunohistochemistry
•Expression of CD34, SOX2, and/or SALL4
•Absent or focal claudin-4 expression

ADENOCRCINOMA

- 1.3.3: Precursor glandular lesions
  - 1.3.3.1: Atypical adenomatous hyperplasia of the lung
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Clear cells and signet ring cells may be noted
but are descriptive terms and not defining of subtype

Atypical Adenomatous Hyperplasia

- **Definition**

a small (usually ≤ 5mm), localized proliferation of atypical type II pneumocytes and/or club cells lining alveolar walls and sometimes respiratory bronchioles.

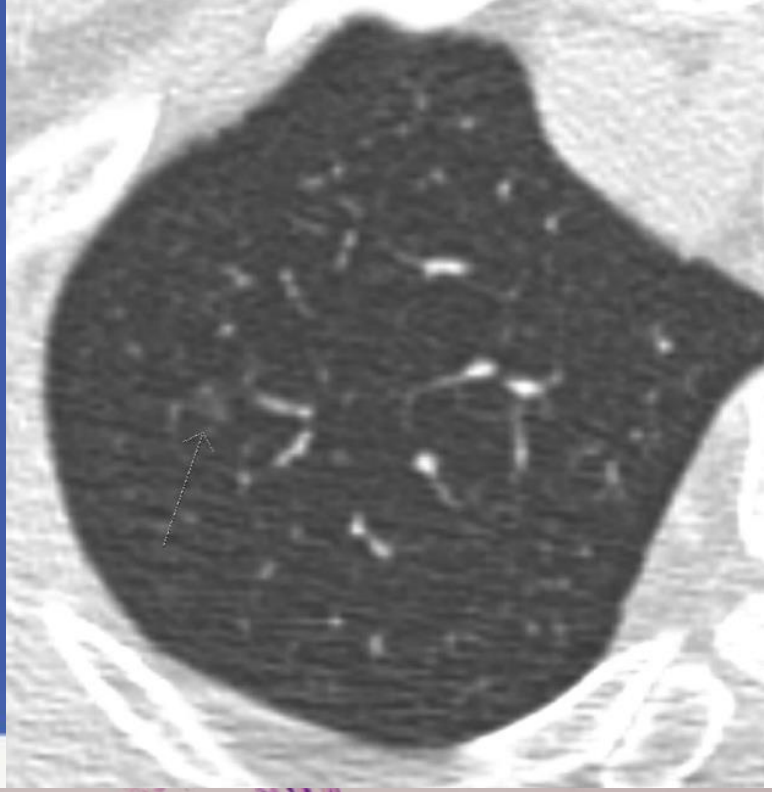
- ***Essential:***

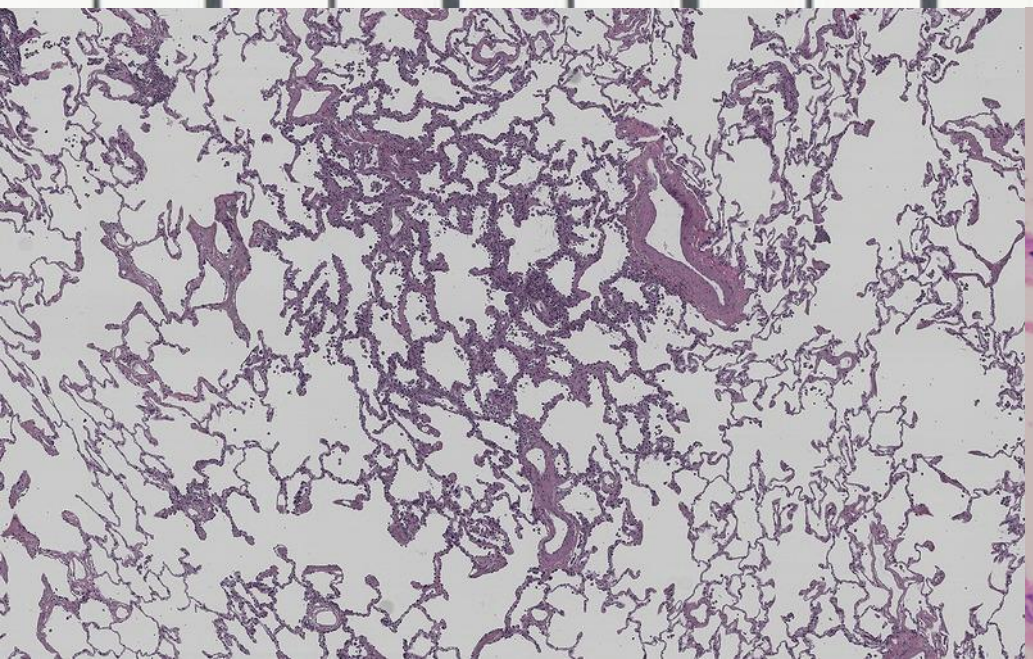
Increased numbers of type 2 pneumocytes and club cells lining alveoli in a discontinuous monolayer

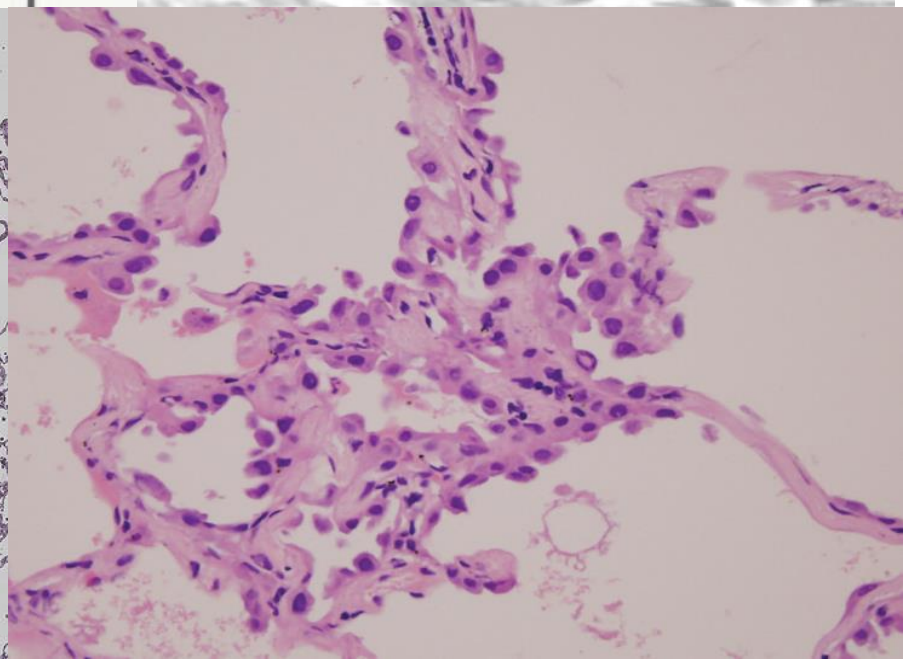
Mild atypia

Localized lesion, discrete from surrounding alveolar parenchyma

Surrounding parenchyma devoid of inflammation or fibrosis







Adenocarcinoma-in-situ

- **Definition**

Adenocarcinoma in situ is a small (≤3 cm), localized adenocarcinoma with growth restricted to neoplastic cells along pre-existing alveolar structures (pure lepidic growth with NO invasive features).

- ***Essential:***

A small (<3cm diameter) localised lesion comprising pure lepidic growth

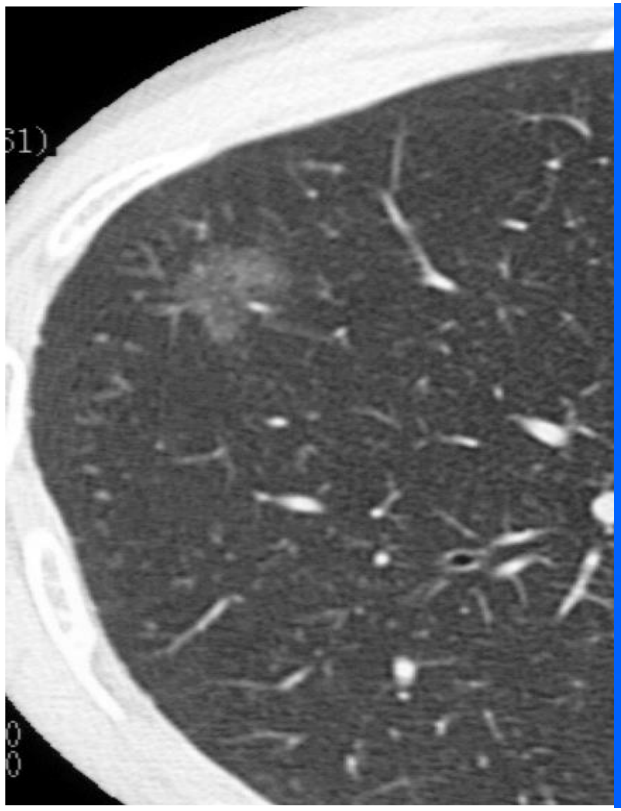
No stromal, vascular or pleural invasion or STAS

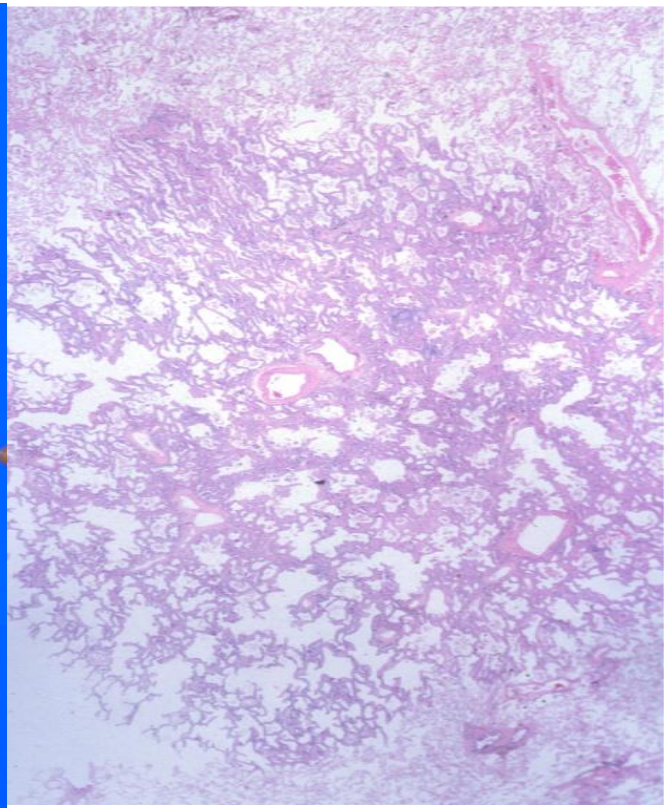
Adenocarcinoma cells line alveolar walls in a continuous layer; tufting and overlapping may be present.

- ***Desirable:***

Nuclear atypia and alveolar septal thickening are variable

Adenocarcinoma-in-situ





- F/46, 8mm pGGO on HRCT
- Frozen Section Diagnosis: AIS
- Limited Surgery
- Lung Cancer (2008) & J Thorac Oncol (2010)

Minimally Invasive Adenocarcinoma

Definition

Minimally invasive adenocarcinoma is a small (≤ 30 mm), solitary adenocarcinoma with a predominantly lepidic pattern and ≤ 5 mm invasion

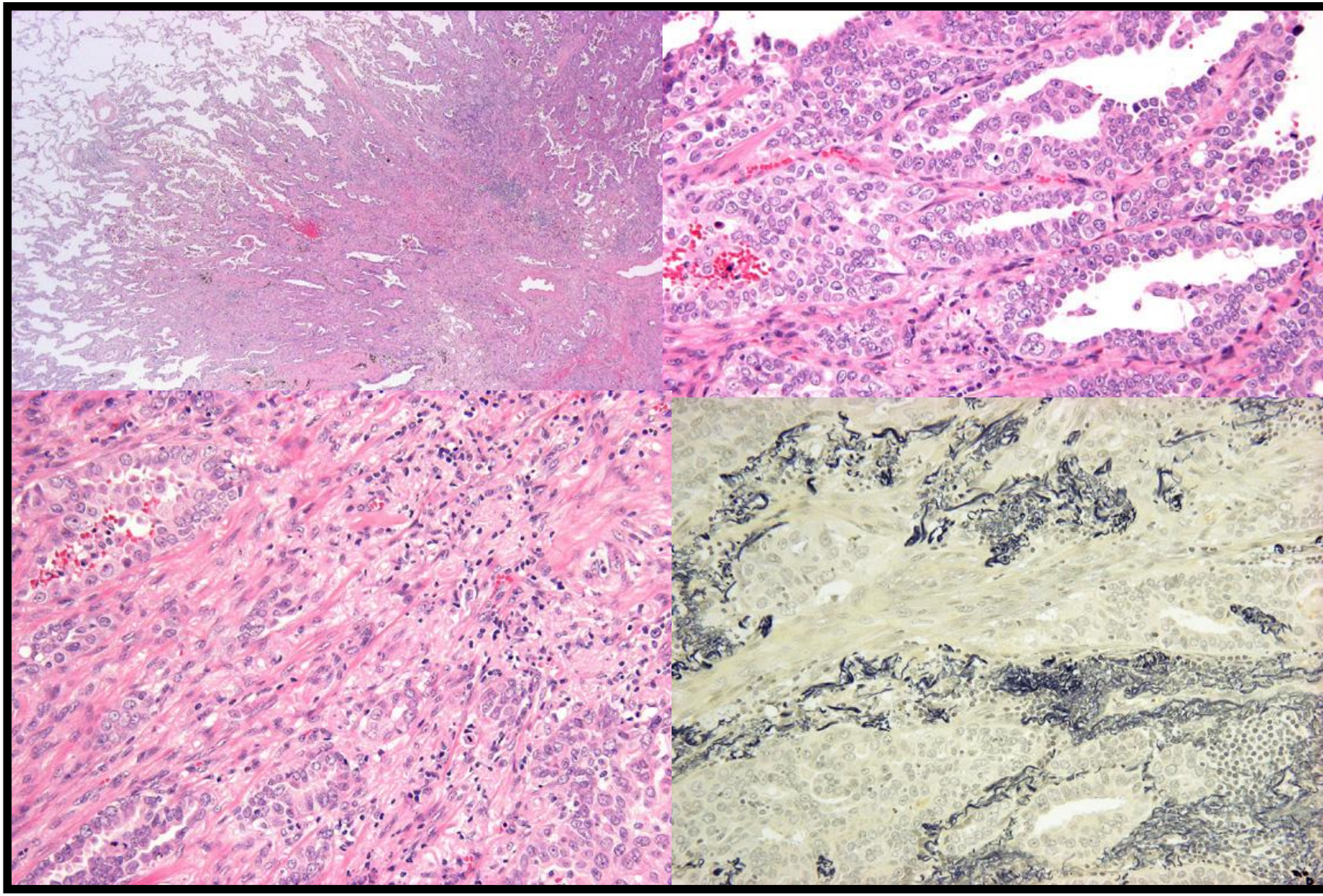
Essential:

- A small ≤30 mm lepidic predominant tumour with an invasive component ≤ 5 mm
- Any histologic subtype other than a lepidic pattern
- No lymphovascular invasion, pleura, STAS or tumour necrosis

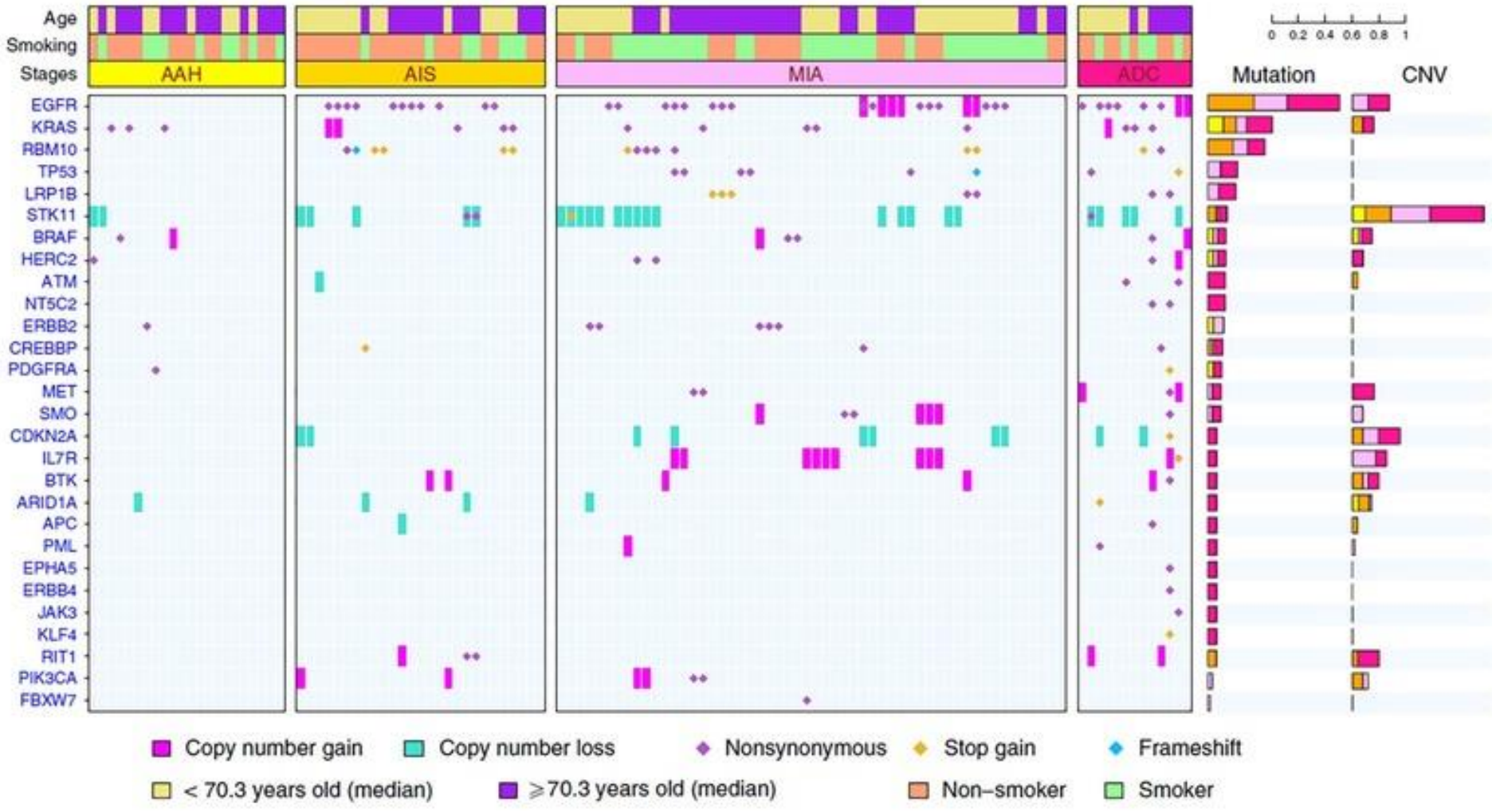
Desirable:

The percentages of each of the invasive components should be recorded.

The tumour can be nonmucinous (type II pneumocytes or club cells), and rarely can be mucinous or mixed mucinous and non-mucinous



Gene mutation in AAH-AIS-MIA- ADC



Hu, X., et al. (2019). Nat Commun 10(1): 2978

What is invasion in lung carcinoma?

- **Histological patterns other than lepidic**
- **Myofibroblastic stroma associated with invasive tumour cells (neofibroplasia)**
- **vascular or pleural invasion**
- **Spread in air spaces (STAS)**

Invasive Non-mucinous Adenocarcinoma

Definition

Invasive non-mucinous adenocarcinomas with morphological or immunohistochemical evidence of glandular differentiation

Essential:

Malignant epithelial tumour with

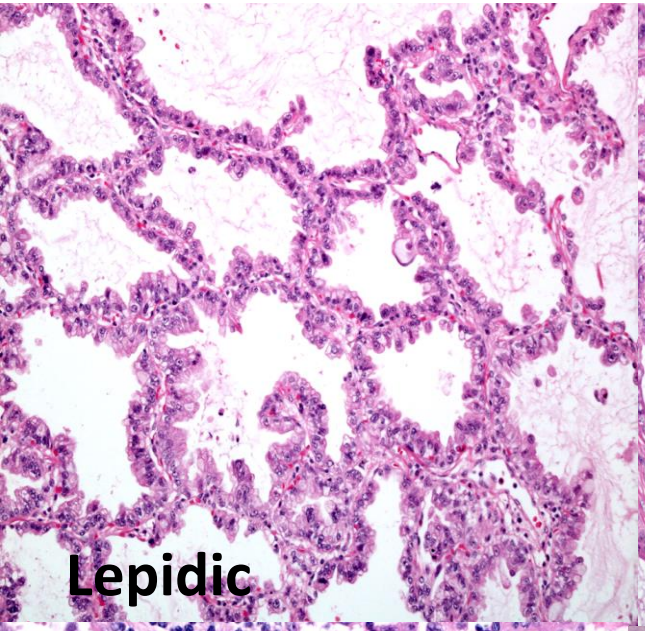
- glandular differentiation by architecture
- a pure solid pattern with:
- a) IHC expression of pneumocyte markers (TTF1 or Napsin A) or
- b) histochemical demonstration of intracytoplasmic mucin (at least 5 tumour cells/2HPF)

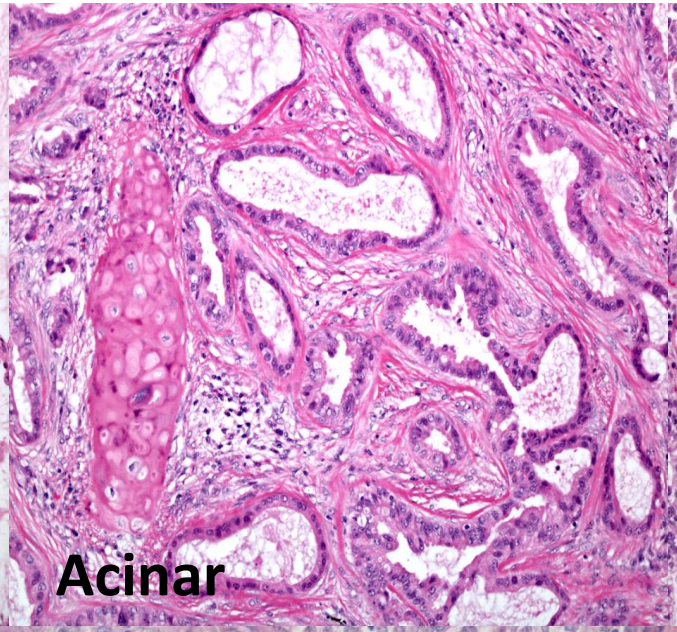
The tumours are classified according to their predominant pattern

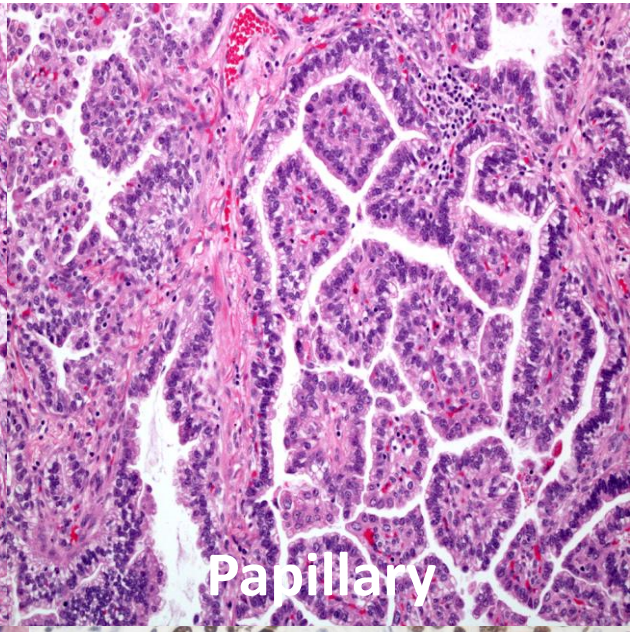
Desirable:

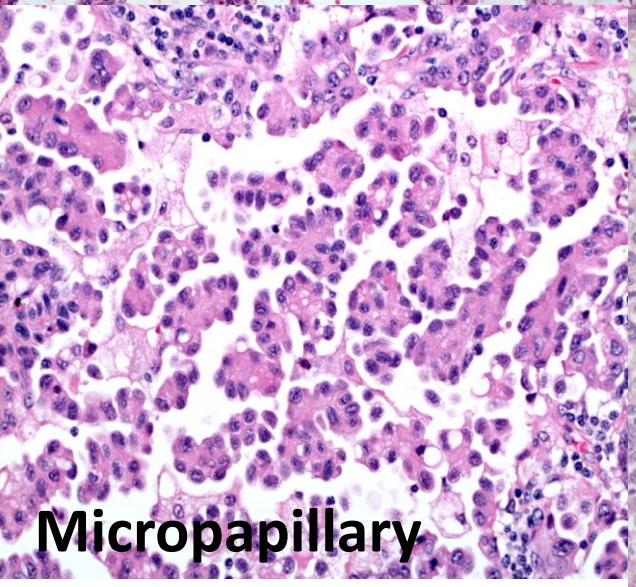
Record the percentages of each histologic pattern in pathology reports to document the predominant histological pattern (subtype) and any components of high grade patterns to determine the tumour grade

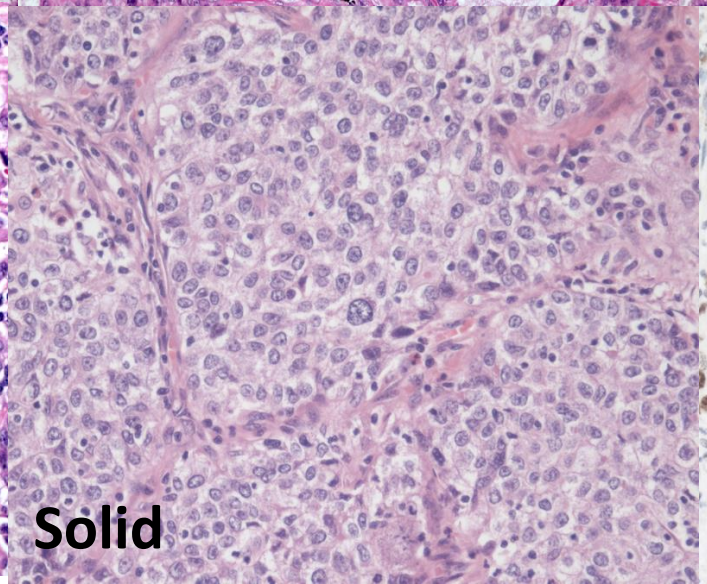
Patterns of Adenocarcinoma

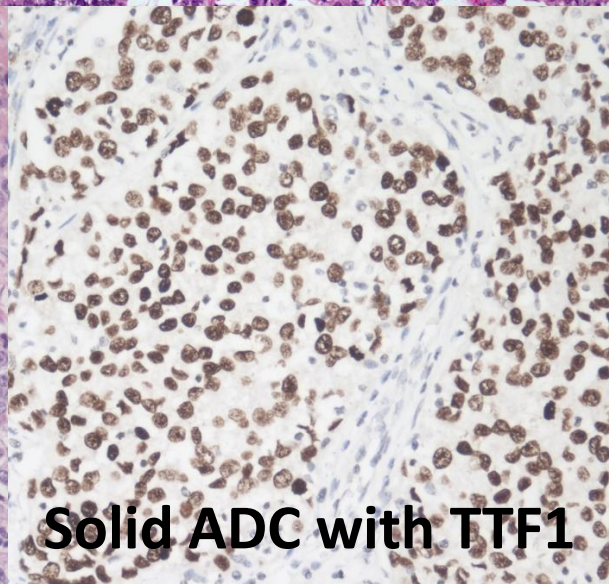




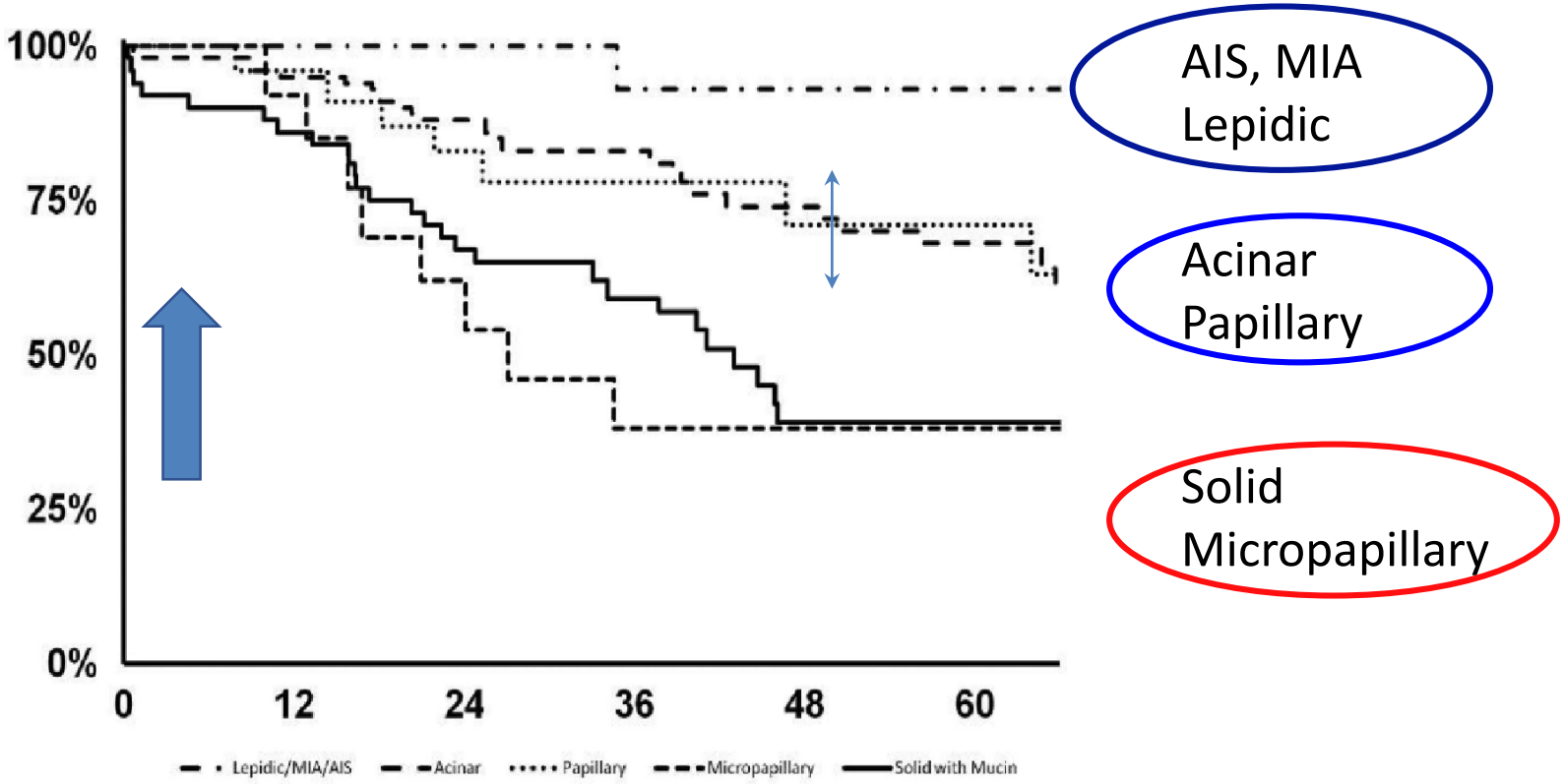








Survival outcomes vs predominant pattern in pulmonary adenocarcinoma



Yoshizawa A et al. Mod Pathol 2011; 24, 653-664 *Stage 1 only*
Russell PA et al. J Thorac Oncol 2011; 6,1496-1504 *Stages 1-3*
Warth A et al. J Clin Oncol 2012; Mar 5 epub *Stages 1-4*

Grading of Adenocarcinomas

- **Prognostic associations by predominant histologic pattern**

  favorable ; non-mucinous lepidic (histologic grade 1)

  intermediate : papillary, acinar (histologic grade 2)

  poor : solid and micropapillary (histologic grade 3)

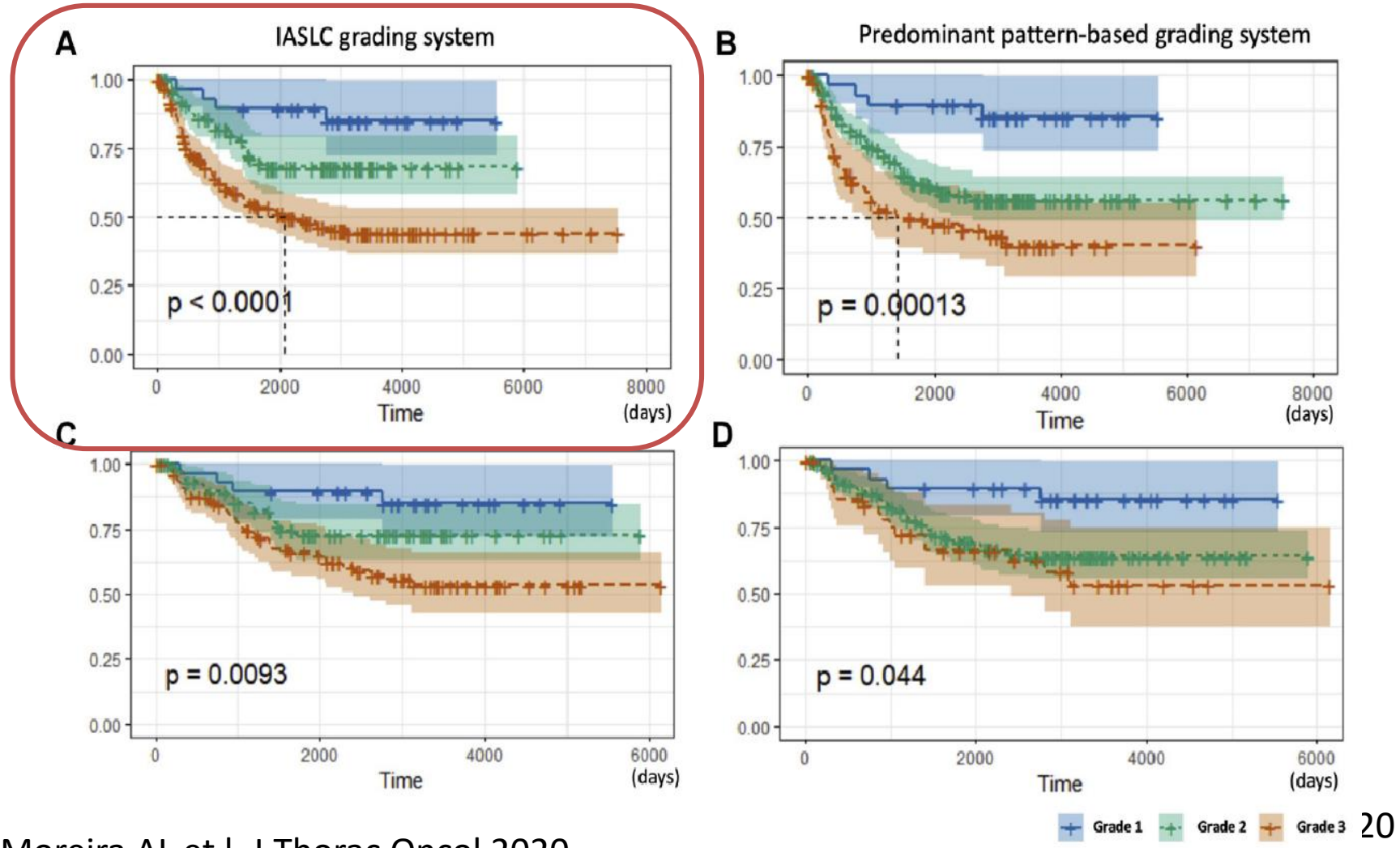
Proposed grading of resected invasive non-mucinous lung adenocarcinoma

Grade	Differentiation	Patterns
1	Well-differentiated	Lepidic-predominant with no or < 20% high-grade pattern
2	Moderately differentiated	Acinar or papillary-predominant with no or < 20% high-grade pattern
3	Poorly differentiated	Any tumour with ≥ 20% high-grade pattern (solid, micropapillary, cribriform, or complex glandular pattern[a])

[a]Fused glands or single cells infiltrating in a desmoplastic stroma.

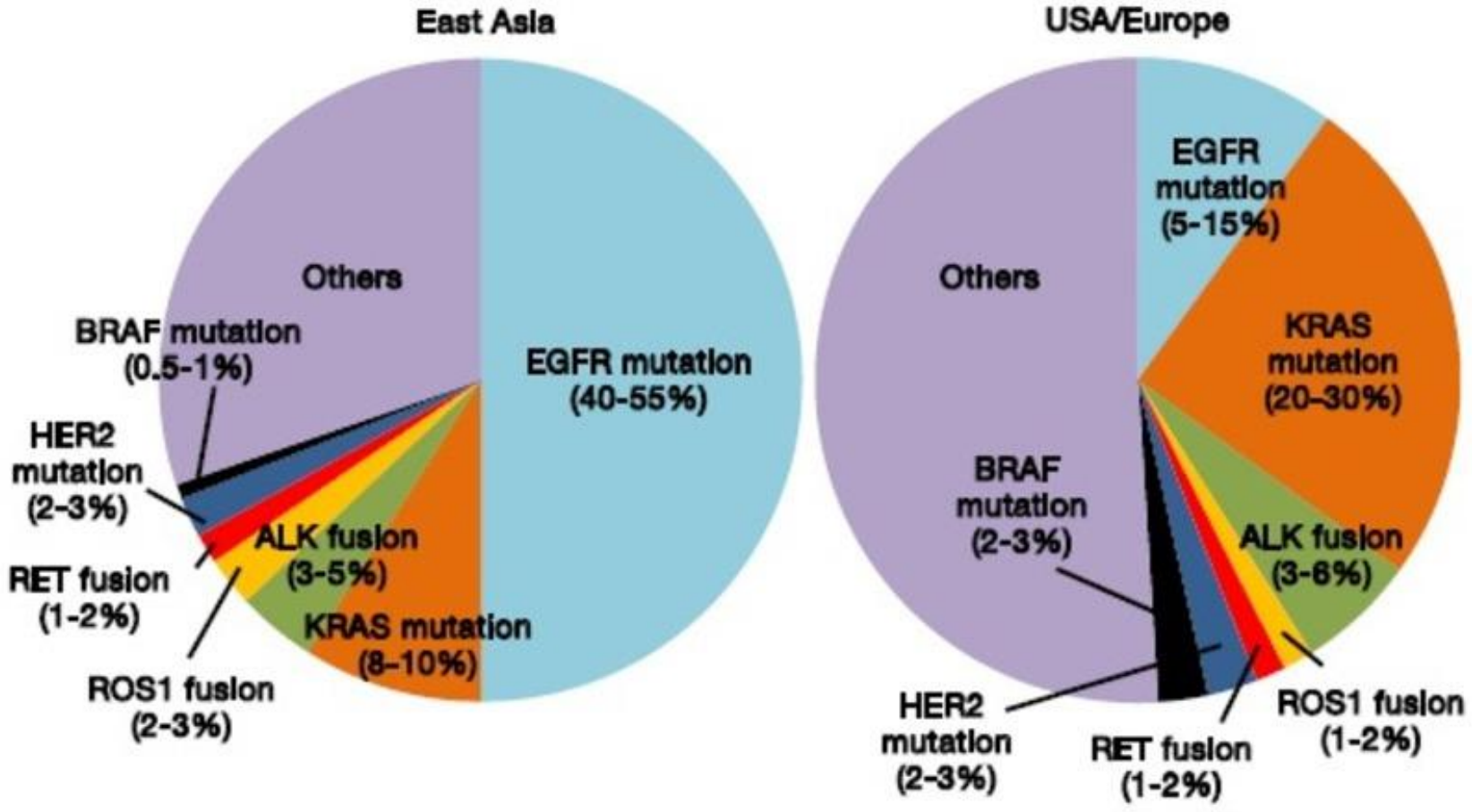
Moreira AL et l. J Thorac Oncol 2020

A Grading System for Invasive Adenocarcinomas : A Proposal of IASLC Pathology Committee



Moreira AL et l. J Thorac Oncol 2020

Genomic alterations in Adenocarcinomas



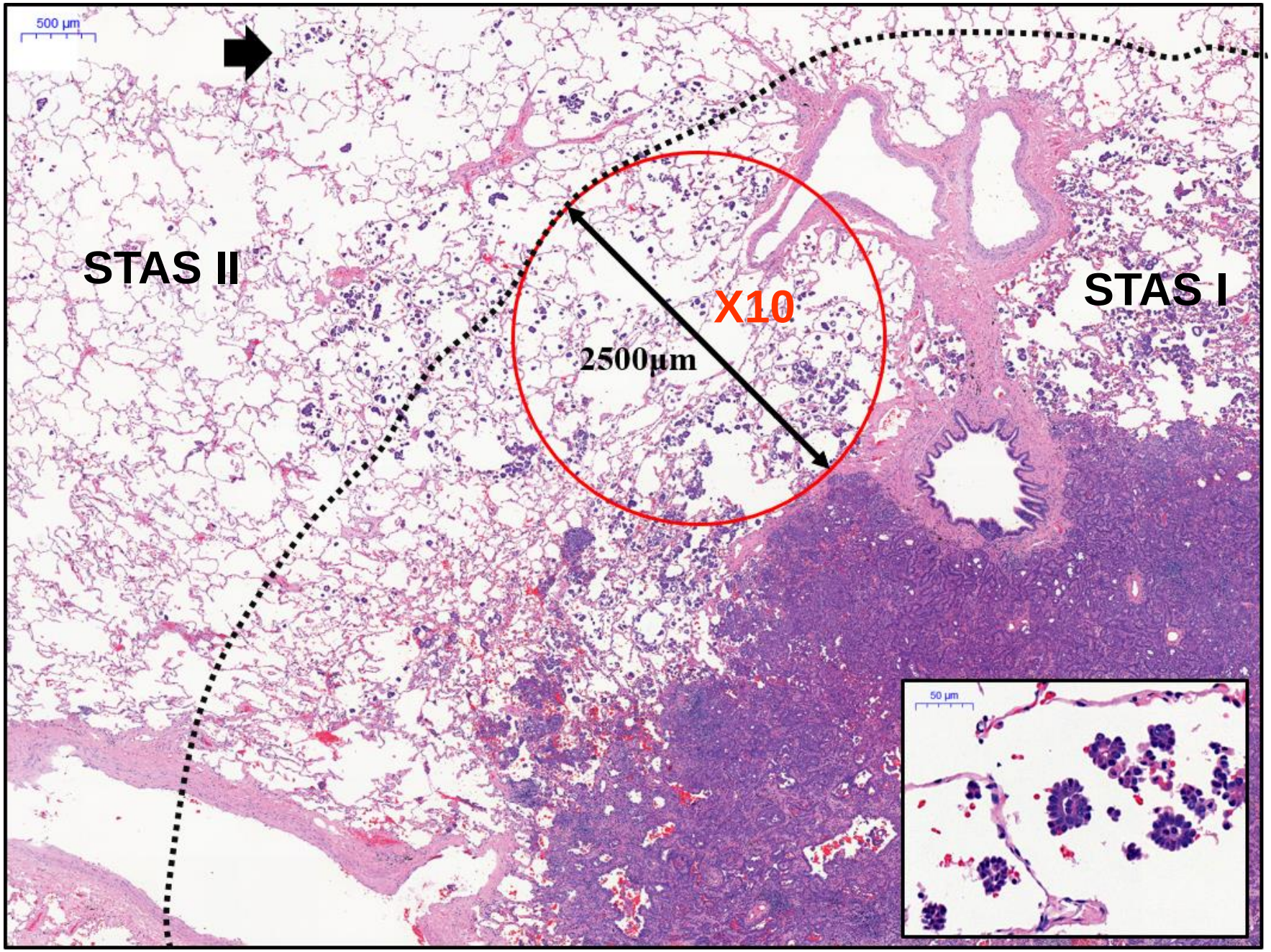
Translational Lung Cancer Research. 2015

Questionable Reproducibility for patterns and invasive size

- AIS vs MIA
- Measurement of Invasion
- Predominant patterns
- STAS vs Artifact

WHO subdiagnostic distribution

pathologist	aci	papi	lepidic	Solid	micopapi	total
A	3360	2420	3505	2320	1655	13300
B	2845	3462	3385	2950	623	13300
C	1885	3990	4077	2545	763	13300
D	1250	1973	6353	2497	1197	13300
E	2040	2985	5345	2270	630	13300
F	2785	395	6259	2500	1471	13300



Han YB et al., Mod Pathol 2020 (epub)

In Adenocarcinoma

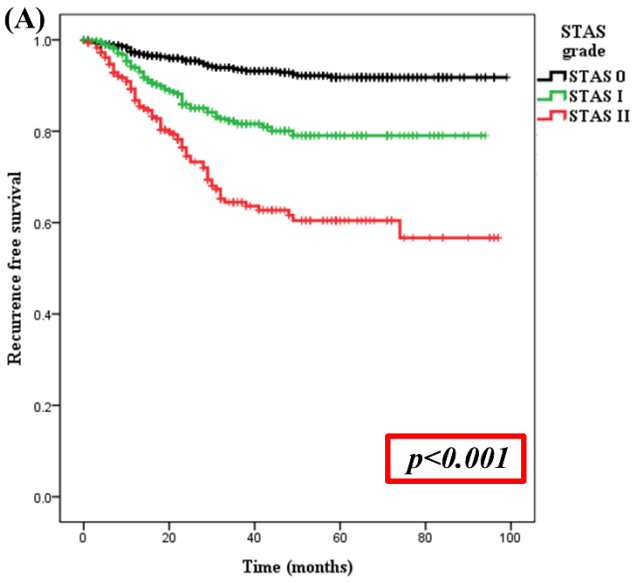
Characteristics	Presence of STAS (n=1544) Absent n (%)	Present n (%)	p value	Grade of STAS (n=684) Gr I n (%)	Gr II n (%)	p value
Necrosis			<0.001			<0.001
Absent	790 (62.9)	466 (37.1)		292 (62.7)	174 (37.3)	
Present	70 (24.3)	218 (75.7)		101 (46.3)	117 (53.7)	
Pathologic stage (AJCC 8th)			<0.001			<0.001
I	770 (66.7)	385 (33.3)		258 (67.0)	127 (33.0)	
II	49 (27.2)	131 (72.8)		73 (55.7)	58 (44.3)	
III	31 (19.5)	128 (80.5)		46 (35.9)	82 (64.1)	
IV	10 (20.0)	40 (80.0)		16 (40.0)	24 (60.0)	
Extent of resection			<0.001			0.058
Limited resection	199 (79.0)	53 (21.0)		37 (69.8)	16 (30.2)	
Wedge resection	108 (78.3)	30 (21.7)		21 (70.0)	9 (30.0)	
Segmentectomy	91 (79.8)	23 (20.2)		16 (69.6)	7 (30.4)	
Radical resection	661 (51.2)	631 (48.8)		356 (56.4)	275 (43.6)	
Lobectomy	655 (51.3)	622 (48.7)		352 (56.6)	270 (43.4)	
Bilobecto						
Pneumonectomy	1 (16.7)	5 (83.3)		3 (60.0)	2 (40.0)	
Surgical approach			0.004			0.649
VATS	821 (56.6)	629 (43.4)		363 (57.7)	266 (42.3)	
Open	39 (41.5)	55 (58.5)		30 (54.5)	25 (45.5)	
Thoracotomy	19 (34.5)	36 (65.5)		19 (52.8)	17 (47.2)	
Conversion to open	17 (50.0)	17 (50.0)		9 (52.9)	8 (47.1)	
Sternotomy	3 (60.0)	2 (40.0)		2 (100.0)	0 (0.0)	

➔ **Associated with more aggressive features and higher stage**

n=1544

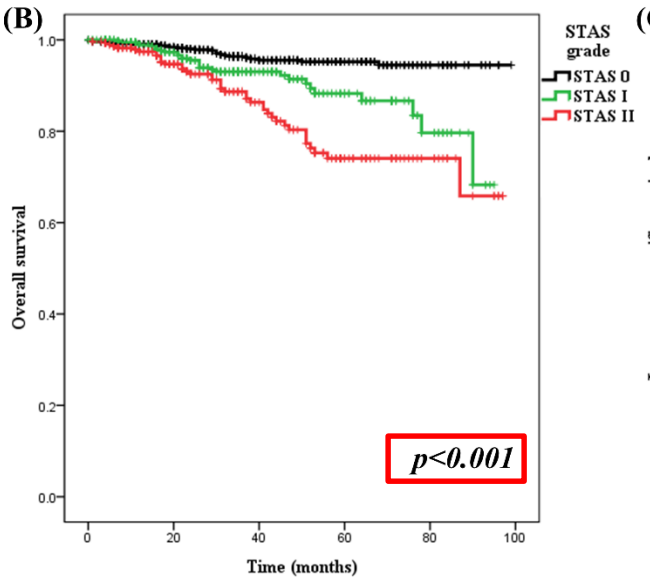
Survival analysis: In Adenocarcinoma

Recurrence free survival



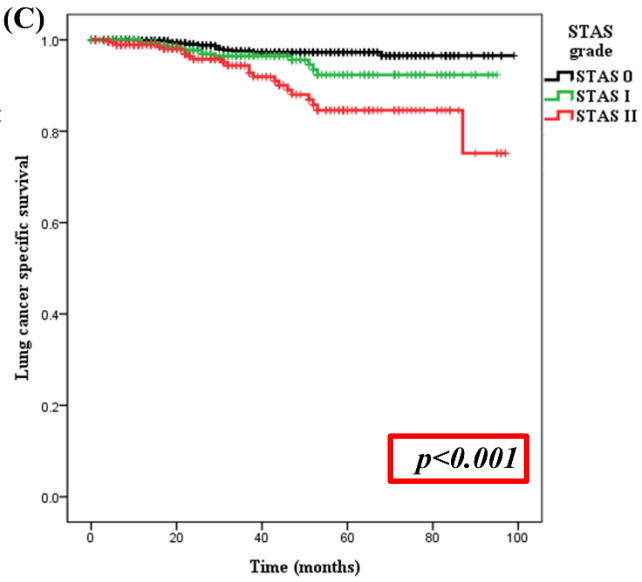
	HR (95% CI)	p value
STAS 0 vs. STAS I	2.847 (1.937-4.184)	<0.001
STAS 0 vs. STAS II	6.018 (4.191-8.641)	<0.001

Overall survival



	HR (95% CI)	p value
STAS 0 vs. STAS I	2.470 (1.461-4.175)	0.001
STAS 0 vs. STAS II	4.665 (2.862-7.604)	<0.001

Lung cancer specific survival



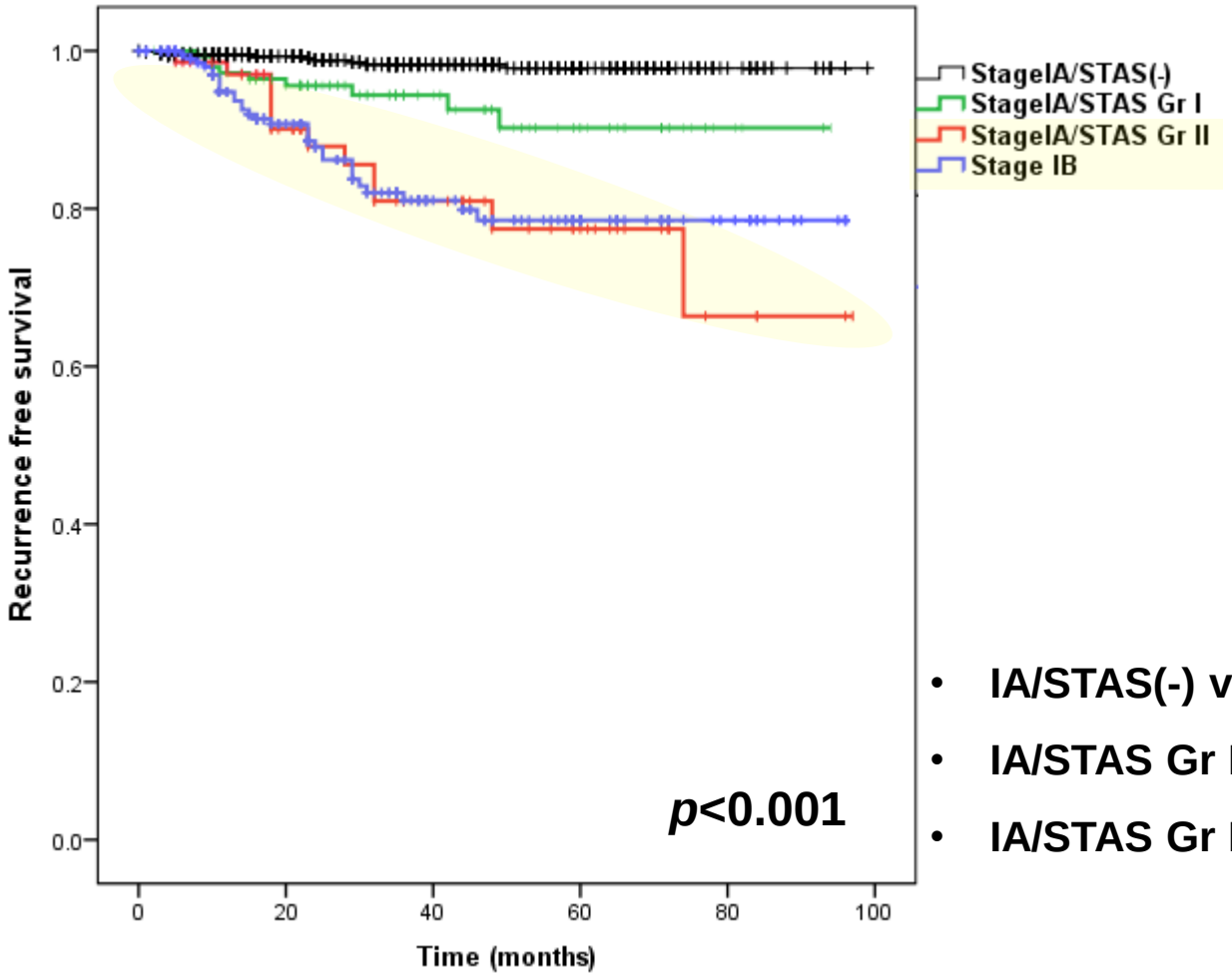
	HR (95% CI)	p value
STAS 0 vs. STAS I	2.152 (1.038-4.464)	0.039
STAS 0 vs. STAS II	4.677 (2.425-9.020)	<0.001

"Recurrence" included distant metastasis and locoregional recurrence

n=1089

Survival analysis: In stage I non-mucinous ADC

Recurrence free survival: Stage IA with STAS status vs. Stage IB



- **IA/STAS(-) vs. IA/STAS Gr I: *p*=0.001**
- **IA/STAS Gr I vs. IA/STAS Gr II: *p*=0.016**
- **IA/STAS Gr II vs. Stage IB: *p*=0.853**

"Recurrence" included distant metastasis and locoregional recurrence

Adenocarcinomas: many unresolved issues

- Reproducibility of invasive patterns
  - Lepidic pattern vs. Invasive pattern
  - Better criteria for invasiveness
  - Measurement of invasion (TNM)
- Grading of adenocarcinomas
- STAS

2021 WHO CLASSIFICATION OF LUNG NEUROENDOCRINE NEOPLASMS

- **Neuroendocrine carcinomas of the lung**
  - Small cell carcinoma
    - Combined SCLC
  - Large cell neuroendocrine carcinoma
    - Combined LCNEC
- **Neuroendocrine tumours of the lung**
  - Carcinoid tumour/Neuroendocrine tumour of lung
    - Typical carcinoid
    - Atypical carcinoid
- Precursor lesion
  - Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)

NEUROENDOCRINE CARCINOMA

SMALL CELL CARCINOMA

Definition: A malignant epithelial tumour composed of small cells with scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli, with a high mitotic count and frequent necrosis.

Most SCLCs express neuroendocrine markers.

Positive IHC for neuroendocrine markers (> 90% of cases)

Up to 25% of SCLC : combined with NSCC

Increased small cell carcinoma transfomation after TKI treatment for adenocarcinoma with *EGFR* mutations.

Essential *– SCLC:*

Tumour composed of small cells (usually less than 3 resting lymphocytes) with scant cytoplasm, and high mitotic count (> 10 mitoses/2 mm^2), often with necrosis

Tumour cells have finely granular nuclear chromatin

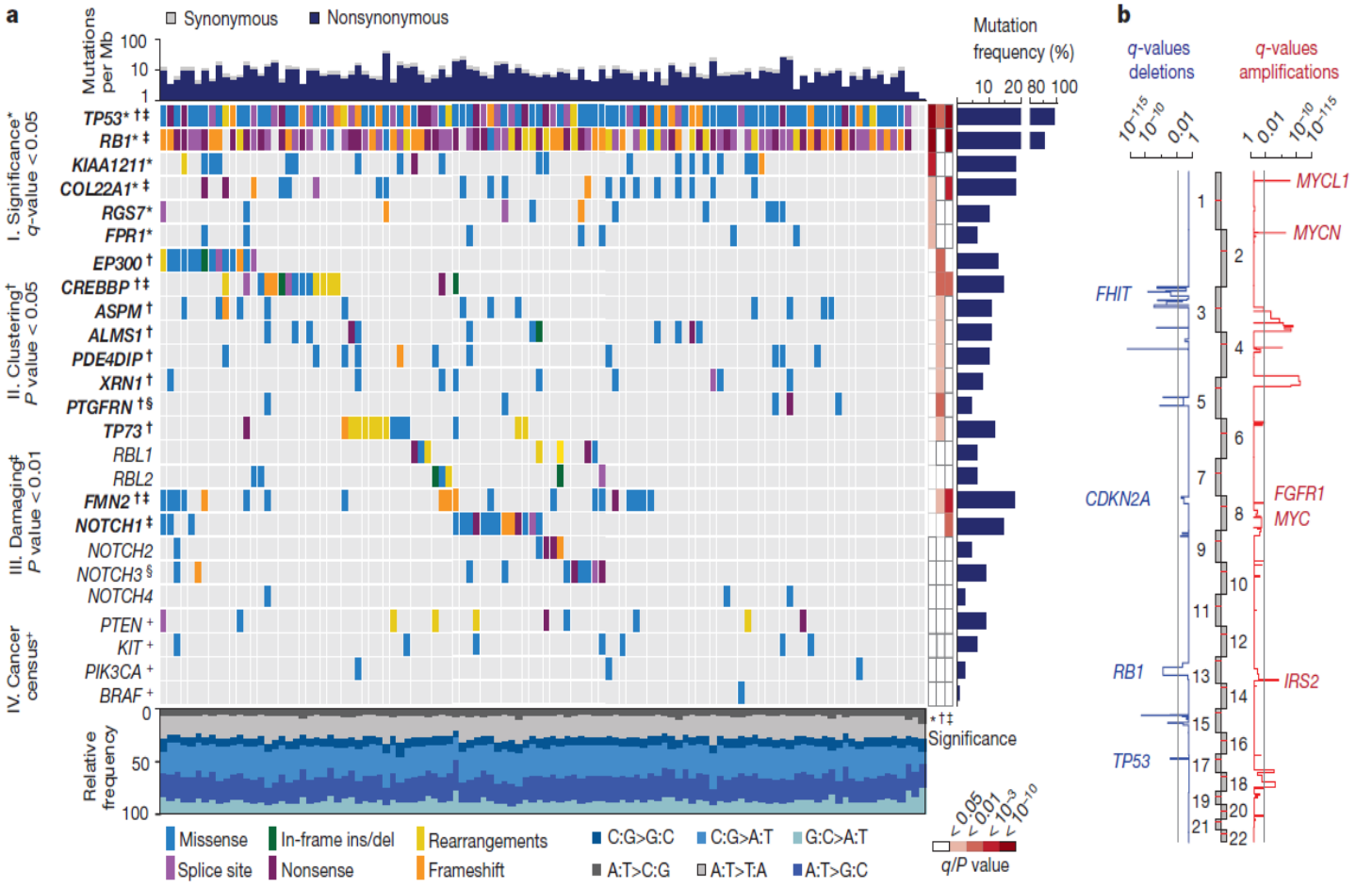
Nucleoli are absent or inconspicuous

Desirable:

Lack of diffuse p40 expression,

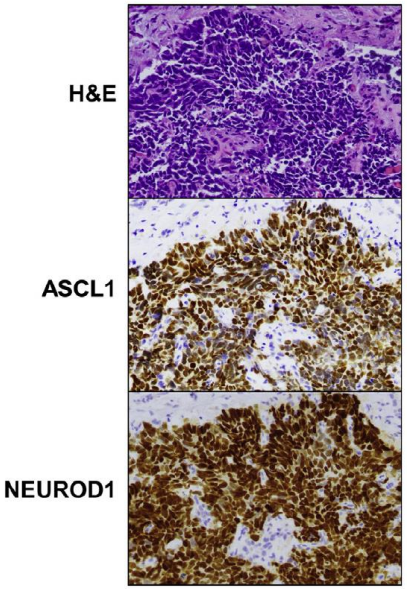
Comprehensive genomic profiles of small cell lung cancer

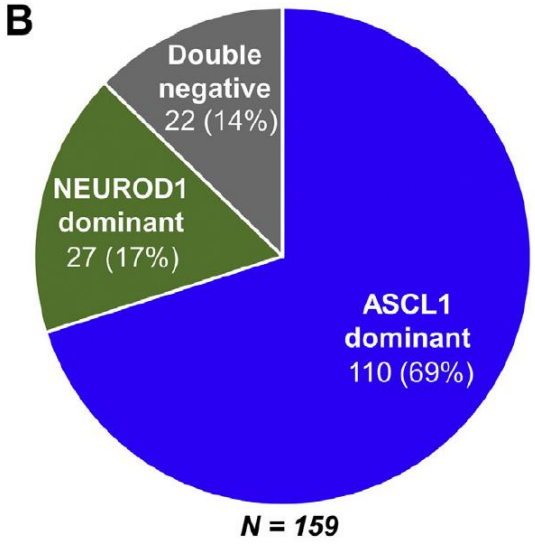
Universal inactivation of TP53 and RB

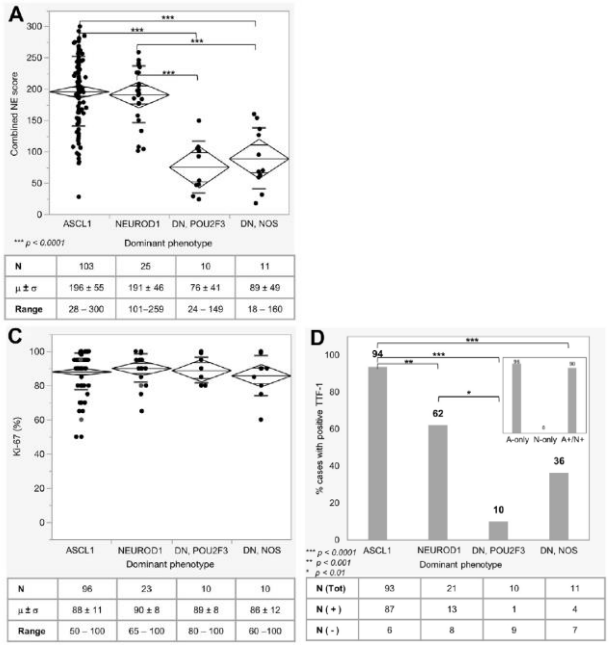


George J, Lim JS, Jang SJ, et al. *Nature* 2015;524:47-53.

SCLC subtypes defined by ASCL, NEUROD1, POU2F3, and YAP1







	ASCL1	NEUROD1	DN, POU2F3	DN, NOS
N	103	25	10	11
μ ± σ	196 ± 55	191 ± 46	76 ± 41	89 ± 49
Range	28 – 300	101–259	24 – 149	18 – 160

	ASCL1	NEUROD1	DN, POU2F3	DN, NOS
N	96	23	10	10
μ ± σ	88 ± 11	90 ± 8	89 ± 8	86 ± 12
Range	50 – 100	65 – 100	80 – 100	60 –100

	ASCL1	NEUROD1	DN, POU2F3	DN, NOS
N (Tot)	93	21	10	11
N (+)	87	13	1	4
N (-)	6	8	9	7

Baine MK, Hsieh MS, Lai WV, Egger JV, et al. J Thorac Oncol. 2020 Dec;15(12):1823-1835

NEUROENDOCRINE CARCINOMA

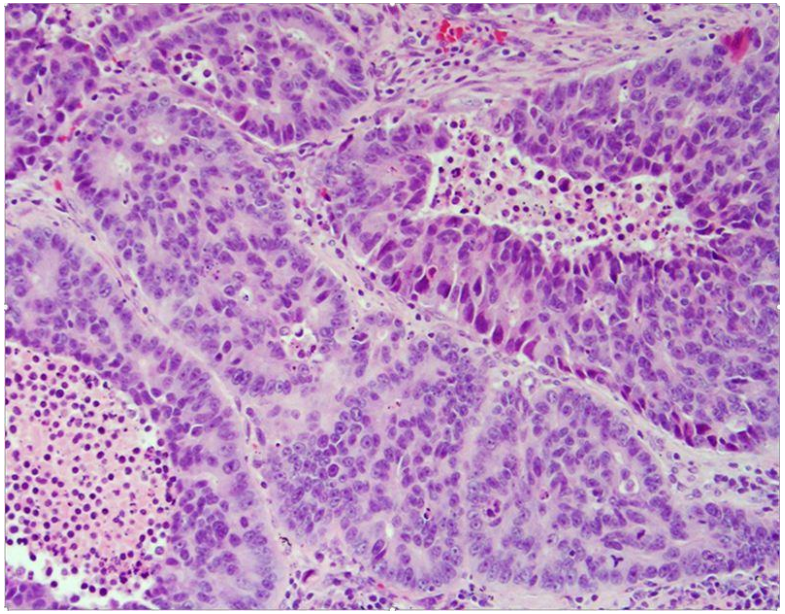
LARGE CELL NEUROEDOCRINE CARCINOMA

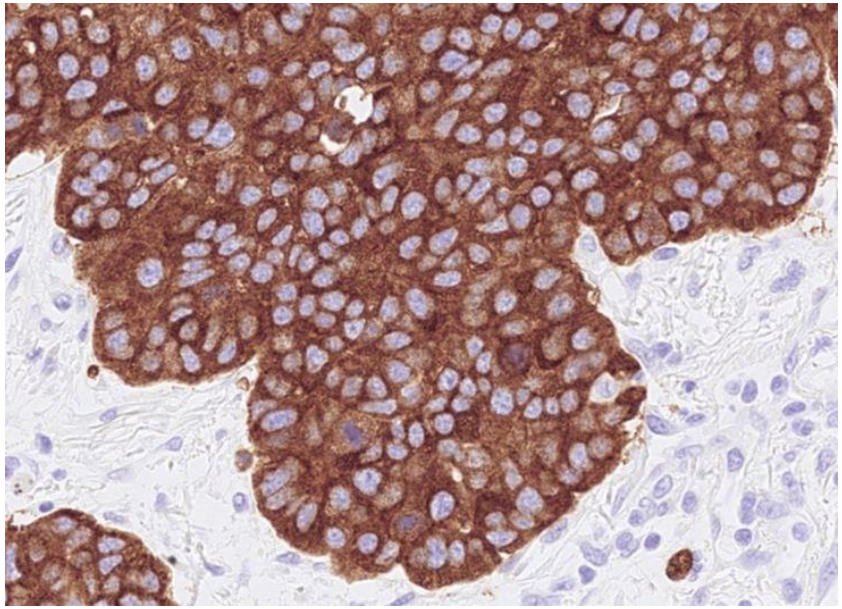
Definition: A high-grade non-small cell carcinoma with

-neuroendocrinemorphology

- mitotic count of > 10 mitoses/2 mm^2

- one or more neuroendocrine immunohistochemical markers.

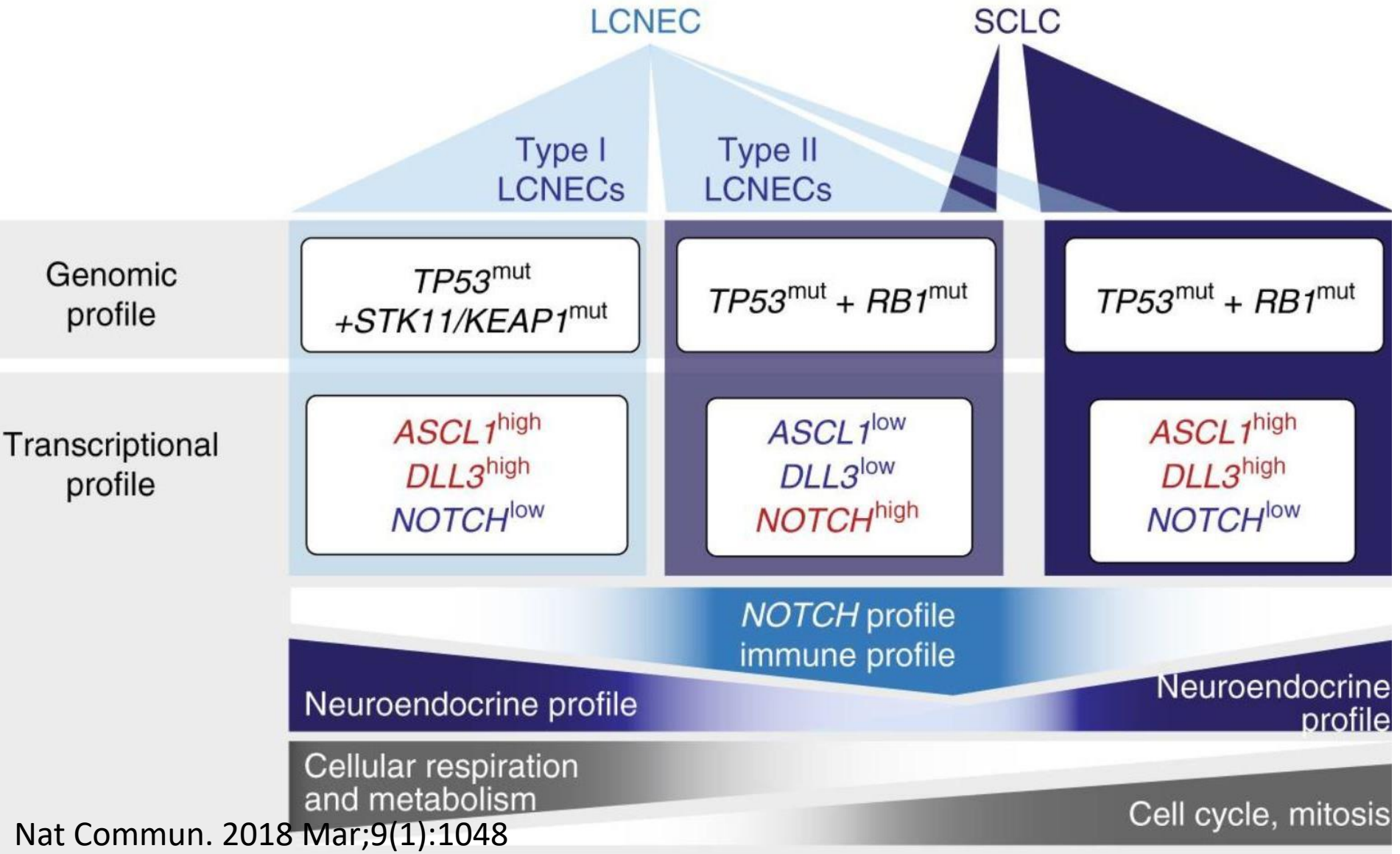




LARGE CELL NEUROEDOCRINE CARCINOMA

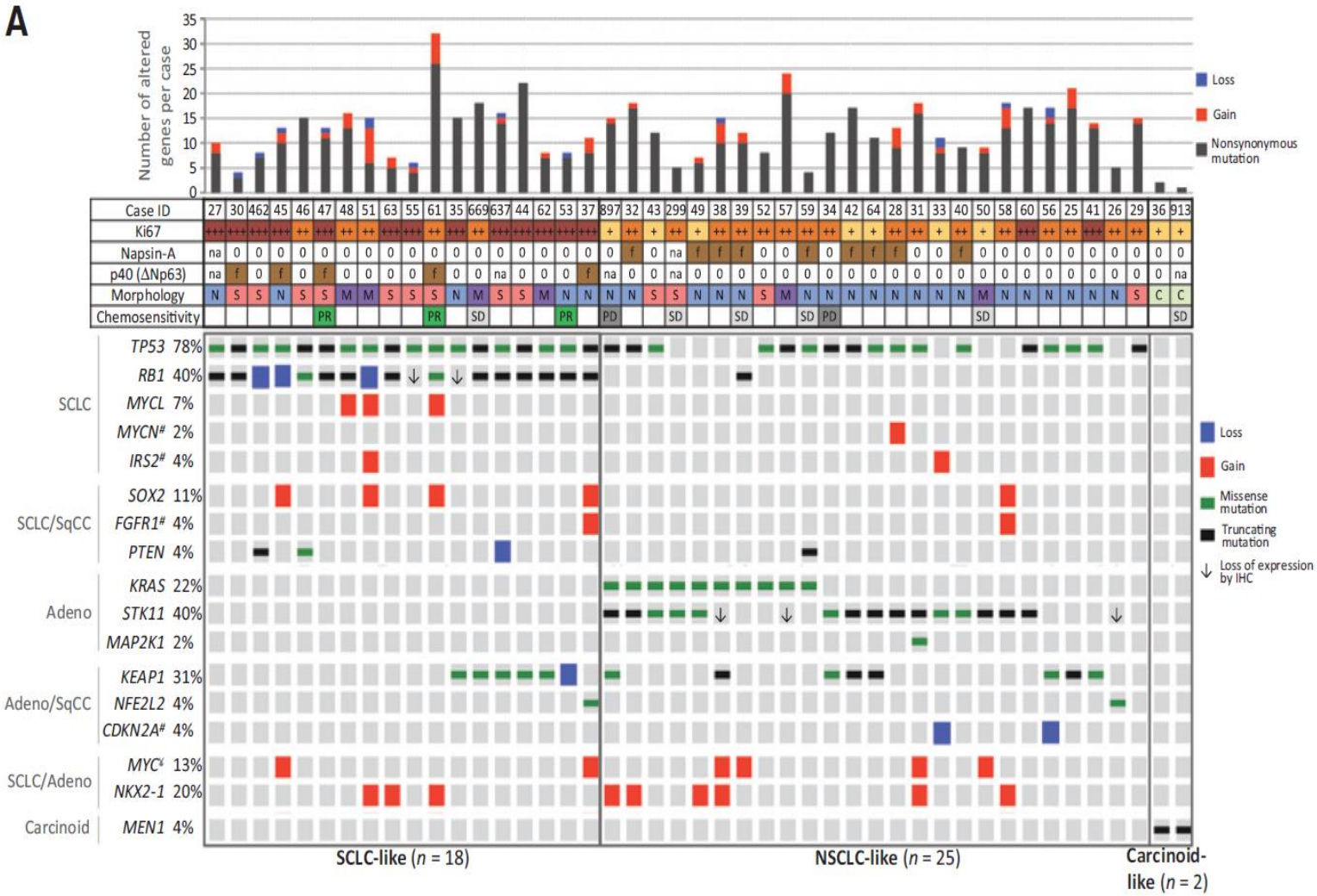
- ***Essential:***
- Neuroendocrine morphology: organoid nesting, trabeculae, peripheral palisading, rosettes
- Non-small cell cytology: prominent nucleoli and/or moderate to abundant cytoplasm, larger cell size than SCLC (> 3 lymphocytes), and chromatin may be either granular/stippled or vesicular
- High proliferation rate: > 10 mitoses/2 mm^2, with a median of 70 mitoses/2 mm^2
- Positive immunohistochemical staining for one or more neuroendocrine markers (other than NSE)
- ***Desirable:***
- Necrosis: generally in large confluent zones but may be limited to the centres of tumour nests
- High Ki-67 index: > 30%, generally 40–80%
- Negative p40 immunohistochemistry

Molecular subset of Neuroendocrine carcinomas



Nat Commun. 2018 Mar;9(1):1048

Molecular Profile of LCNEC : subdivisions

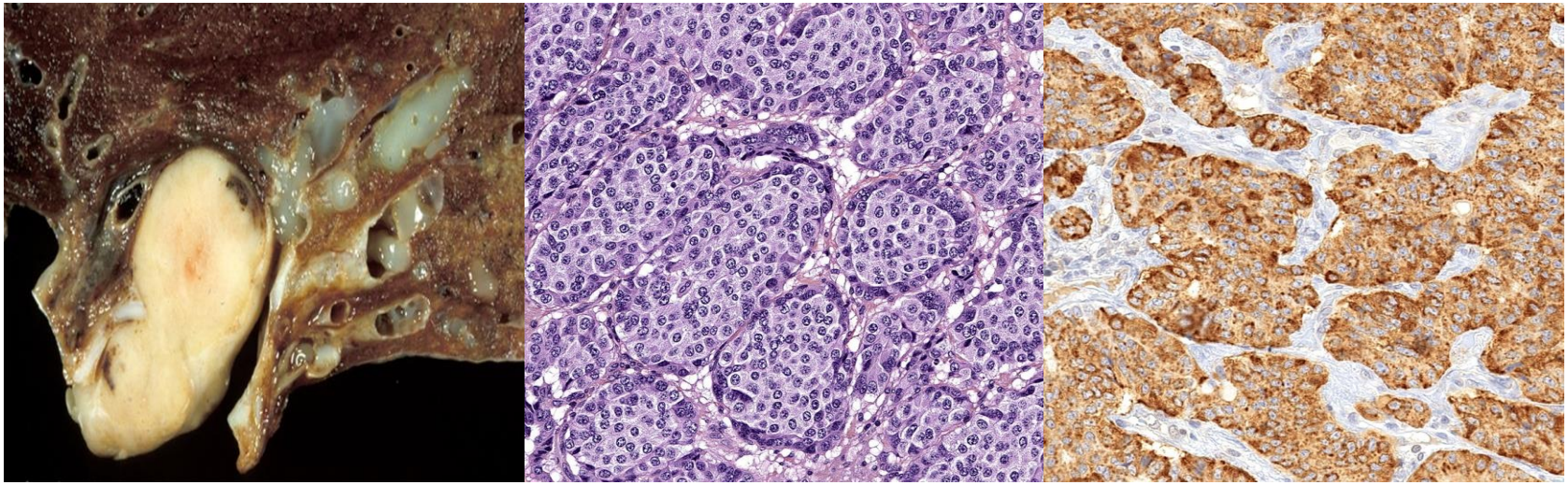


Clin Cancer Res. 2016;22(14):3618-3629.

Carcinoid tumour/Neuroendocrine tumour of lung

- Typical carcinoid
- Atypical carcinoid

- NE tumours by definition >5mm
- Divided into typical and atypical on basis of mitotic count (+/- Ki-67) and/or necrosis

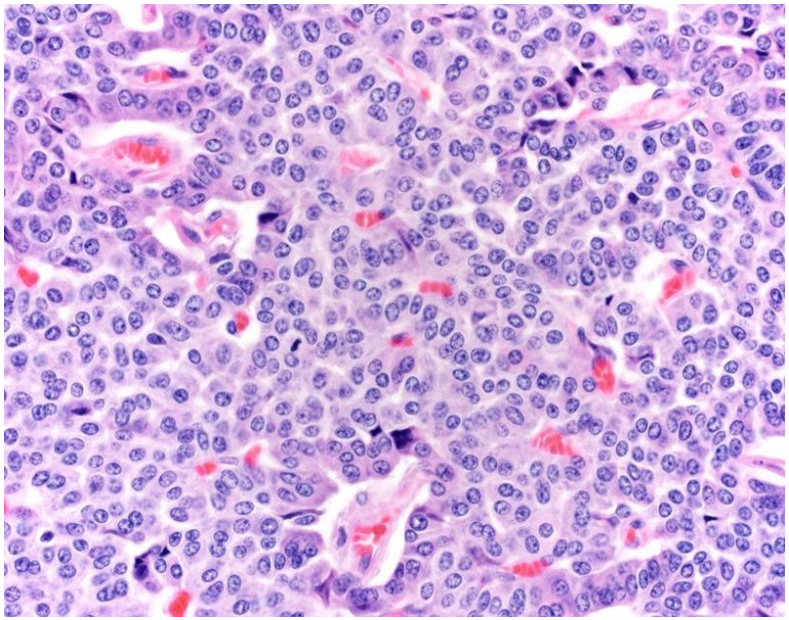


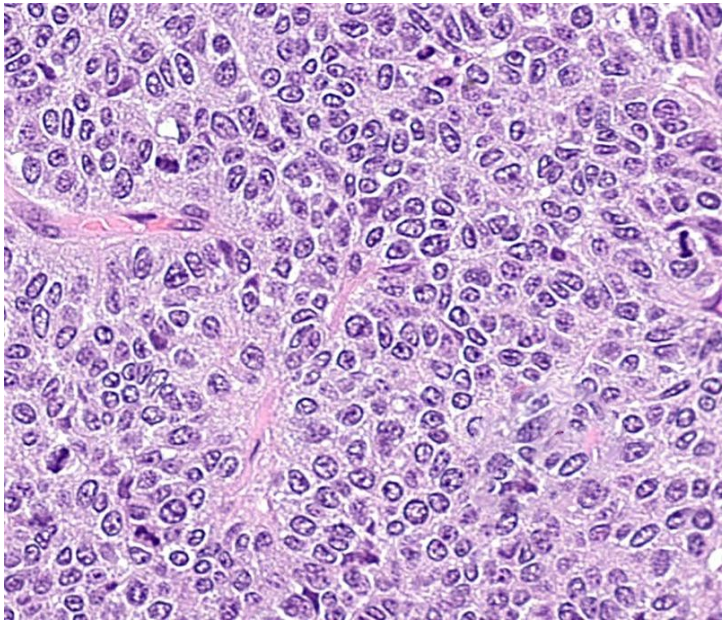
Neuroendocrine tumours of the lung

Introduction of the term “carcinoid tumour NOS”

1) In a small biopsy or cytology
2) Metastatic carcinoids
3) Only representative slides of a resected carcinoid tumour are provided for review

Atypical carcinoid tumor



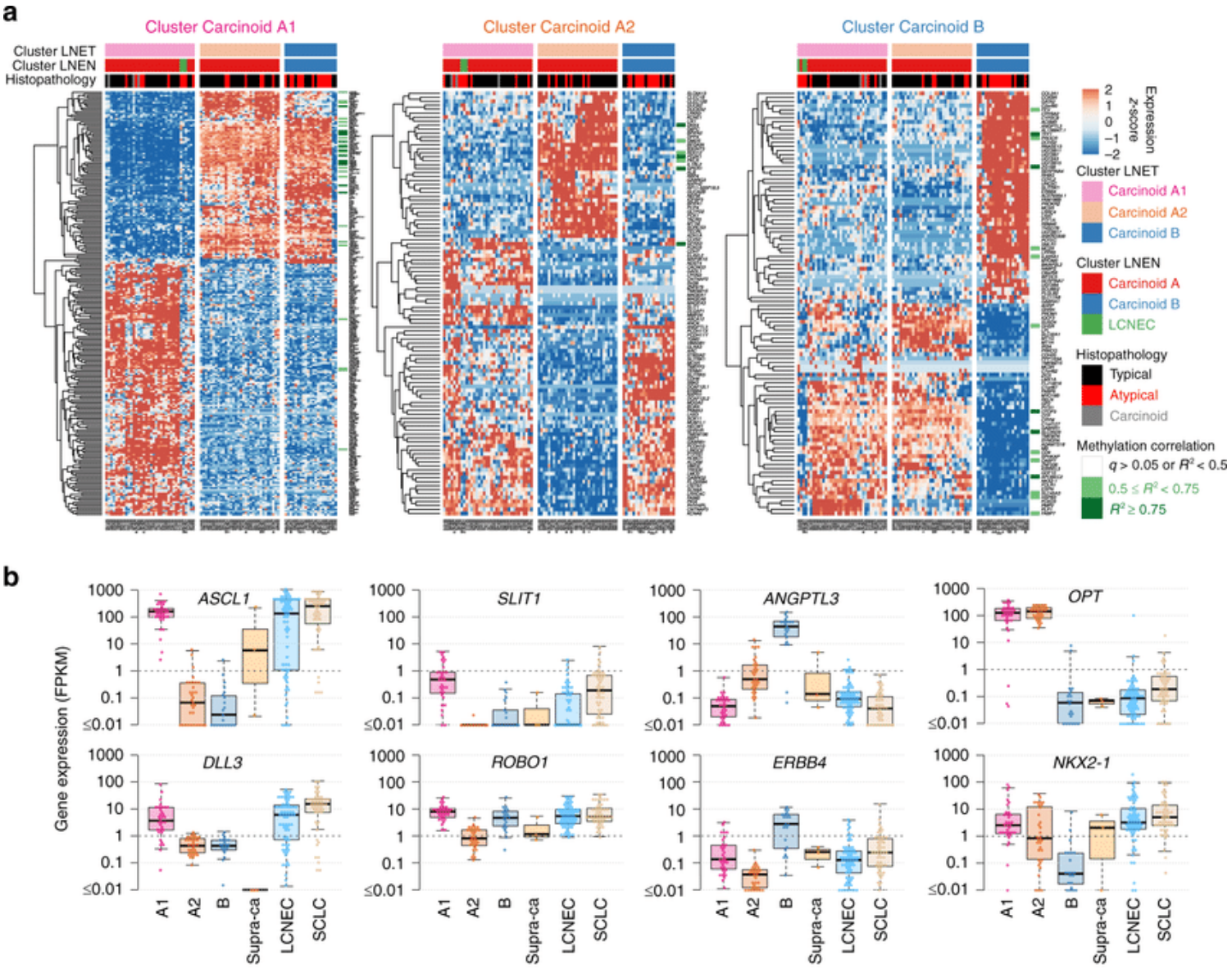


Carcinoid morphology with more than 10 mitoses per $2mm^2$

Is it a grade 3 NET but with CD-like morphology ?

Baine MK, Rekhtman N. Transl Lung Cancer Res. 2020;9:860-878.

Carcinoids –Molecular subdivisions



Alcala N, Leblay N, Gabriel AAG, et al.. Nat Commun. 2019;10(1):3407

Take Home Messages

- Histopathological definitions remain largely the same
- Grading system of Adenocarcinoma (20% rule)
- Structural changes for more consistency
- Significant advances in molecular subgroupings for NENs
- Newly included entities
  - SMARCA4-deficient undifferentiated tumour
  - Bronchiolar adenoma / ciliated muconodular papillary tumour