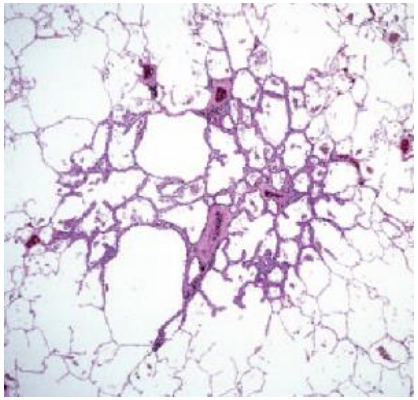
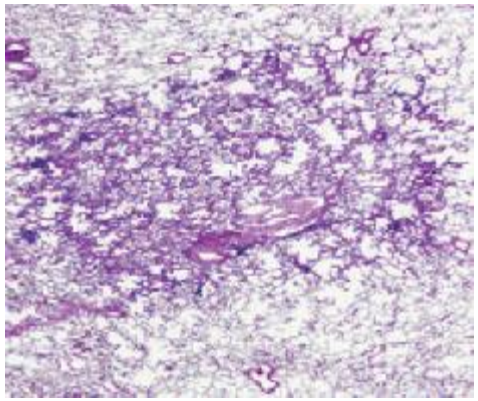
早期肺腺癌的病理診斷

台北榮總病理檢驗部
葉奕成
2019-12-07

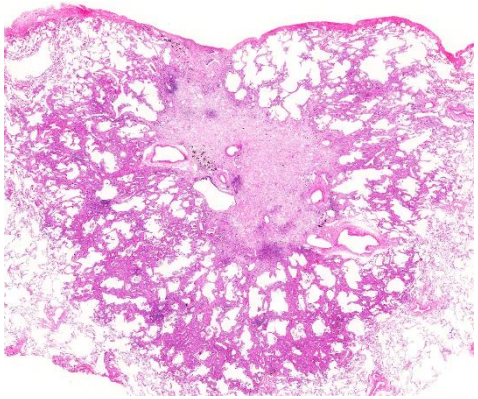
Sequential progression of lung adenocarcinoma

Atypical adenomatous hyperplasia (AAH) → **Adenocarcinoma in situ (AIS)** → **Minimally invasive adenocarcinoma (MIA)** → **Invasive adenocarcinoma (ADC)**

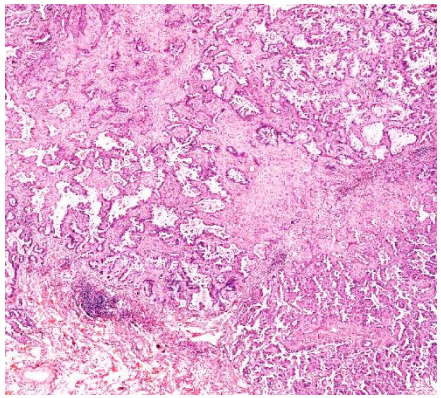




Preinvasive lesions (no stromal invasion)

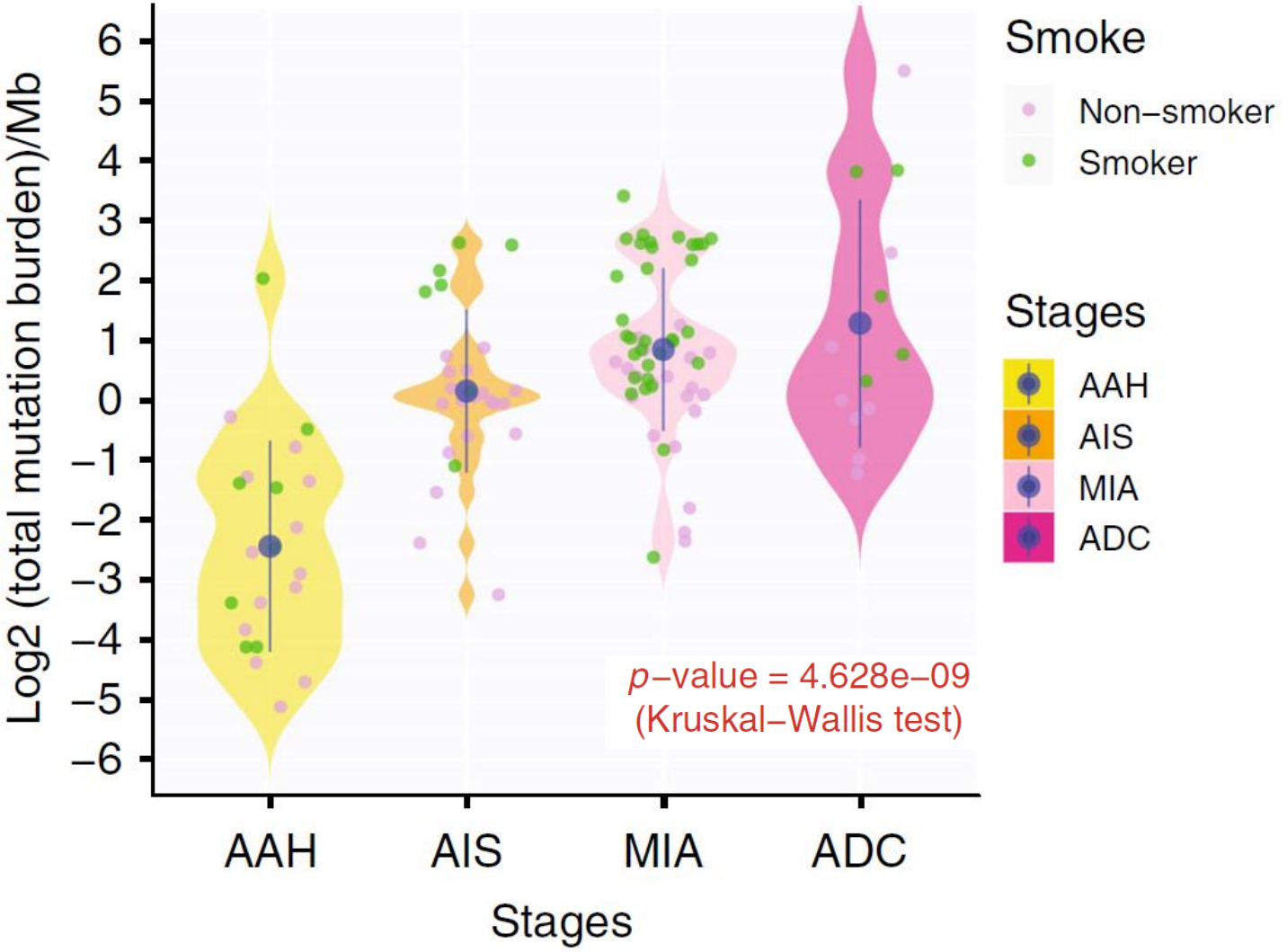


Minimally invasive (invasion <= 5 mm)



Invasive (invasion > 5 mm)

Progressive genomic evolution from AAH to ADC

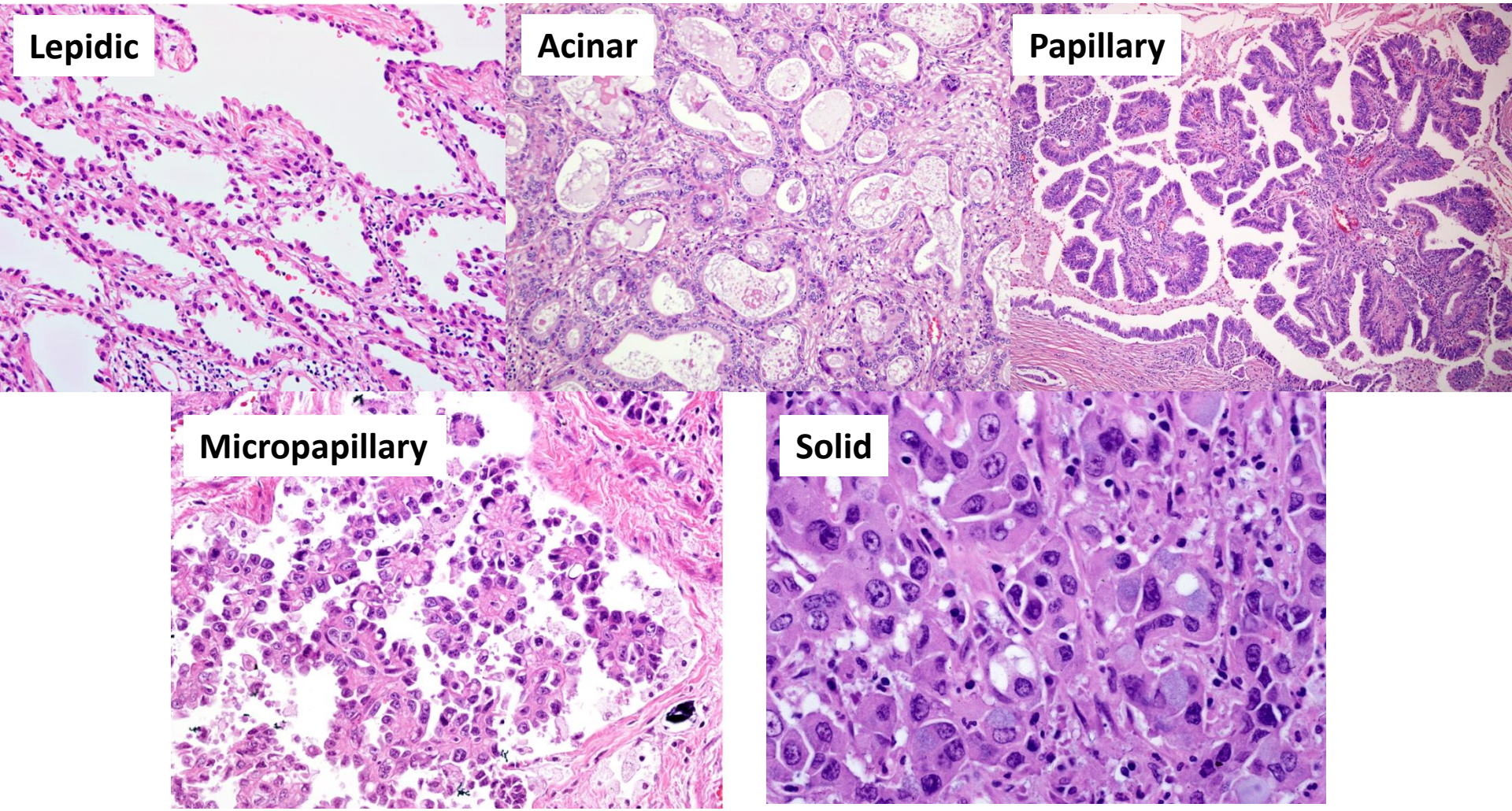


Nat Commun. 2019 Jul 5;10(1):2978.

Progressive genomic evolution from AAH to ADC

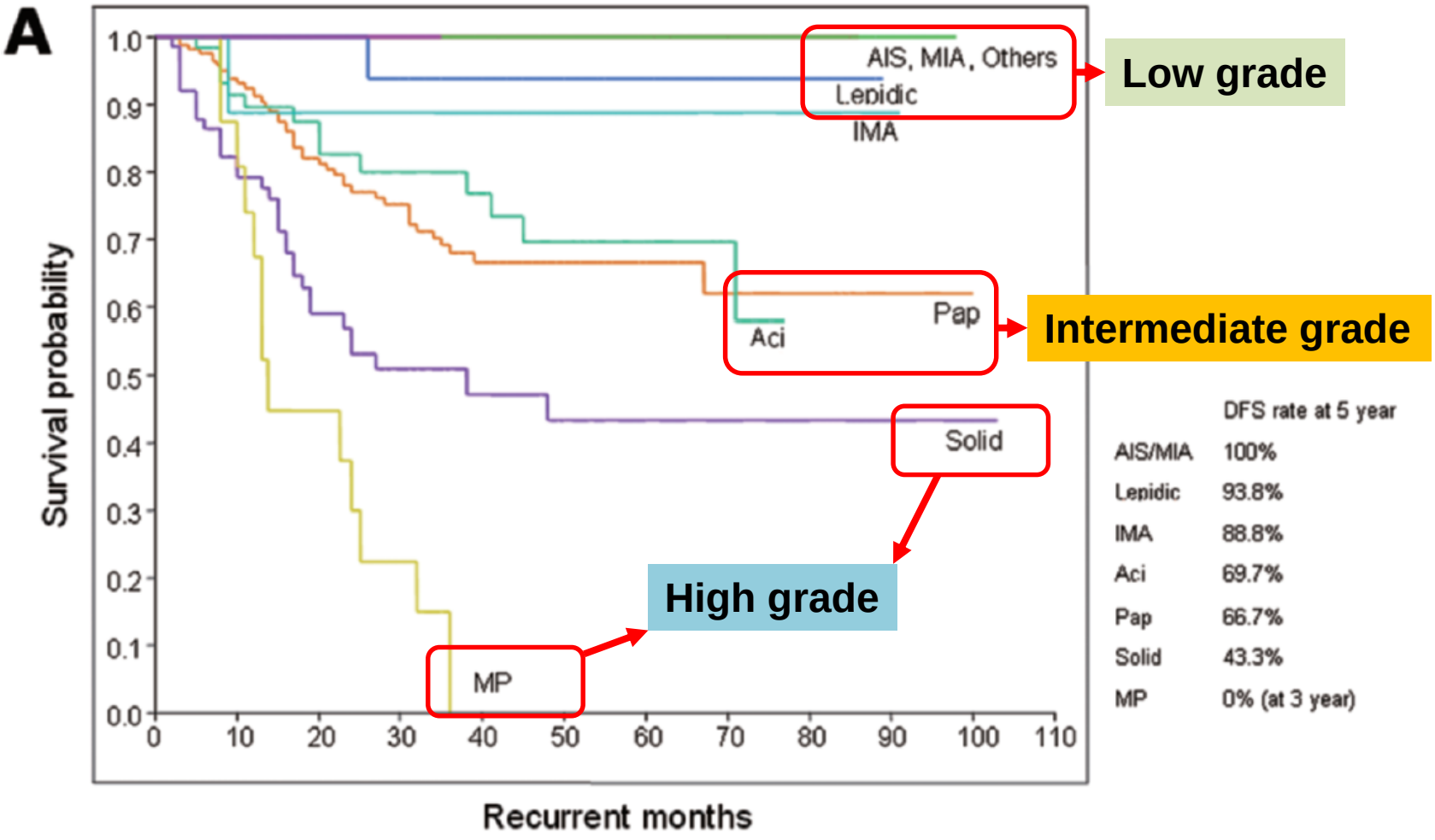
Nat Commun. 2019 Jul 5;10(1):2978.

Histology patterns of adenocarcinoma



Invasive ADC is classified by its predominant histology

Histologic subtype correlates with post-operative outcome



Yoshizawa A. et al. *J Thorac Oncol*. 2013 Jan;8(1):52-61

Surgical implications

- **Limited resection for early-stage lung adenocarcinomas?**

(1) AIS & MIA (& Lepidic predominant AdCA?)

– Limited resection may be appropriate

(2) Invasive predominant adenocarcinoma

– Limited resection may not be sufficient, especially for tumors containing high grade components

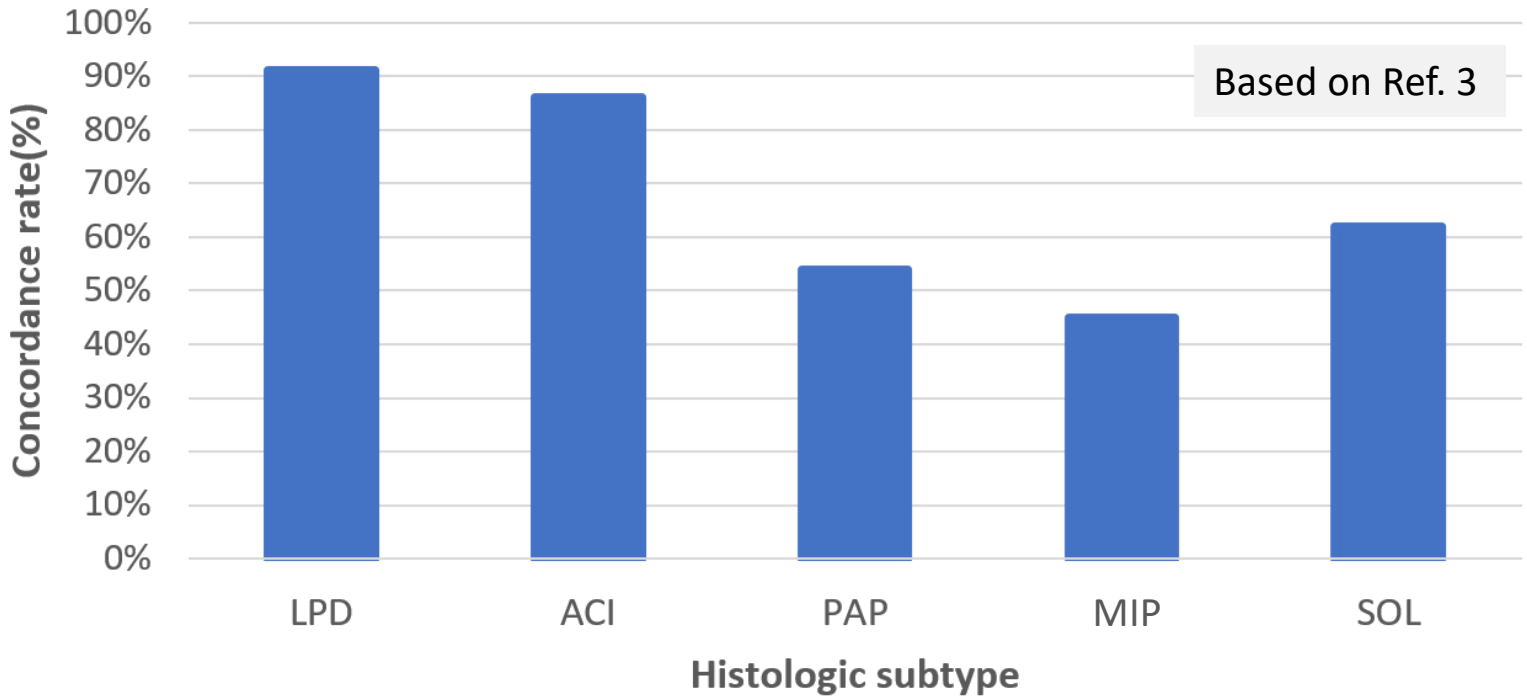
Challenges in pathological diagnosis of early small lung adenocarcinoma

- Preoperative biopsies
- Frozen sections
- Reproducibility and interobserver agreement

Histologic subtyping using preoperative biopsy specimen

Concordance between biopsy and resection:

- Histologic subtype → Overall accuracy = 58% - 77% [1-4]



1. J Thorac Cardiovasc Surg. 2017 Jul;154(1):332-339.
2. Lung Cancer. 2016 Apr;94:1-6.
3. Ann Thorac Surg. 2019 Aug;108(2):392-398.
4. Tsai et al. (VGH-TPE data, in submission)

Histologic subtyping using preoperative biopsy specimen

Concordance between biopsy and resection:

- Presence/absence of high grade patterns (MIP/SOL):

  → Low sensitivity, high specificity

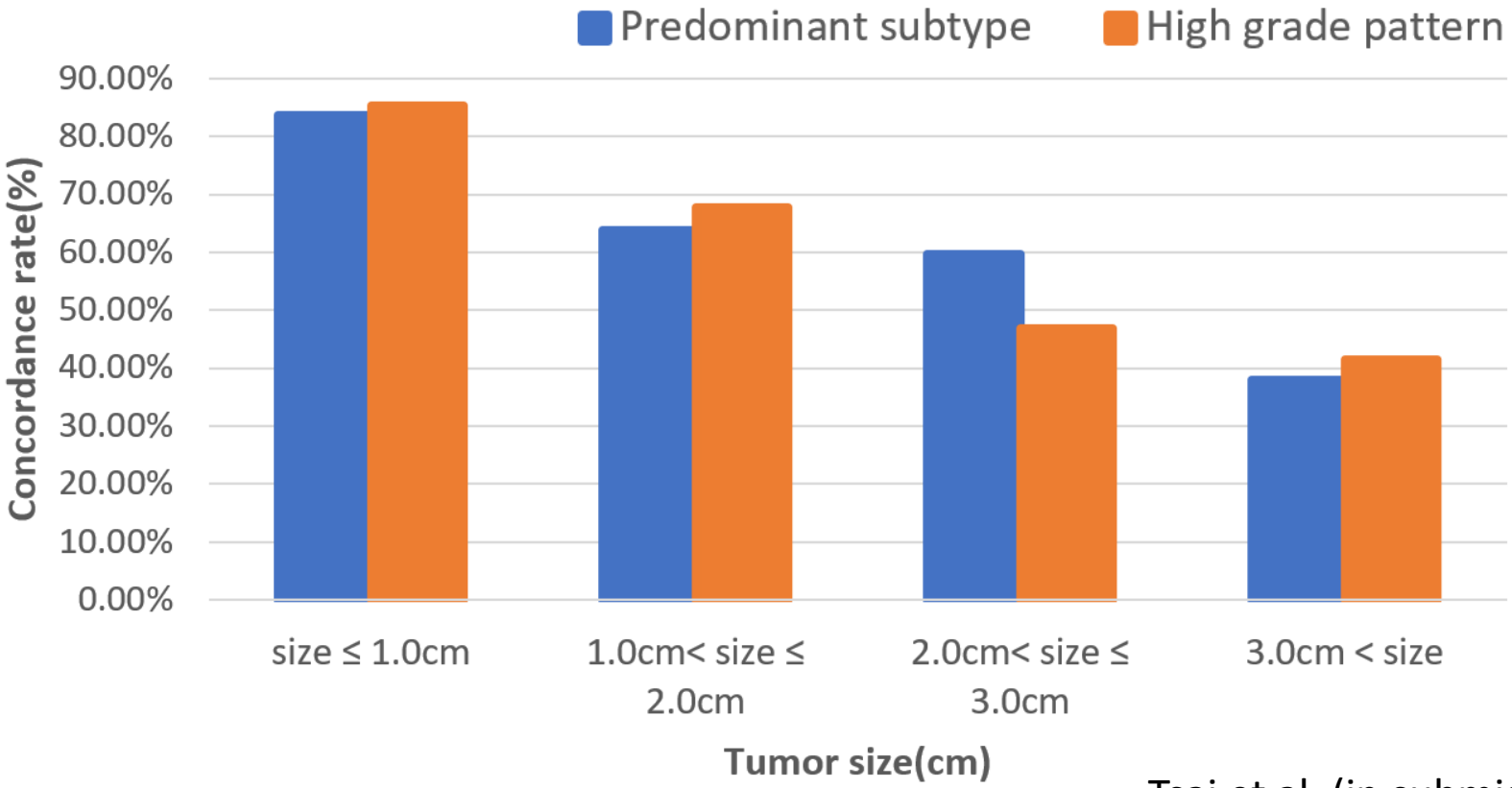
Histologic pattern	Sensitivity	Specificity
Micropapillary	7.8% – 30%	95% – 97.4%
Solid	14.6% – 44%	97% – 97.7%

J Thorac Cardiovasc Surg. 2017 Jul;154(1):332-339.
Lung Cancer. 2016 Apr;94:1-6.
Ann Thorac Surg. 2019 Aug;108(2):392-398.
Tsai et al. (VGH-TPE data, in submission)

Histologic subtyping using preoperative biopsy specimen

Factors influencing concordance:

(1) Tumor size

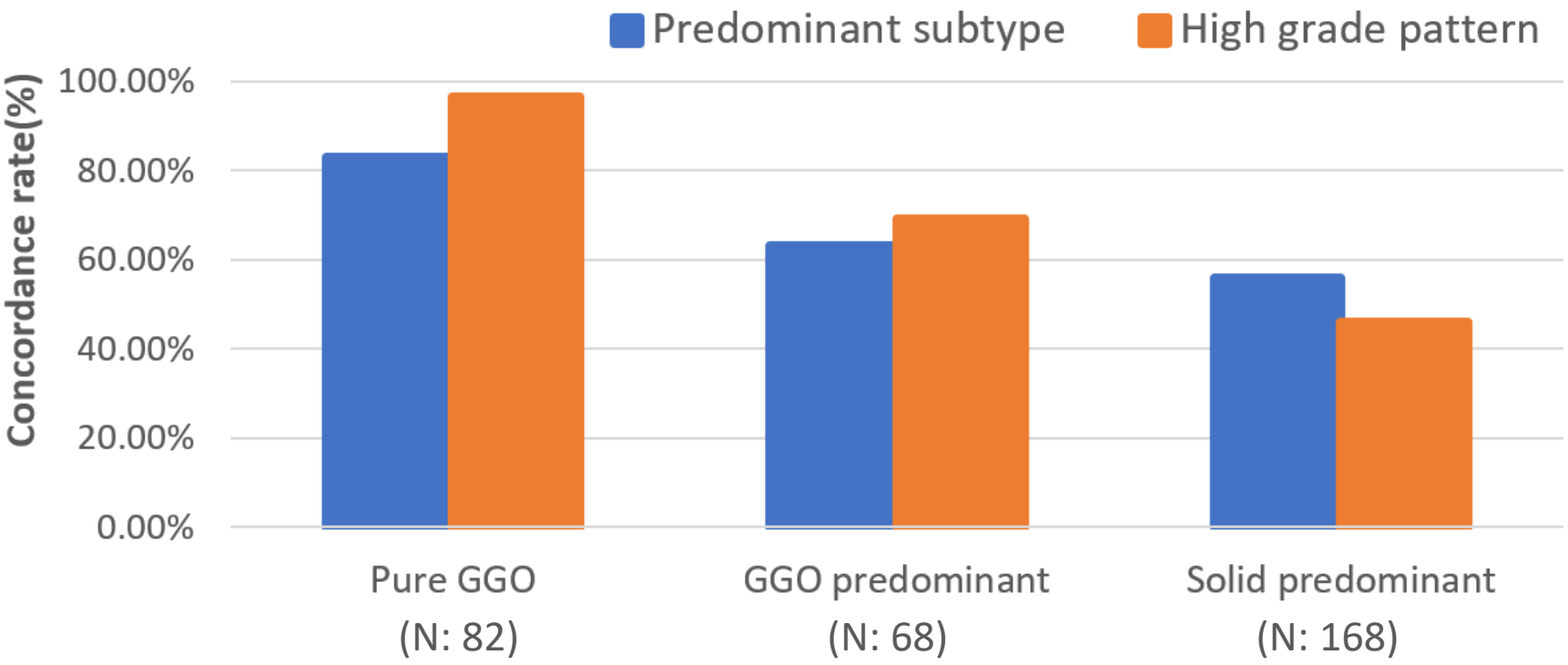


Tsai et al. (in submission)

Histologic subtyping using preoperative biopsy specimen

Factors influencing concordance:

(2) Radiologic appearance

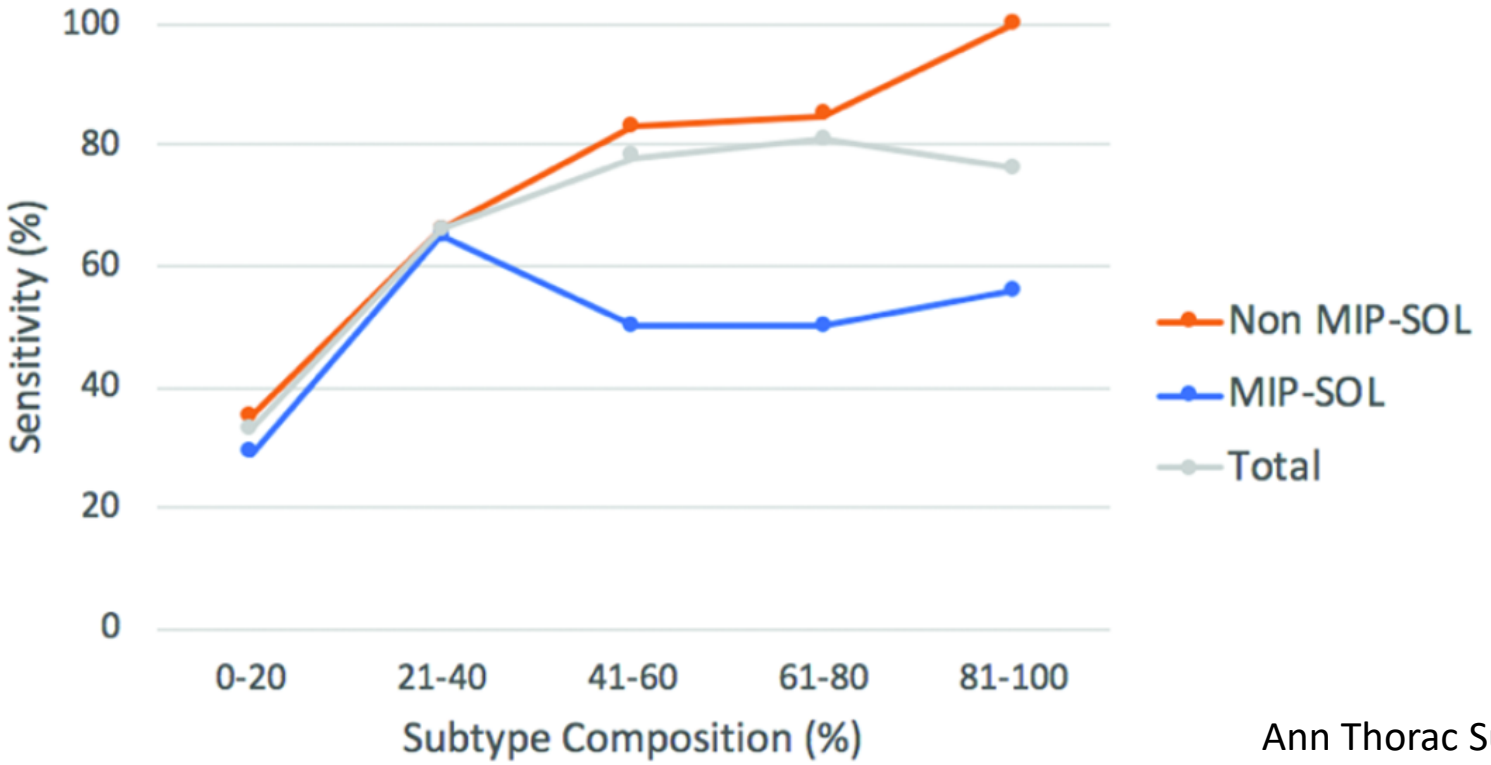


Tsai et al. (in submission)

Histologic subtyping using preoperative biopsy specimen

Factors influencing concordance:

(3) Percentage of subtype component



Ann Thorac Surg.
2019 Aug;108(2):392-398.

Challenges in pathological diagnosis of early small lung adenocarcinoma

- Preoperative biopsies
- Frozen sections
- Reproducibility and interobserver agreement

Potential applications of frozen sections in early small lung adenocarcinoma

- Histologic subtyping?
  - Lepidic, acinar, papillary, micropapillary, solid,..
- Detect high grade histologic features?
  - Micropapillary & solid growth patterns
- Evaluate degree of invasion?
  - AIS vs. MIA vs. Invasive adenocarcinoma

Accuracy of FS: Predominant histologic subtype

- Study in MSKCC: 361 cases

Overall accuracy for histology subtype: 68%

Predominant histologic subtype	Sensitivity	Specificity	Kappa
Lepidic	75%	93%	0.681
Acinar	70%	79%	0.481
Papillary	62%	91%	0.527
Micropapillary	21%	99%	0.277
Solid	79%	94%	0.700

Histopathology. 2015 Jun;66(7):922-38.

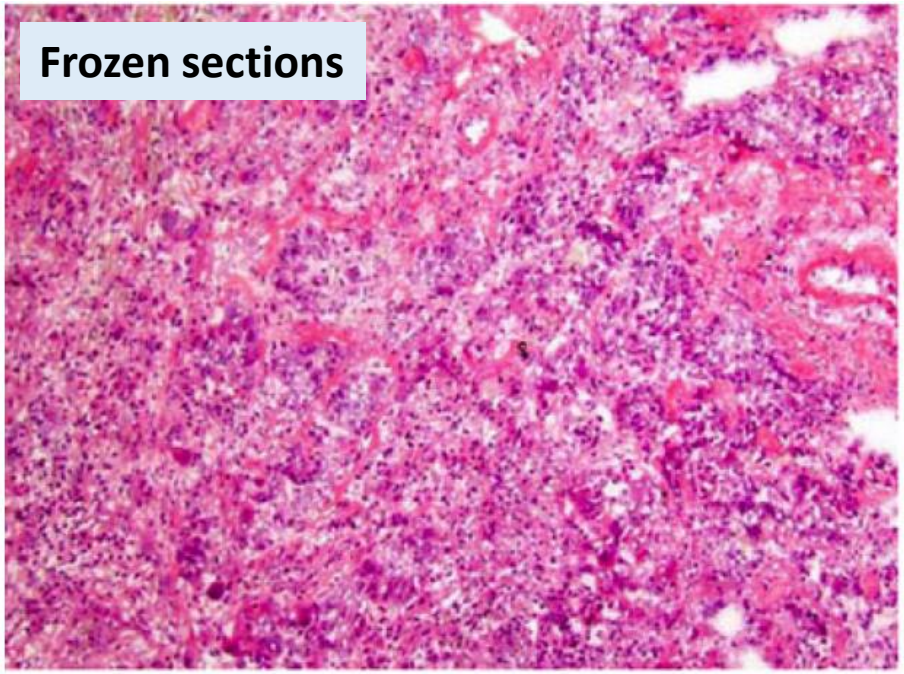
Accuracy of FS: Presence/absence of histologic patterns

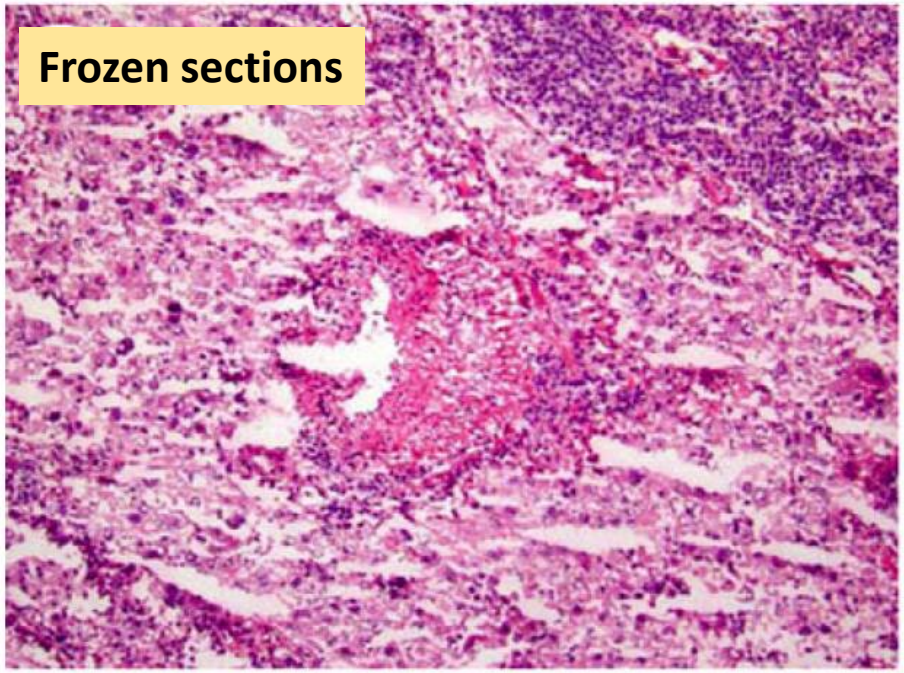
- Study in MSKCC: 361 cases

Histologic pattern (yes/no)	Sensitivity	Specificity	Kappa
Lepidic	75%	91%	0.588
Acinar	90%	67%	0.252
Papillary	70%	79%	0.397
Micropapillary	37%	94%	0.321
Solid	69%	96%	0.670

High specificity, but low sensitivity for MIP and SOL patterns

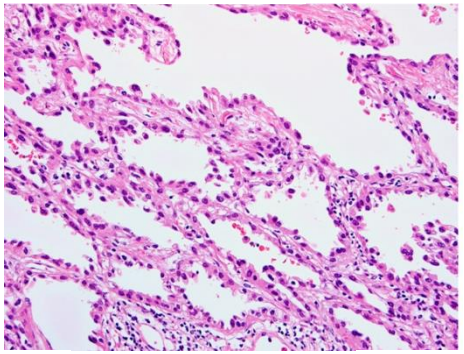
Histopathology. 2015 Jun;66(7):922-38.



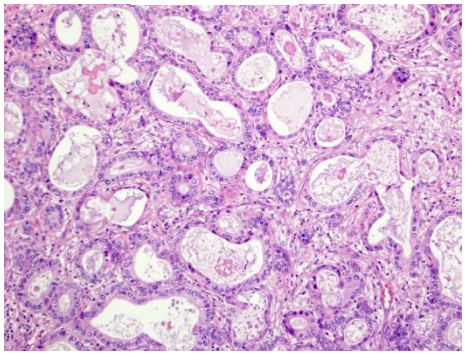


?

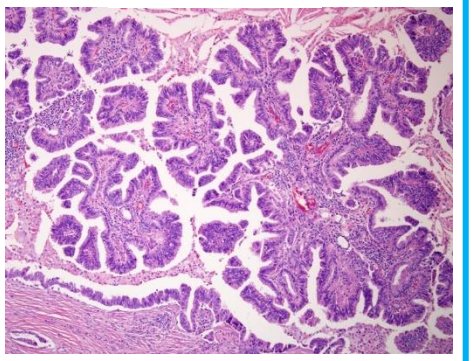
Lepidic



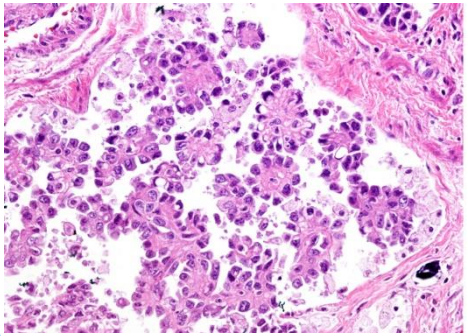
Acinar



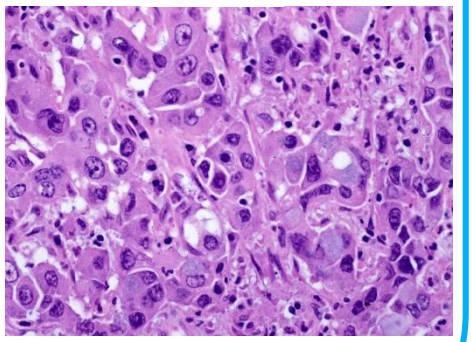
Papillary

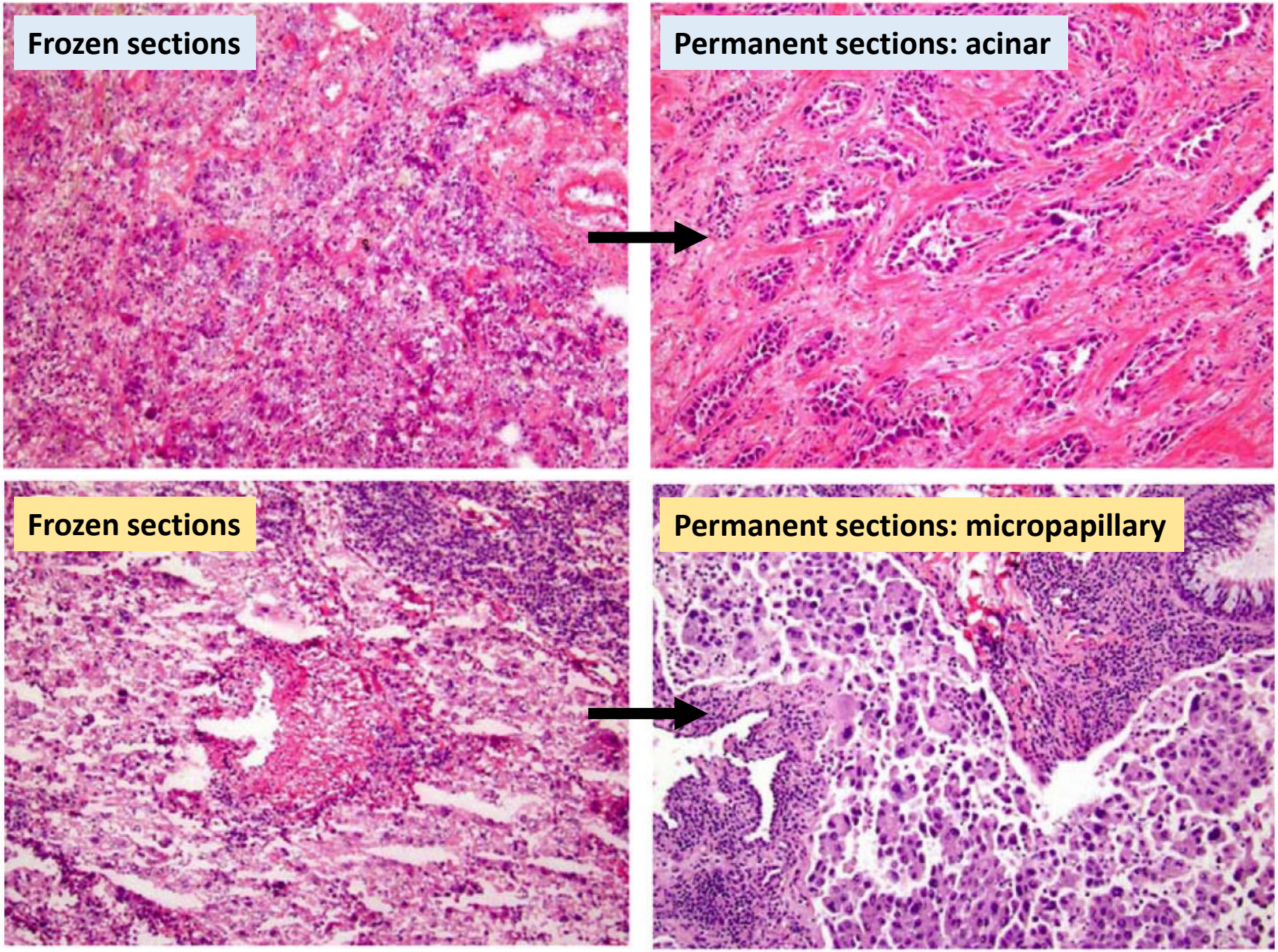


Micropapillary



Solid




Frozen sections
Permanent sections: acinar
Frozen sections
Permanent sections: micropapillary

Reason for discrepancy in frozen sections

Parameters	No. (%) of each type of error		
	Sampling error	Interpretation error	Sampling + interpretation error
Predominant histological subtype			
Overall	58 (69.0)	17 (20.2)	9 (10.7)
Lepidic	8 (57.1)	5 (35.7)	1 (7.1)
Acinar	19 (79.2)	4 (16.7)	1 (4.2)
Papillary	18 (78.3)	4 (17.4)	1 (4.3)
Micropapillary	5 (41.7)	3 (25.0)	4 (33.3)
Solid	8 (72.7)	1 (9.1)	2 (18.2)
Presence/absence of histological pattern			
Lepidic	32 (64.0)	18 (36.0)	0 (0)
Acinar	20 (74.1)	7 (25.9)	0 (0)
Papillary	44 (67.7)	21 (32.3)	0 (0)
Micropapillary	47 (62.7)	28 (37.3)	0 (0)
Solid	26 (72.2)	10 (27.8)	0 (0)

Sampling error is the most common source of errors (67%)

Histopathology. 2015 Jun;66(7):922-38.

Accuracy of frozen section diagnosis for AIS/MIA/Invasive AdCA (1)

Study from Cedars-Sinai Medical Center:

- 224 lung adenocarcinoma with frozen sections
- Cases accurately diagnosed at FS:
  - AIS: 16 / 27 cases (59%)
  - MIA: 21 / 46 cases (46%)
  - Invasive AdCA: 146 / 151 cases (97%)
- Most common FS errors

  → Overdiagnosis of MIA as invasive AdCA (n=13, 28%)

Arch Pathol Lab Med. 2012 Dec;136(12):1515-21.

Accuracy of frozen section diagnosis for AIS/MIA/Invasive AdCA (2)

Study from MSKCC:

FS diagnosis by 5 pathologists	Permanent section diagnosis (Final diagnosis)		
	AIS (n=2)	MIA (n=15)	LPD AdCA (n=18)
AIS	100%	6.7%	3.3%
MIA	0%	41.3%	17.7%
LPD AdCA	0%	**52.0%**	79.0%

Most common error: Overdiagnosis of MIA as invasive AdCA (lepidic)

Histopathology. 2015 Jun;66(7):922-38.

Accuracy of frozen section diagnosis for AIS/MIA/Invasive AdCA (3)

Study from Fudan University Shanghai Cancer Hospital:

FS diagnosis	Permanent section diagnosis (Final diagnosis)			
	AAH (n=32)	AIS (n=126)	MIA (n=273)	Inv AdCA (n=372)
AAH	100%	**21.4%**	**2.6%**	0
AIS	0%	73.8%	**20.9%**	**1.6%**
MIA	0%	0.8%	75.5%	**4.6%**
Inv AdCA	0%	0%	0.7%	93.3%
Benign	0%	4.0%	0.4%	0.5%

Most common error: Underdiagnosis of AIS, MIA and Inv AdCA

J Clin Oncol. 2016 Feb 1;34(4):307-13.

VGH-TPE experience (2013-2018)

FS diagnosis	Permanent section diagnosis (Final diagnosis)			
	AIS (n=80)	MIA (n=42)	AdCA-LPD (n=41)	AdCA-Others (n=89)
AdCA, Lepidic	79%	69%	54%	**2%**
AdCA, Invasive	**21%**	**31%**	**46%**	98%

Most common error: Overestimate of invasion

***Only include primary lung adenocarcinomas**

***Only include cases with FS diagnosis made by the two pulmonary pathologist**

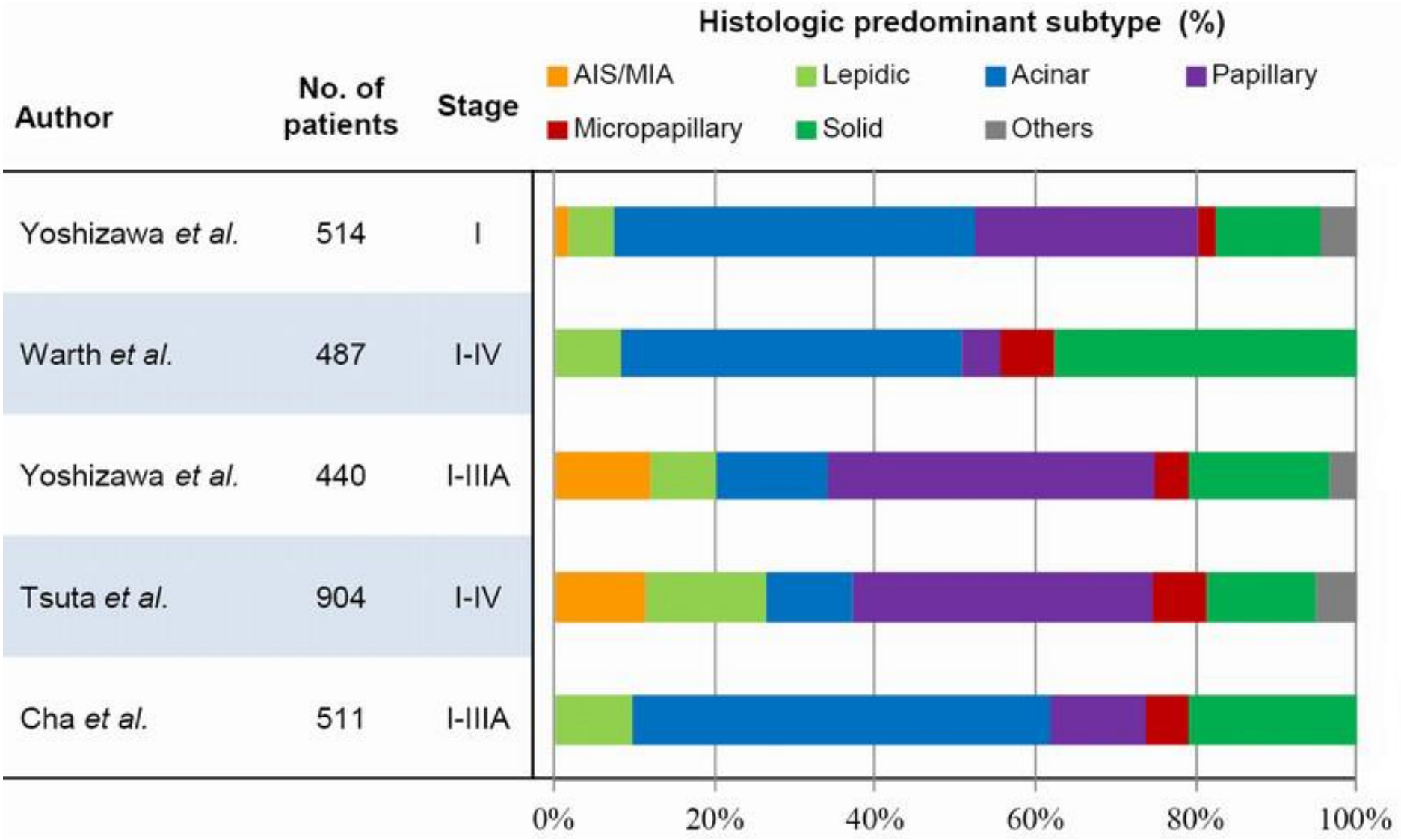
Potential applications of frozen sections in early small lung adenocarcinoma

- Histologic subtyping?
  → Accuracy about 70%, hampered by sampling error
- Detect high grade histologic features?
  → Low sensitivity, despite high specificity
- Evaluate degree of invasion?
  → Challenging
  → Overdiagnosis (USA, VGH-TPE) / Underdiagnosis (China)
  → Invasive predominant AdCA: > 90% accuracy

Challenges in pathological diagnosis of early small lung adenocarcinoma

- Frozen sections
- Preoperative biopsies
- Reproducibility and interobserver agreement

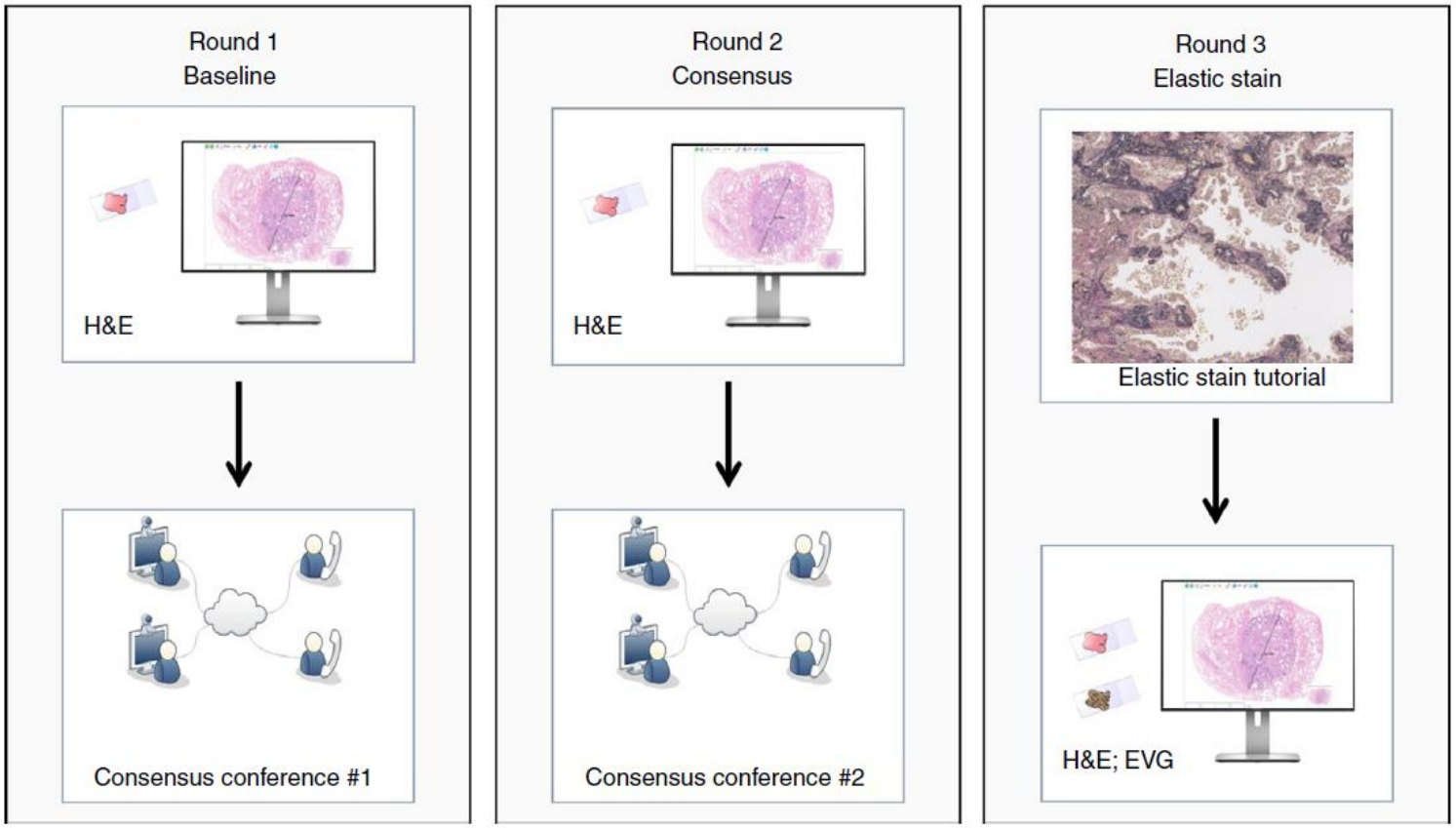
Distribution of histologic subtypes



Lee MC et al. *J Thorac Dis*. 2014 Oct;6(Suppl 5):S568-80.

Reproducibility of small adenocarcinoma classification International interobserver study

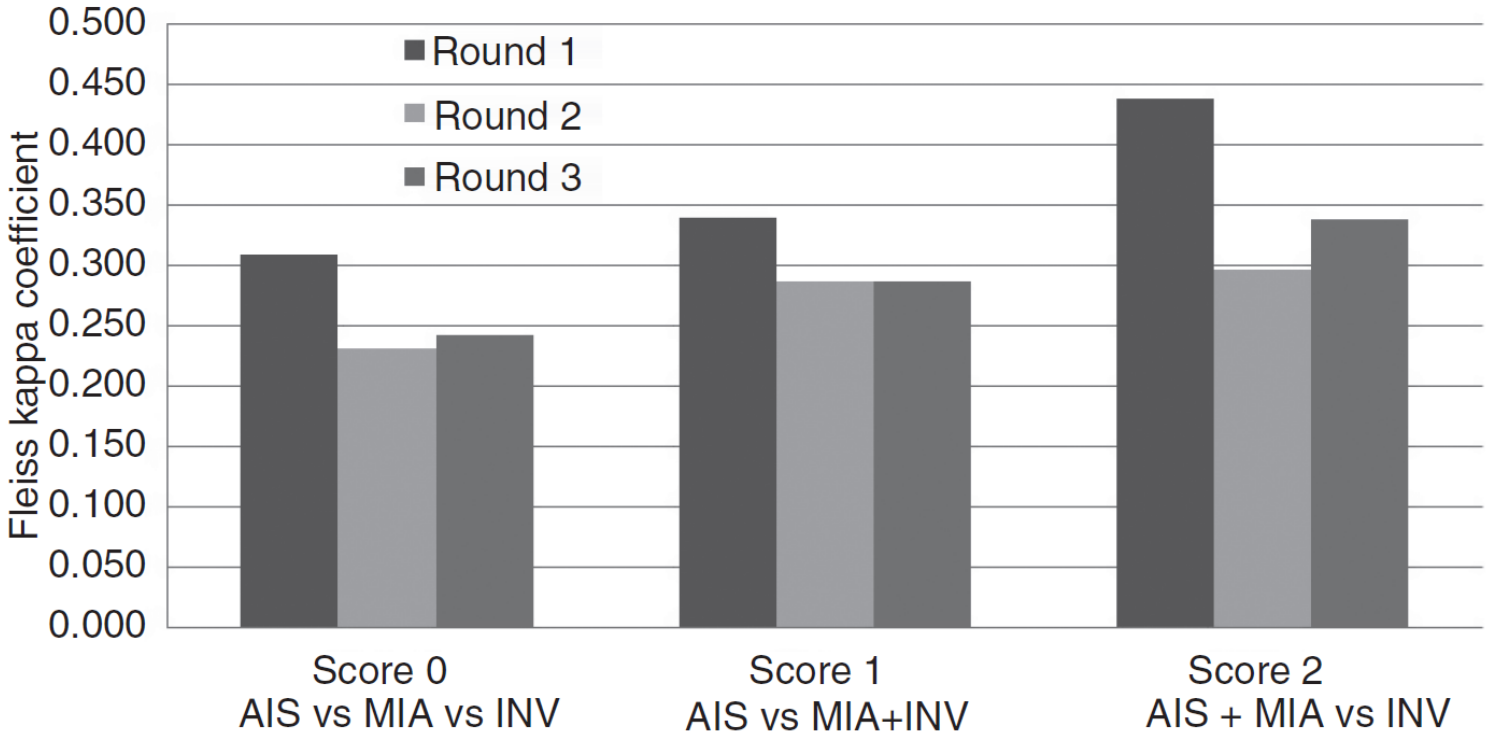
- 60 cases of AIS/MIA/Inv AdCA from Massachusetts General Hospital
- Six expert lung pathologists from 4 countries
- Whole slide images as materials



Histopathology. 2019 Nov;75(5):649-659.

Reproducibility of small adenocarcinoma classification
International interobserver study

Agreement on degree of invasion

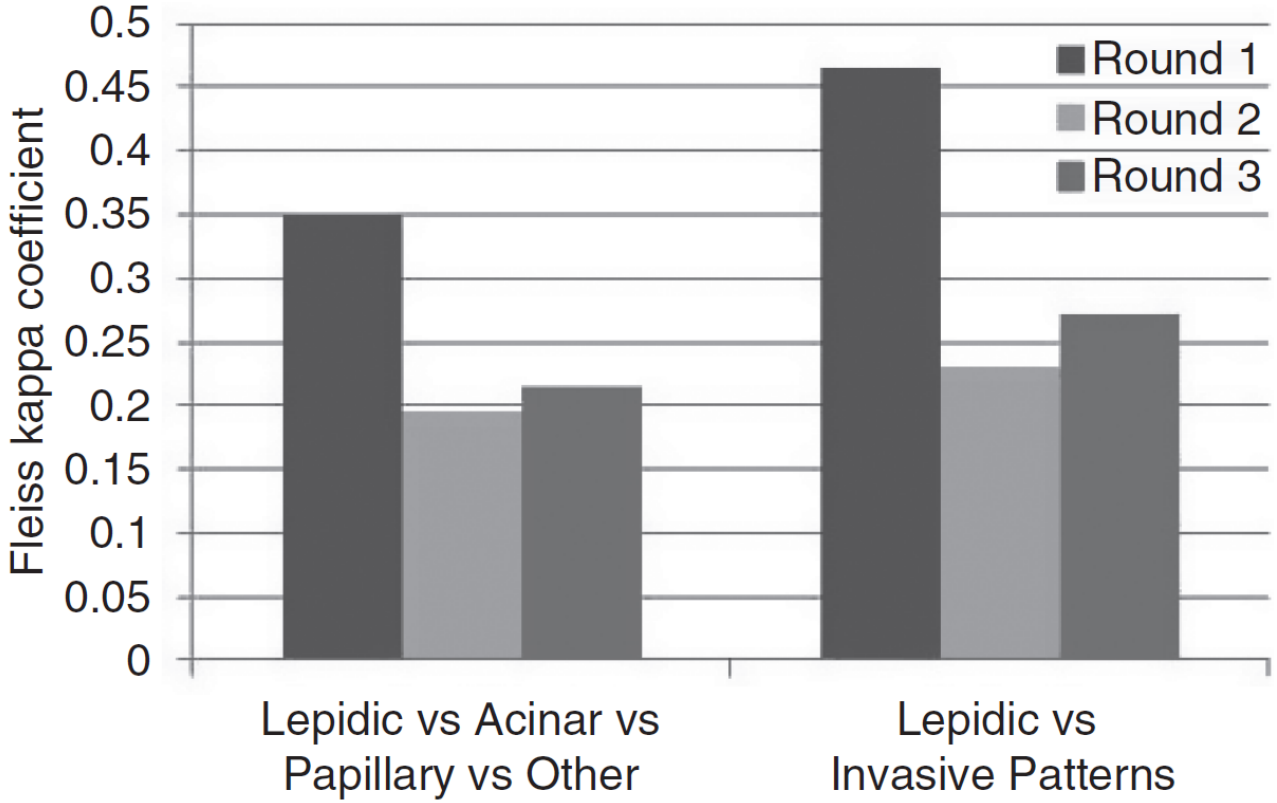


Fleiss Kappa:
0.21 – 0.40 Fair agreement
0.41 – 0.60 Moderate agreement

Histopathology. 2019 Nov;75(5):649-659.

Reproducibility of small adenocarcinoma classification
International interobserver study

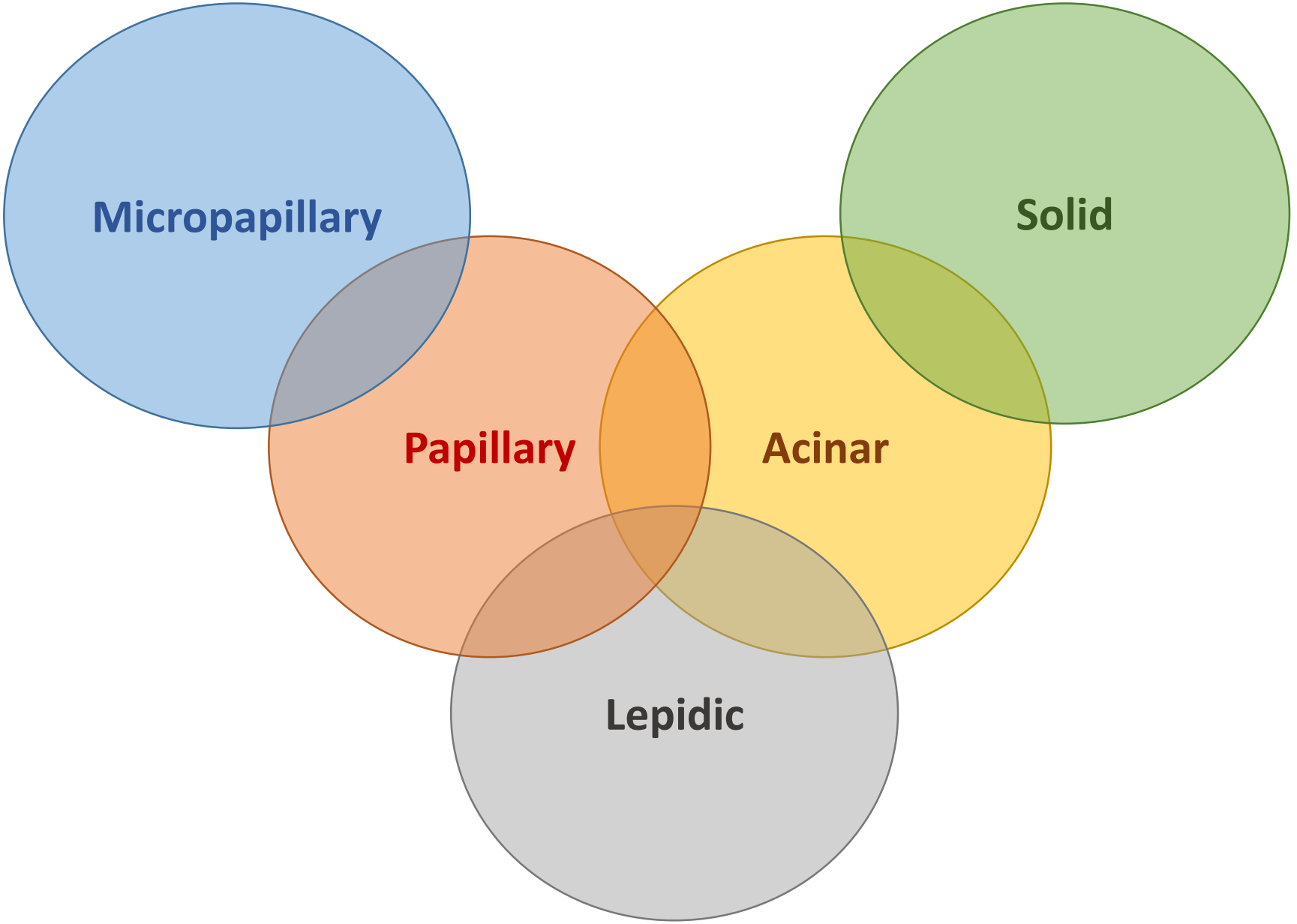
Agreement on predominant pattern



Fleiss Kappa:
0.21 – 0.40 Fair agreement
0.41 – 0.60 Moderate agreement

Histopathology. 2019 Nov;75(5):649-659.

Morphological overlap of histologic pattterns



Summary

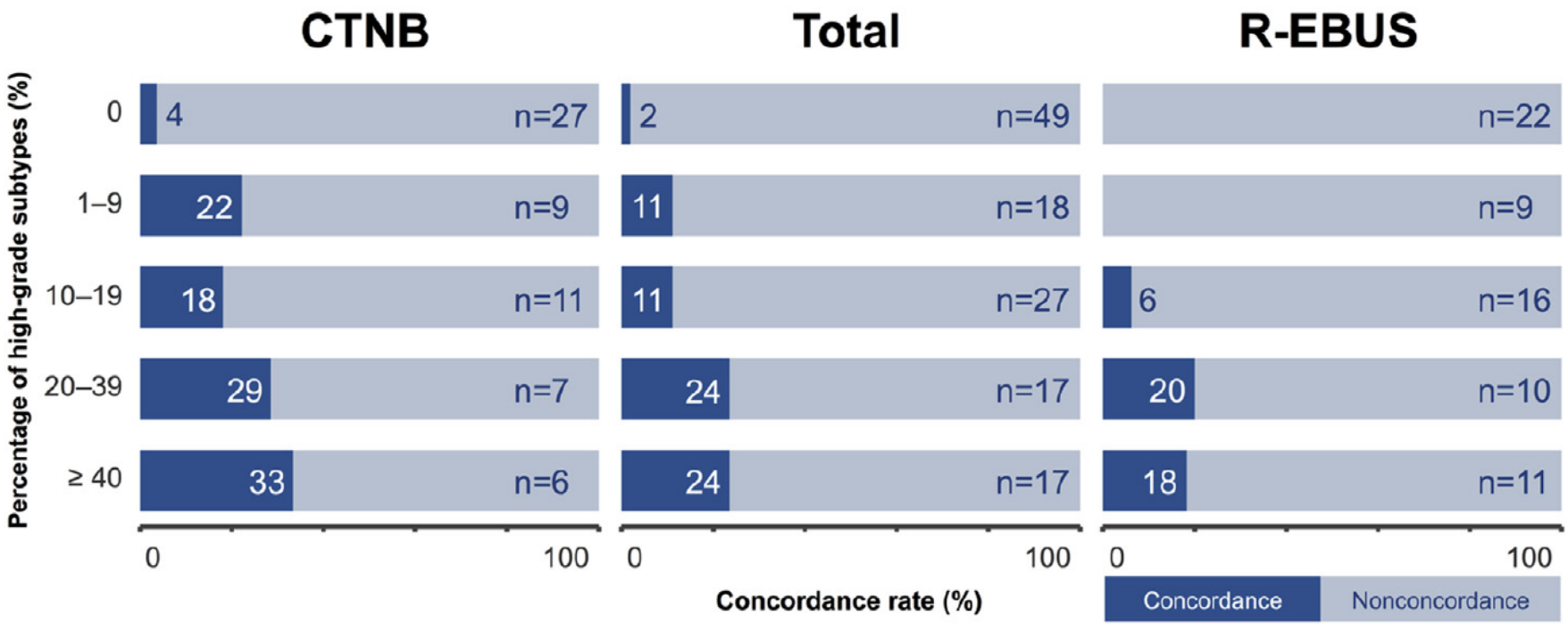
- Adenocarcinoma consists of a biological spectrum
  - From preinvasive lesions, minimally invasive adenocarcinomas, to invasive adenocarcinomas
  - Progressive genomic evolution
  - Histology is of prognostic significance
- Diagnosis in preoperative biopsy and frozen sections
  - Predominant subtype: around 60-70% accuracy
  - Detect MIP/SOL pattern: low sensitivity, high specificity
  - AIS vs. MIA vs. Lepidic AdCA: challenging
  - Invasive predominant AdCA: > 90% accuracy in FS
- Reproducibility and interobserver agreement
  - Only fair to moderate agreement


Thanks for your attention
Have a nice day!

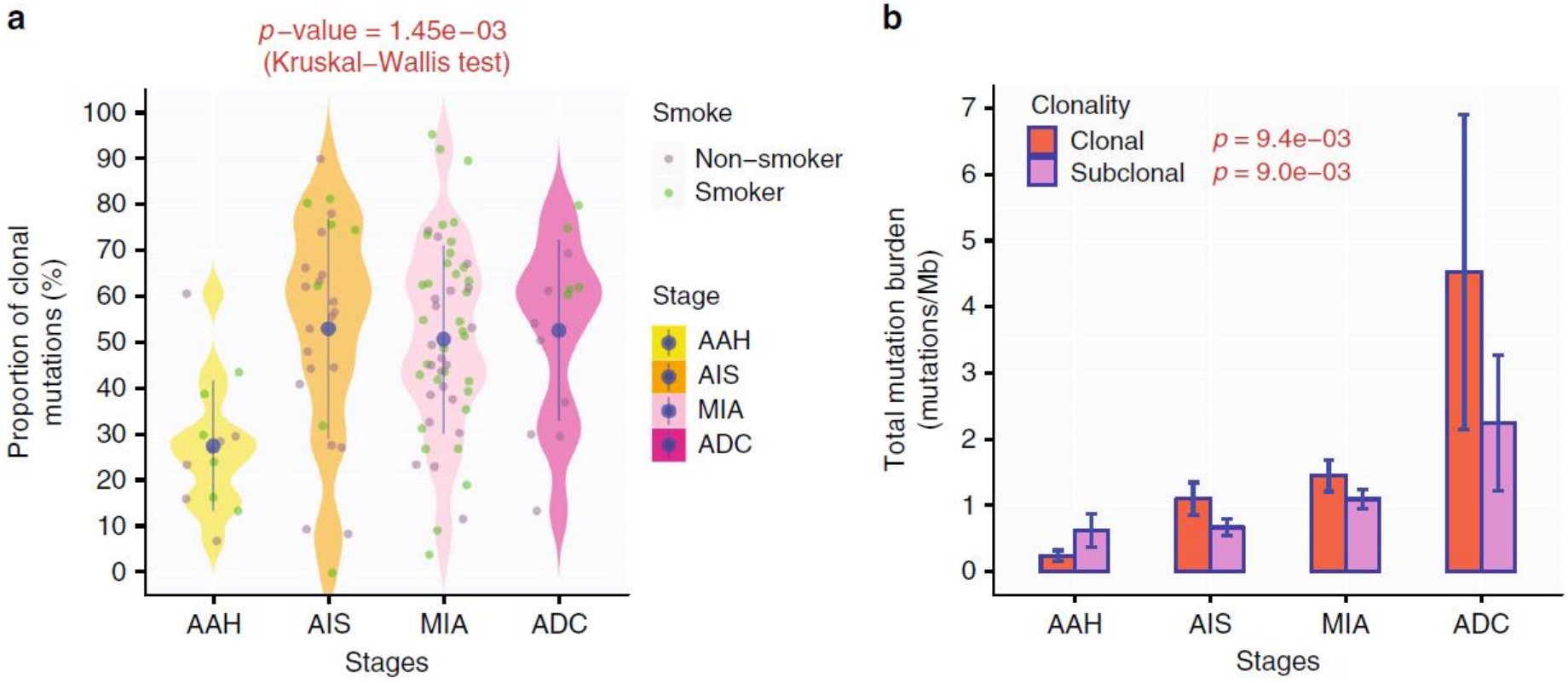
Histologic subtyping using preoperative biopsy specimen

Factors influencing concordance (for aggressive pattern):

(3) Percentage of the MIP/SOL component



J Thorac Cardiovasc Surg. 2017 Jul;154(1):332-339.

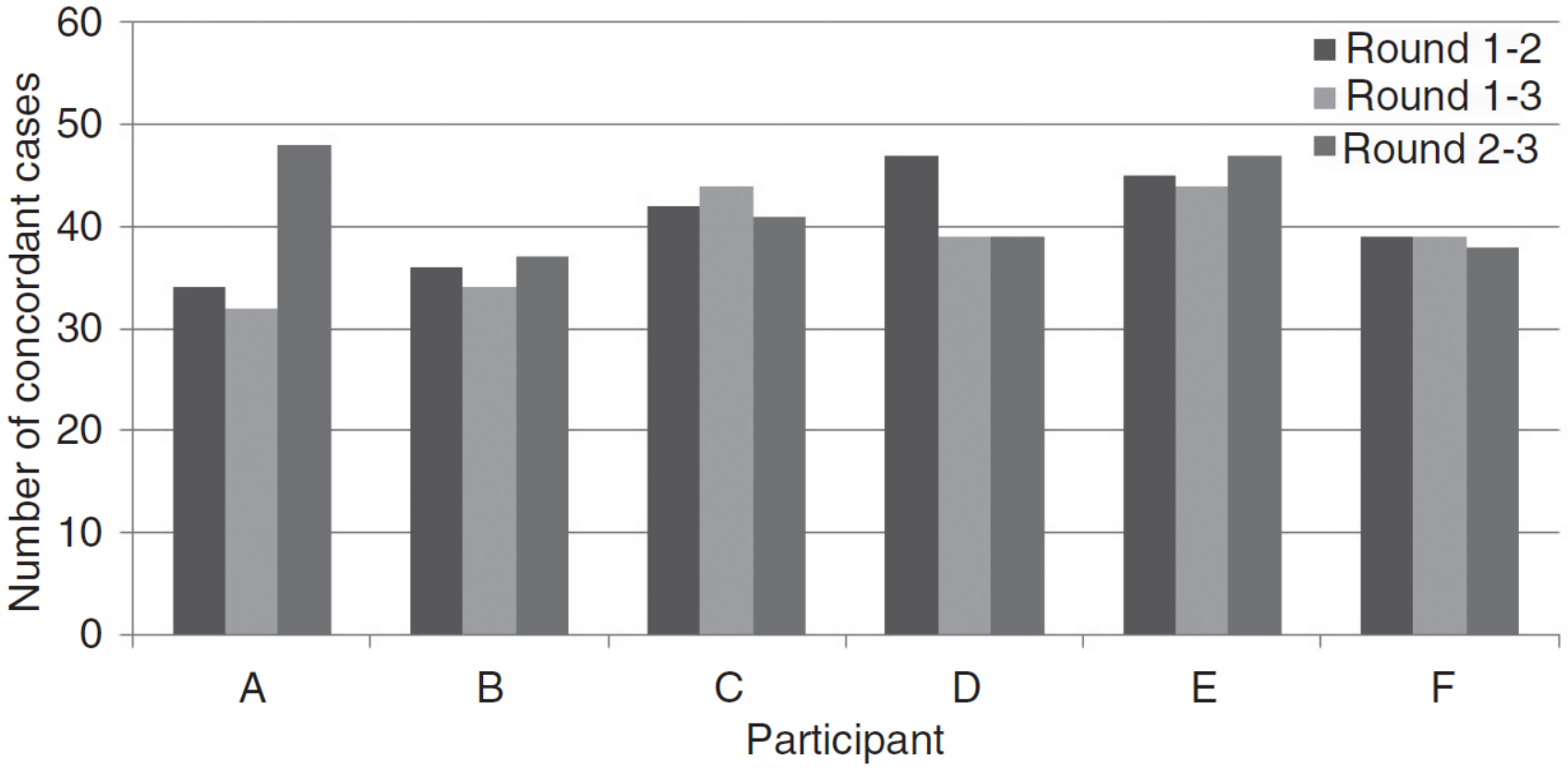


Selective clonal sweep during neoplastic evolution of AAH

Nat Commun. 2019 Jul 5;10(1):2978.

Reproducibility of small adenocarcinoma classification International interobserver study

Intra-observer agreement



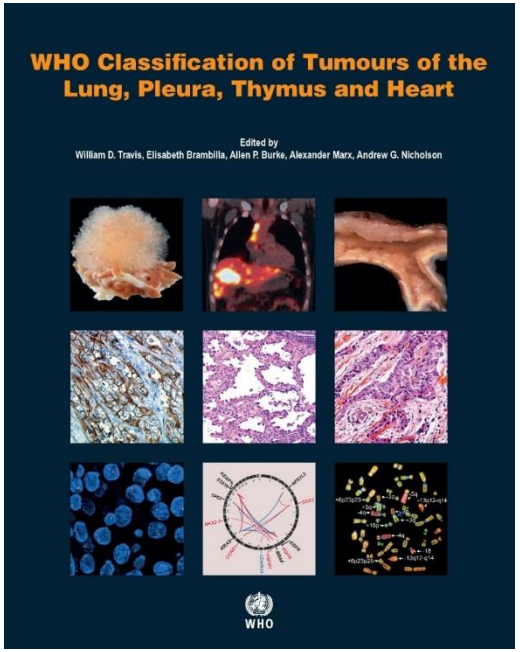
Histopathology. 2019 Nov;75(5):649-659.

WHO Classification of tumours of the lung[a,b]

Epithelial Tumours	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma	8250/3*
Acinar adenocarcinoma	8551/3*
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma	8253/3*
Mixed invasive mucinous and non-mucinous adenocarcinoma	8254/3*
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma	8144/3
Minimally invasive adenocarcinoma	
Non-mucinous	8250/2*
Mucinous	8257/3*
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0*
Adenocarcinoma in situ	
Non-mucinous	8410/2
Mucinous	8253/2
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma	8071/3
Non-keratinizing squamous cell carcinoma	8072/3
Basaloid squamous cell carcinoma	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine Tumours	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumours	
Typical carcinoid tumour	8240/3
Atypical carcinoid tumour	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0*
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinoma	8033/3
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma	8023/3*
Salivary gland-type tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous cell and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumours	
Pulmonary hamartoma	8992/0
Chondroma	9220/0
PEComatous tumours	
Clear cell tumour	8005/0
Lymphangioleiomyomatosis	9174/1
PEComa, benign	8714/0
Congenital peribronchial myofibroblastic tumour	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumour	8825/1
Epithelioid haemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation	8842/3*
Myoepithelial tumours	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumours	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large B-cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9680/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim-Chester disease	9750/1
Tumours of ectopic origin	
Germ cell tumours	
Teratoma mature	9080/0
Teratoma immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8720/3
Meningioma, NOS	9530/0
Metastatic tumours	

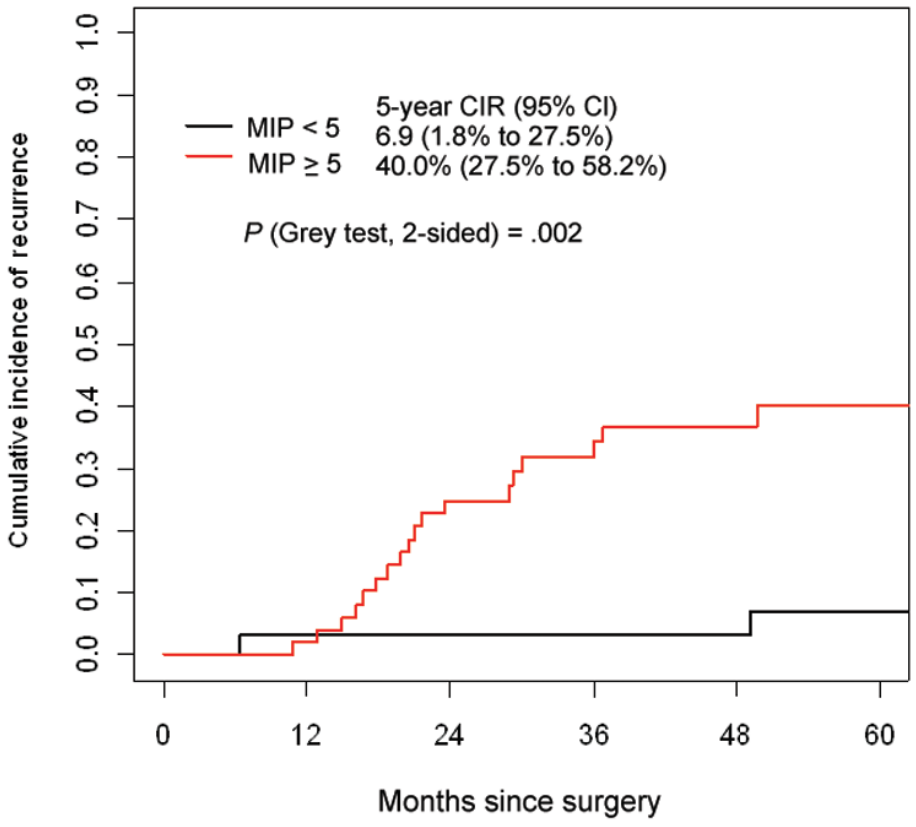
Lung adenocarcinoma

- Preinvasive lesions
  - Atypical adenomatous hyperplasia (AAH)
  - Adenocarcinoma in situ (AIS)
- Minimally invasive adenocarcinoma (MIA)
- Invasive adenocarcinoma
  - Lepidic
  - Acinar
  - Papillary
  - Micropapillary
  - Solid
- Uncommon variants

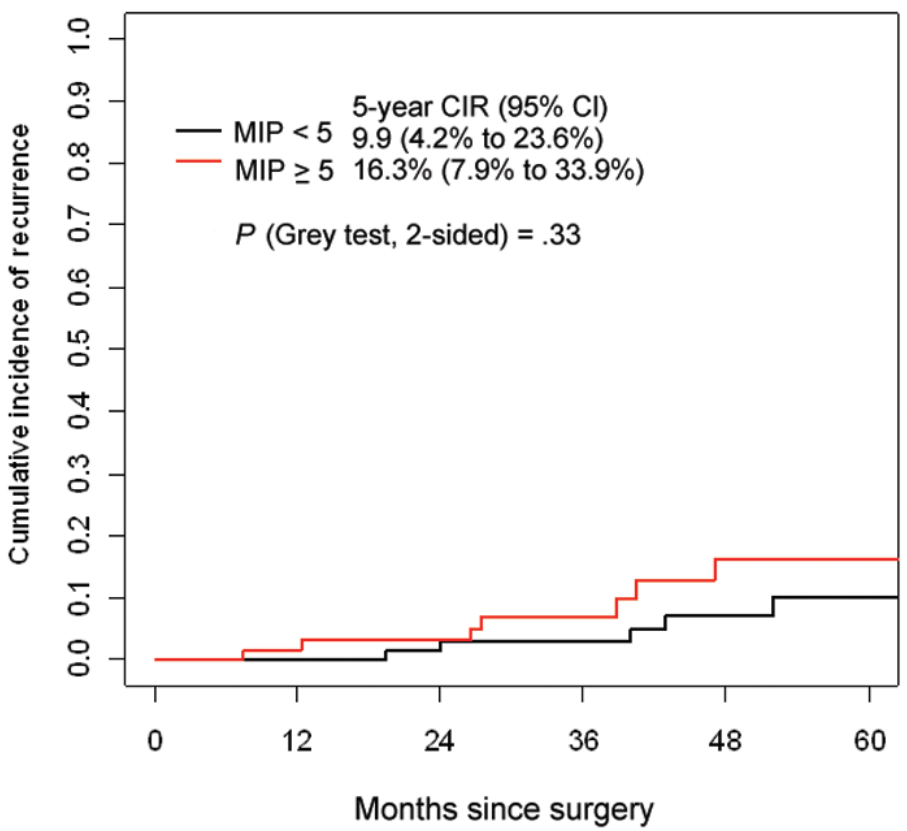


Procedure-specific risk of recurrence in MIP (+) patients

Limited resection patients



Lobectomy patients



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