New WHO classification: Putting it into practice

Small biopsy and cytology diagnosis

ELCC, Geneva

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Disclosure slide

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	Astra Zeneca
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Participation in a company sponsored speaker's bureau:	Astra Zeneca, Roche

IASLC/ATS/ERS ADENOCARCINOMA MULTIDISCIPLINARY PANEL
New York, 2008

Rationale For New ADC Classification IASLC/ATS/ERS sponsored meeting(s)

Multidisciplinary criticisms in relation to 2004 classification…

- Bronchioloalveolar carcinoma (BAC) – confusing used many different ways despite 99/04 WHO; mucinous and non-mucinous
- **No classification for biopsies**
- Greater clinical relevance (too “for pathologists by pathologists”…)
- Take into account rapid evolving molecular advances (EGFR)

1-1B Rationale for classification in small biopsies and cytology and 1-1C Terminology and criteria in non-resection specimens:

(1999/2004) Malignant ⇒ Ca ⇒ NSCLC

- (2008-9) NSCLC → SQCa

- Poorly diff NSCLC

  <u>If clinically relevant</u>

  - IHC (CK5/6,34BE12,p63,TTF-1)
  - Mucin stain
  - Expert referral
  - Another sample

- ADC

  Architecture (BAC/pap/acinar)
  Grade

CLINICAL DATA
MOLECULAR DATA
IMAGING DATA

TTF-1,mucin +ve, others –ve …..”favours ADC”
TTF-1,mucin –ve others +ve …..”favours SQCa”

ADENOCARCINOMA CLASSIFICATION

Travis WD et al. JTO Feb 2011;6:244-286

- PREINVASIVE LESIONS
  - *AAH*
  - *ADC-in-situ (formerly pure BAC) *most non-mucinous (NM) (30mm or less)*
- INVASIVE
  - *Minimally invasive (< 5mm invasion) (30mm or less)*
  - *Lepidic pattern predominant*
  - *Acinar pattern predominant/pure*
  - *Papillary pattern predominant/pure*
  - *Micropapillary pattern predominant/pure*
  - *Solid pattern predominant/pure*
  - *Invasive mucinous carcinomas*
  - *Colloid*
  - *Fetal (low and high grade)*
  - *Enteric*

… A multidisciplinary approach

Respiratory Physician
Imaging
Surgery
Oncology
Pathology
Molecular Biology

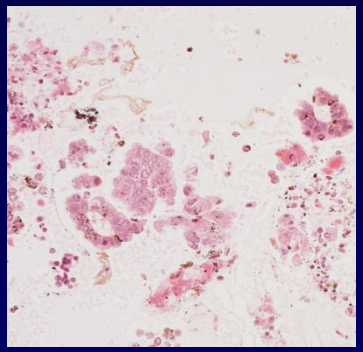
2015 WHO CLASSIFICATION

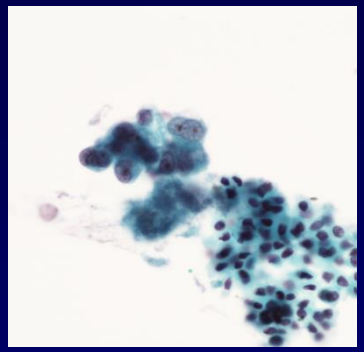
- **1-1: Introduction**
  - 1-1A Lung cancer staging and grading
  - 1-1B Rationale for classification in small biopsies and cytology
  - 1-1C Terminology and criteria in non-resection specimens
  - 1-1D Molecular testing for treatment selection in lung cancer

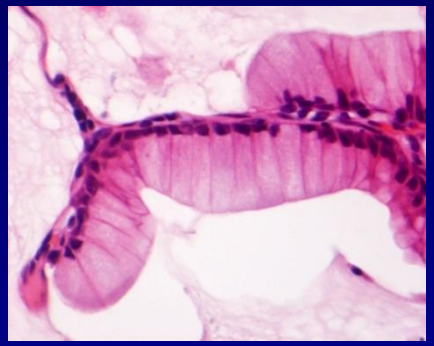
- **1-2: Adenocarcinoma**
  - 1-2A Invasive adenocarcinoma
  - 1-2B Variants of invasive adenocarcinoma
  - 1-2C Minimally invasive adenocarcinoma
  - 1-2D Preinvasive lesions
    - 1-2D-i: Atypical adenomatous hyperplasia
    - 1-2D-ii: Adenocarcinoma in situ
- **1-3: Squamous cell carcinoma**
  - 1-3A: Keratinizing and nonkeratinizing squamous cell carcinoma
  - 1-3B: Basaloid carcinoma
  - 1-3C: Preinvasive lesion: Squamous carcinoma in situ
- **1-4: Neuroendocrine Tumours**
  - 1-4A: Small cell carcinoma
  - 1-4B: Large cell neuroendocrine carcinoma
  - 1-4C: Carcinoid tumors
  - 1-4D: Preinvasive lesion: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- **1-5: Large cell carcinoma**
- **1-6: Adenosquamous carcinoma**
- **1-7: Sarcomatoid carcinoma**
  - 1-7A: Pleomorphic, spindle cell and giant cell carcinoma
  - 1-7B: Carcinosarcoma
  - 1-7C: Pulmonary blastoma
- **1-8: Other carcinomas**
  - 1-8A: Lymphoepithelioma-like carcinoma
  - 1-8B: NUT-carcinoma

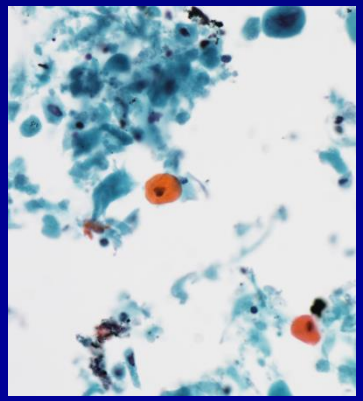
SPECIFIC TERMINOLOGY AND CRITERIA FOR ADENOCARCINOMA, SQUAMOUS CELL **CARCINOMA AND NON-SMALL CELL CARCINOMA-NOS IN SMALL BIOPSIES AND CYTOLOGY†**

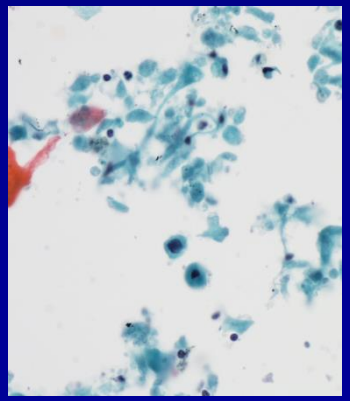
New Small Biopsy/Cytology Terminology	Morphology/Stains	2015 WHO Classification in resection specimens
Adenocarcinoma (describe identifiable patterns present)	Morphologic adenocarcinoma patterns clearly present	ADENOCARCINOMA (Predominant pattern) Acinar Papillary Solid Micropapillary
Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)		Lepidic (nonmucinous)
Invasive mucinous adenocarcinoma (describe patterns present; use term mucinous adenocarcinoma with lepidic pattern if pure lepidic pattern – see text) **Adenocarcinoma with mucinous features** **Adenocarcinoma with fetal features** **Adenocarcinoma with enteric features ††**		Invasive mucinous adenocarcinoma Colloid adenocarcinoma Fetal adenocarcinoma Enteric adenocarcinoma
Squamous cell carcinoma	Morphologic squamous cell patterns clearly present	SQUAMOUS CELL CARCINOMA



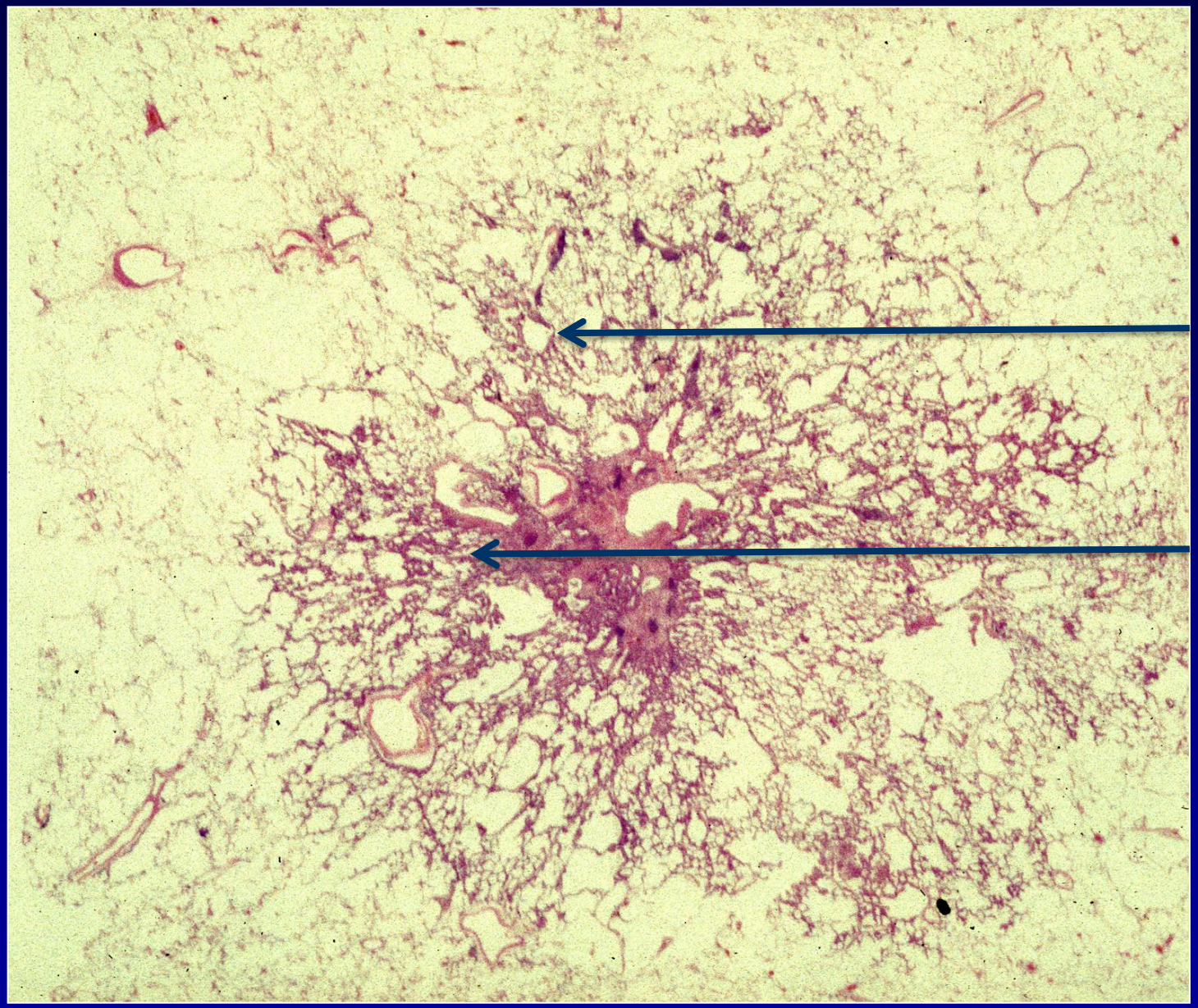






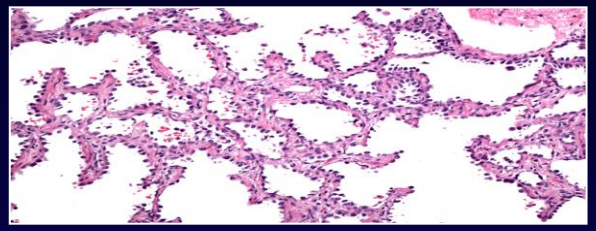


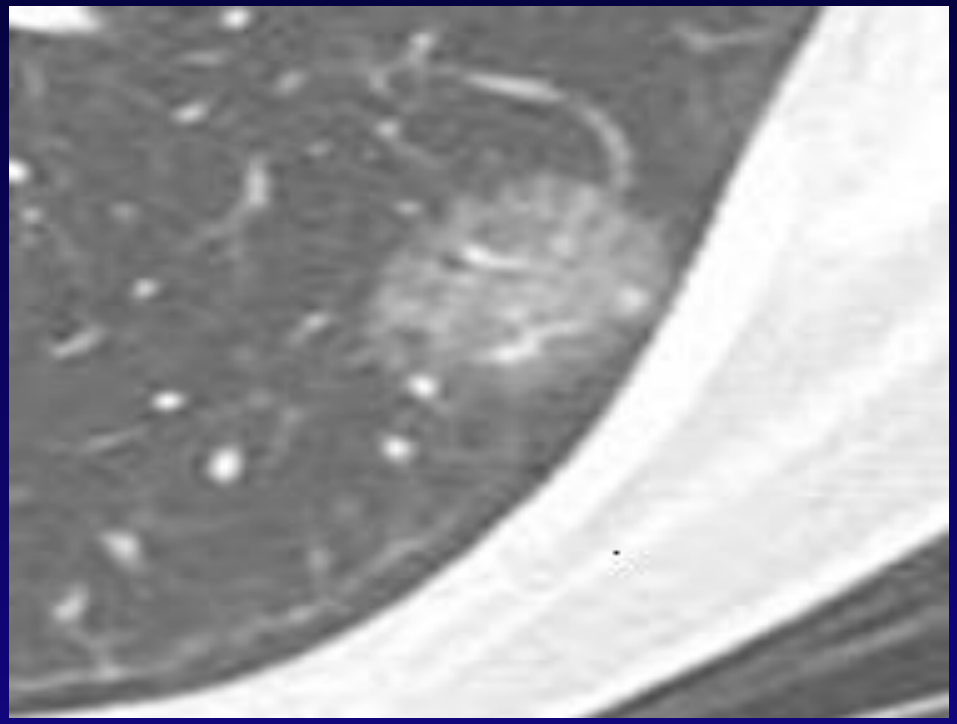
Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285



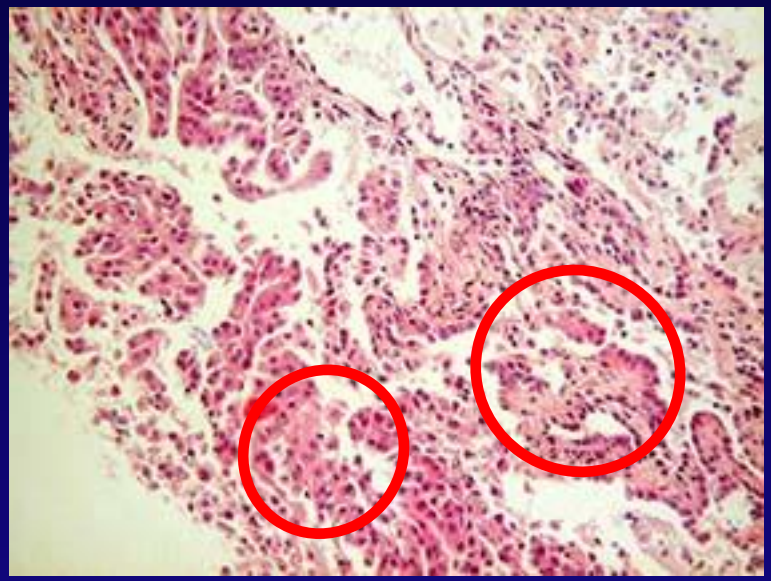
Classification of sampled tissue

"Adenocarcinoma with a purely lepidic pattern in this sample

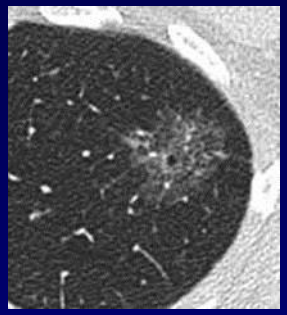




"Adenocarcinoma with both lepidic and micropapillary patterns"



Pure Ground Glass Nodules ≥10mm and solitary: Recent Data: Pre-invasive vs invasive adenoca



46 pure GGNs >10mm resected

41% In Situ

20% Minimally invasive

39% Invasive

14.4mm

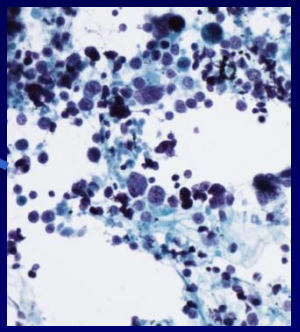
18.9mm

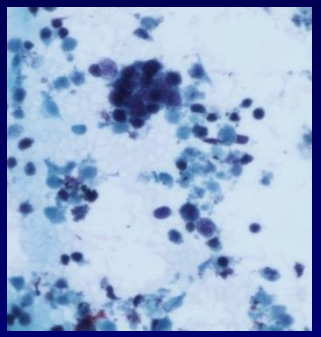
Lim HJ et al. Persistent pure ground-glass nodules>10mm at CT: histopathologic comparisons. Chest 2013;144

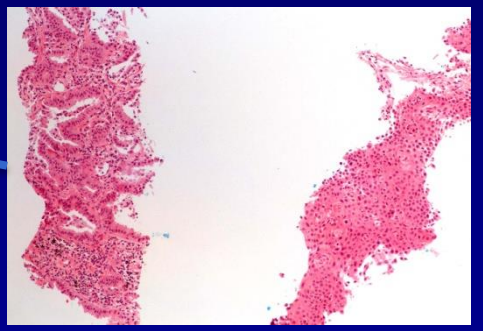
Courtesy of Dr A Devaraj

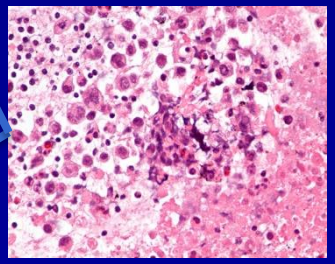
CLASSIFICATION FOR SMALL BIOPSIES/CYTOLOGY COMPARING 2015 WHO TERMS WITH NEW TERMS FOR SMALL CELL CARCINOMA, LARGE CELL NEUROENDOCRINE CARCINOMA, ADENOSQUAMOUS CARCINOMA AND SARCOMATOID CARCINOMA †

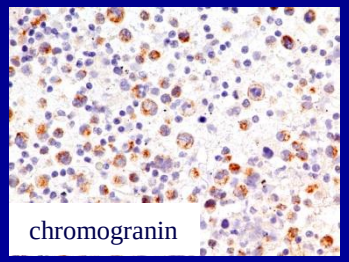
SMALL BIOPSY/CYTOLOGY: IASLC/ATS/ERS	2015 WHO Classification
Small cell carcinoma	SMALL CELL CARCINOMA
Non-small cell carcinoma with neuroendocrine (NE) morphology and positive NE markers, possible LCNEC	Large cell neuroendocrine carcinoma (LCNEC)
Morphologic squamous cell and adenocarcinoma patterns present: Non-small cell carcinoma, NOS, (comment that adenocarcinoma and squamous components are present and this could represent adenosquamous carcinoma).	ADENOSQUAMOUS CARCINOMA
Morphologic squamous cell or adenocarcinoma patterns not present but immunostains favor separate glandular and adenocarcinoma components Non-small cell carcinoma, NOS, (specify the results of the immunohistochemical stains and the interpretation) Comment: this could represent adenosquamous carcinoma.	No counterpart in 2015 WHO classification
NSCC with spindle and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)	Pleomorphic, spindle and/or giant cell carcinoma







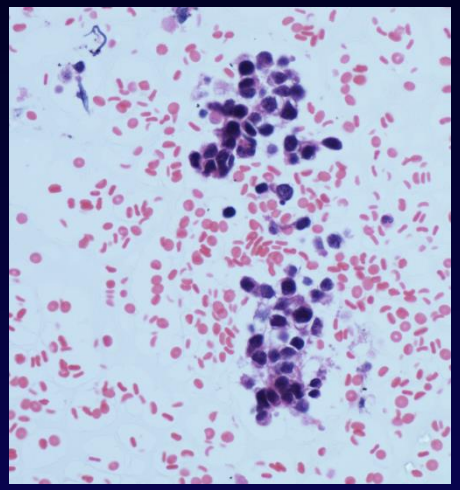




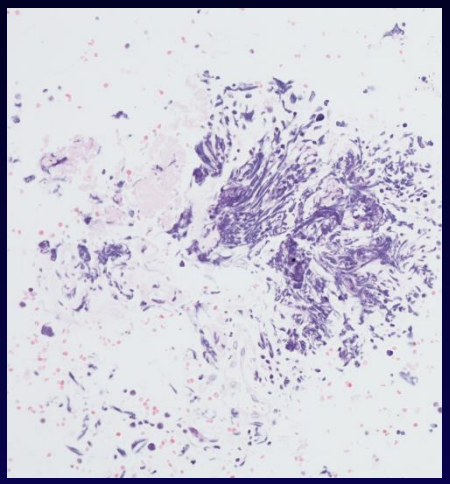
chromogranin

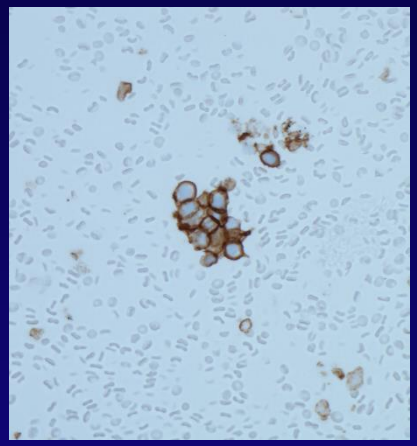
Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285

Small cell carcinoma

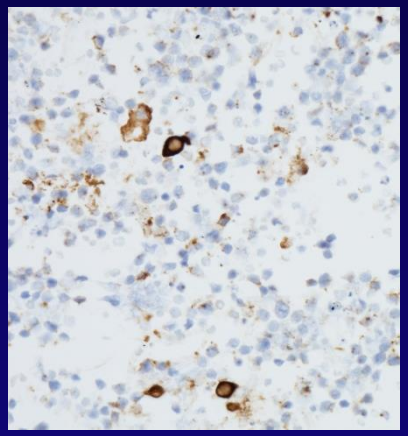


Cell pellet

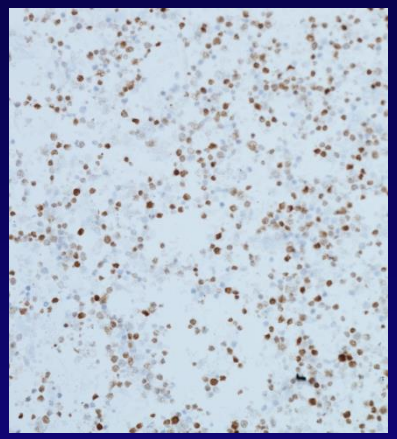




CD56



Cytokeratin

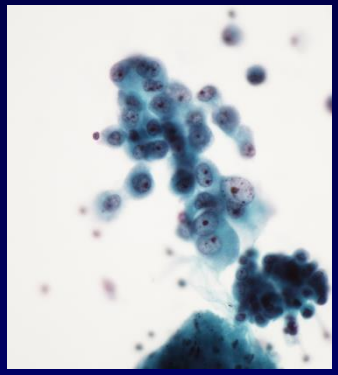


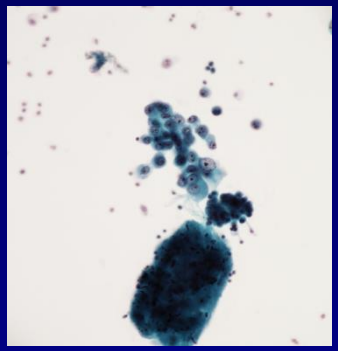
TTF-1

High proliferation rate on Ki-67

SPECIFIC TERMINOLOGY AND CRITERIA FOR ADENOCARCINOMA, SQUAMOUS CELL **CARCINOMA AND NON-SMALL CELL CARCINOMA-NOS IN SMALL BIOPSIES AND CYTOLOGY † (continued)**

New Small Biopsy/Cytology Terminology	Morphology/Stains	2015 WHO Classification in resection specimens
Non-small cell carcinoma, favor adenocarcinoma‡	Morphologic adenocarcinoma patterns not present, but supported by special stains, i.e. +TTF-1	Adenocarcinoma (solid pattern may be just one component of the tumor) ‡
Non-small cell carcinoma, favor squamous cell carcinoma‡	Morphologic squamous cell patterns not present, but supported by stains i.e. +p40	Squamous cell carcinoma, (nonkeratinizing pattern may be just one component of the tumor) ‡
Non-small cell carcinoma, not otherwise specified NSCLC-NOS‡‡	No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern	LARGE CELL CARCINOMA



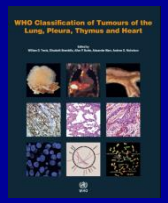


†† Metastatic carcinomas should be carefully excluded with clinical and appropriate but judicious immunohistochemical examination.

‡The categories do not always correspond to solid predominant adenocarcinoma or non-keratinizing squamous cell carcinoma respectively. Poorly differentiated components in adenocarcinoma or squamous cell carcinoma may be sampled.

‡‡ NSCLC-NOS pattern can be seen not only in large cell carcinomas but also when the solid poorly differentiated component of adenocarcinomas or squamous cell carcinomas are sampled but do not express immunohistochemical markers or mucin

Thyroid transcription factor-1 (TTF-1), WHO – World Health Organization



Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285

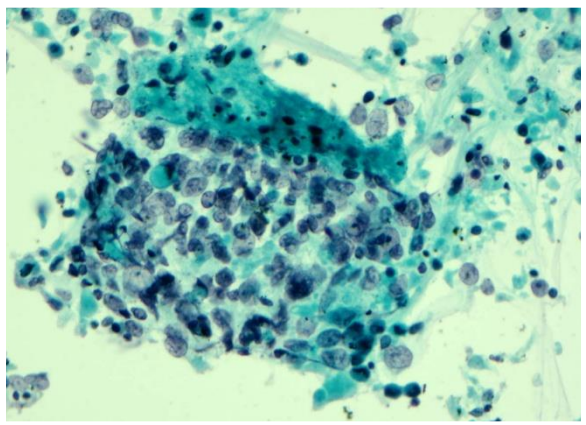
What IHC should I do....?

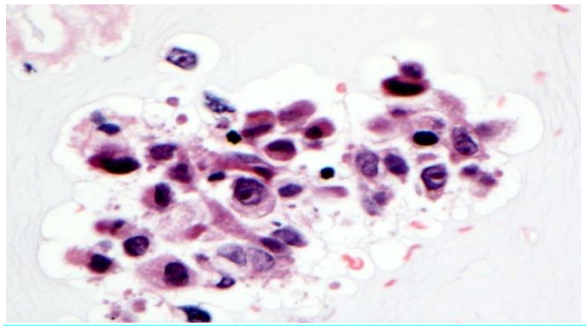
Marker	Result	Description
AE1/AE3	Positive	Keratins: 40, 48, 50, 52, 54, 56.5, 58, 59, 64, 65, 67
CK7	Positive-Diffuse/Strong	Keratin: 54 kD, Subset of Carcinomas (OV-TL 12/30)
TTF-1	Positive-Diffuse/Strong	Thyroid Transcription Factor-1, Lung and Thyroid Carcinomas
Napsin A	Positive-Diffuse/Strong	Lung Adenocarcinomas
ER (1D5)	Negative	Estrogen Receptor (1D5)
Mammaglobin	Negative	Breast, Uterine, Salivary Gland and Skin Appendage Tumors
S100	Negative	S100 Protein, Nerve Sheath Tumor, Melanomas, Chondrocytes
WT-1 (N-terminus)	Negative	Mesothelial & Mullerian Tumors, DSRCT
CA125	Positive-Few Cells	Ovarian, Breast, other Adenocarcinomas
CEA (p)	Positive	Carcinoembryonic Antigen (Polyclonal), Adenocarcinomas
Synaptophysin	Negative	Synaptophysin, Neural, Neuroendocrine Tumors
CA19.9	Negative	Pancreas, GI, Ovary, Lung and Bladder Carcinoma
CDX2	Negative	Colorectal Carcinoma
GCDFP-15	Positive-Rare Cells	Gross Cystic Disease Fluid Protein-15, Breast, Salivary Gland
MOC 31	Positive	Epithelial Cells, Adenocarcinoma
PR (PgR 636)	Negative	Progesterone Receptor (PgR 636)
p63	Positive-Rare Cells	Prostatic basal cells, breast myoepithelial cells, squamous carcinoma
CK5,6	Negative	Keratin: Mesothelial & Squamous Cells, some Adenocarcinomas

Courtesy of Bill Travis

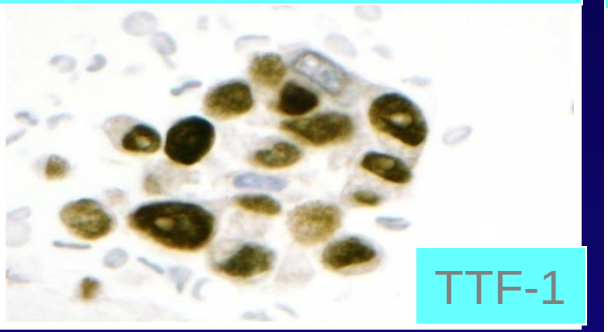
BIOPSY SUBCLASSIFICATION VALIDATION 2010-2011

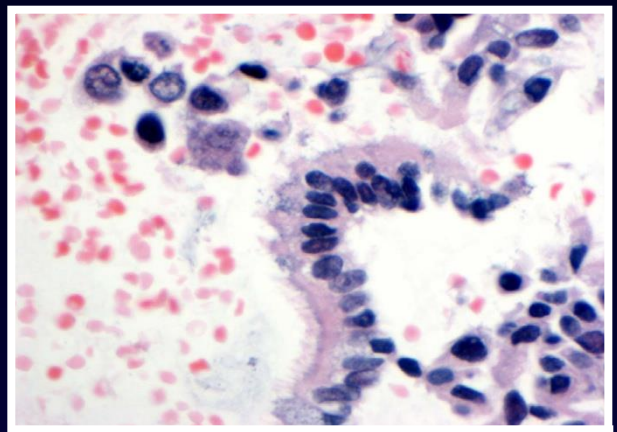
- Evaluation of adjunct immunohistochemistry on reporting patterns of non-small cell lung carcinoma diagnosed histologically in a regional pathology centre. McLean EC et al. J Clin Pathol. 2011
- Immunhistochemistry by Means of Widely Agreed-Upon Markers (Cytokeratins 5/6 and 7, p63, Thyroid Transcription Factor-1, and Vimentin) on Small Biopsies of Non-small Cell Lung Cancer Effectively Parallels the Corresponding Profiling and Eventual Diagnoses on Surgical Specimens. Pelosi G et al. J Thorac Oncol. 2011;6:1039-1049
- Suitability of thoracic cytology for new therapeutic paradigms in non-small cell lung carcinoma: high accuracy of tumor subtyping and feasibility of EGFR and KRAS molecular testing. Rekhtman N et al. J Thorac Oncol. 2011;6:451-8
- Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. Rekhtman N et al. Mod Pathol. 2011
- Rapid Multiplex Immunohistochemistry Using the 4-antibody Cocktail YANA-4 in Differentiating Primary Adenocarcinoma From Squamous Cell Carcinoma of the Lung. Yanagita E et al. Appl Immunohistochem Mol Morphol. 2011
- Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. Mukhopadhyay S, Katzenstein AL. Am J Surg Pathol. 2011;35:15-25
- Role of fine needle aspiration cytology, cell block preparation and CD63, P63 and CD56 immunostaining in classifying the specific tumor type of the lung. Kim DH, Kwon MS. Acta Cytol. 2010;54:55-9
- Subtyping of undifferentiated non-small cell carcinomas in bronchial biopsy specimens. Loo PS et al. J Thorac Oncol. 2010 ;5:442-7.
- Refining the diagnosis and EGFR status of non-small cell lung carcinoma in biopsy and cytologic material, using a panel of mucin staining, TTF-1, cytokeratin 5/6, and P63, and EGFR mutation analysis. Nicholson AG et al. J Thorac Oncol. 2010 Apr;5(4):436-41.

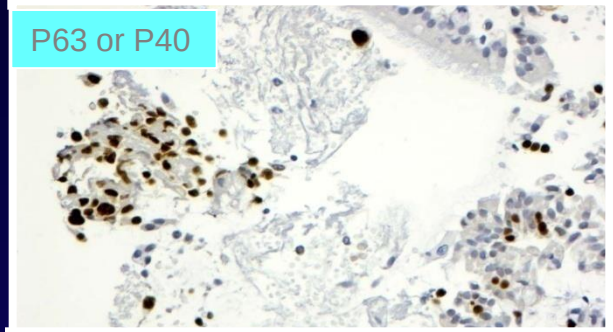




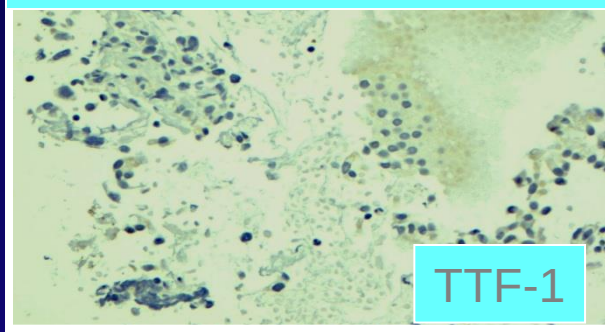
NSCLC, favouring ADC







NSCLC, favouring SQCC



Fix quickly

Only cut tissue once unless absolutely necessary (take spare sections)

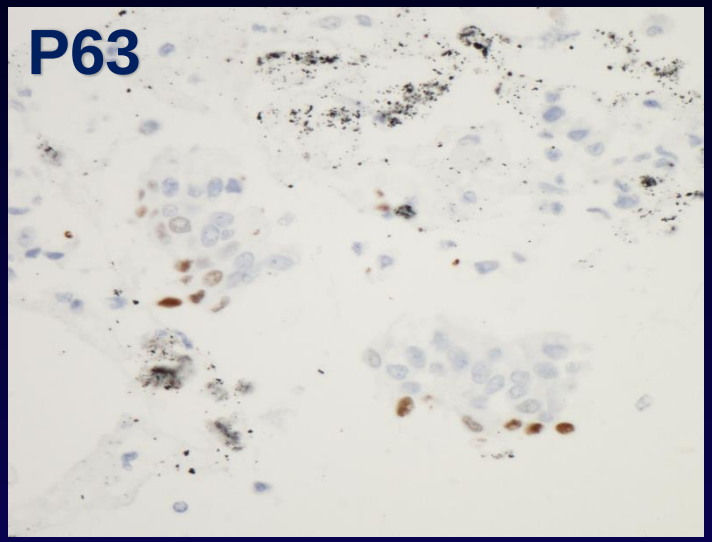
H&E (diagnosis in ~ 60% of cases)

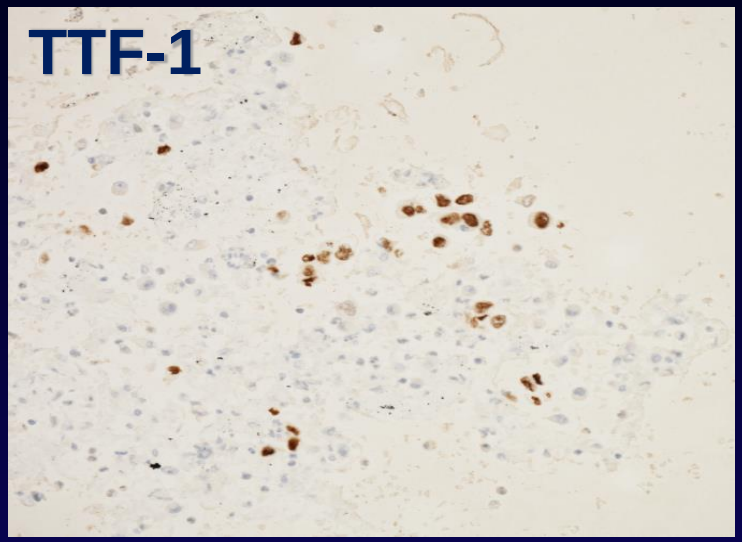
↓

TTF-1 and P40, P63, or CK5/6 (diagnosis in ~90% of cases)

NSCLC-NOS rates are mainly below 15% in the UK (aim for 10%)

Divergent immunohistochemistry…

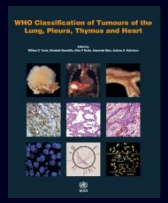




If there is diffuse positivity for TTF-1 and staining P63 (or P40) in the same cells, then this should be classified as:

Non-small cell carcinoma favouring adenocarcinoma on IHC

If there is diffuse positivity for TTF-1 and staining P63 (or P40) in the different cells, then consider adenosquamous carcinoma



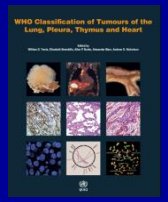
IHC typing of CK + morphologically undifferentiated NSCLC (mucin stains already undertaken to exclude solid pattern ADC**). Focal = 0-10% of cells positive, Diffuse = >10% of cells positive

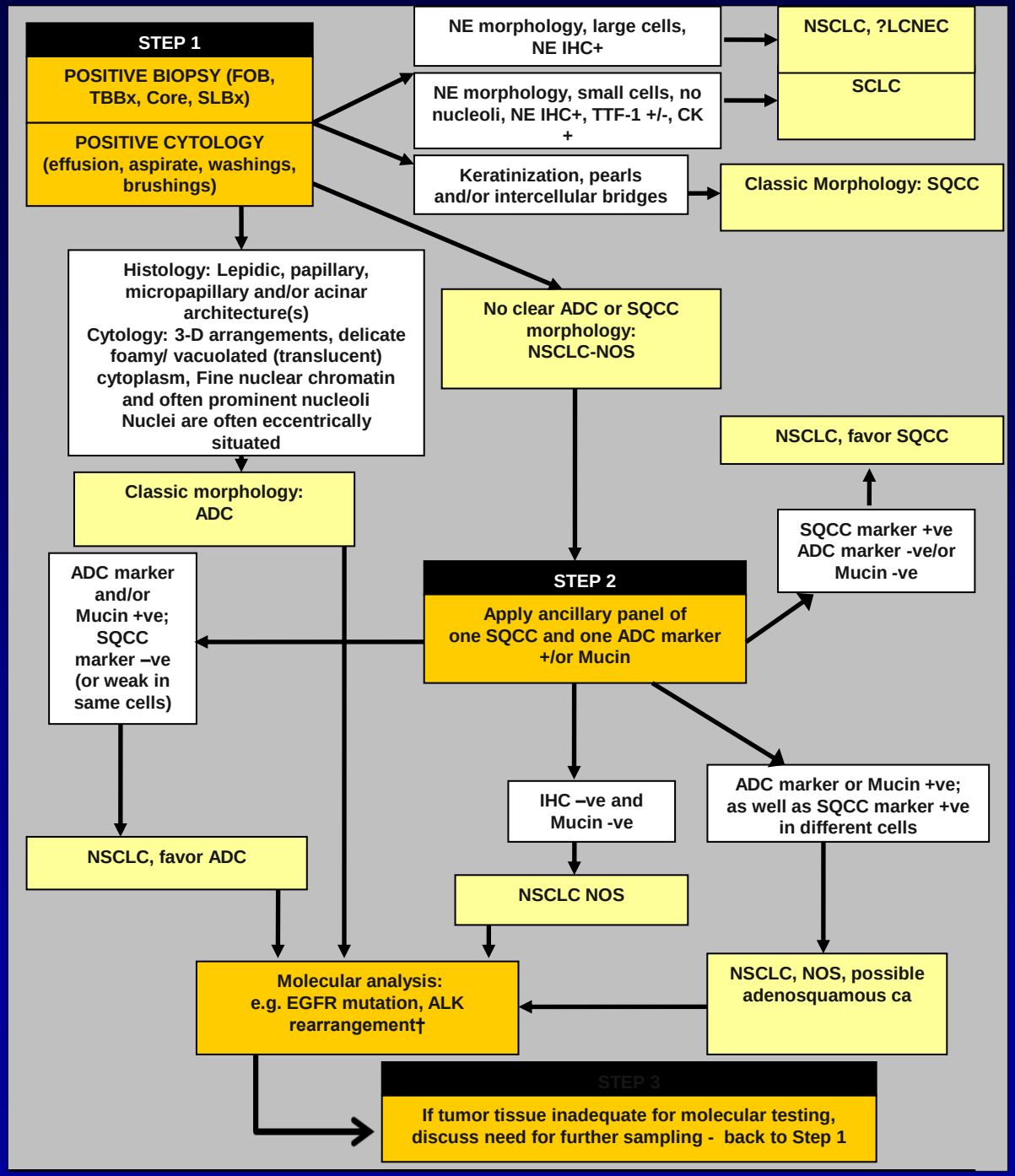
TTF-1		P63	P40	CK5/6		DIAGNOSIS (RESECTION)	DIAGNOSIS (BIOPSY/CYTO)
Positive focal or diffuse		Negative	Negative	Negative		ADC	NSCLC, favour ADC
Positive focal or diffuse		Positive, focal or diffuse	Negative	Negative		ADC	NSCLC, favour ADC
Positive focal or diffuse		Positive, focal or diffuse	Positive, focal	Negative		ADC	NSCLC, favour ADC
Positive focal or diffuse		Negative	Negative	Positive, focal		ADC	NSCLC, favour ADC
Negative		Any one of above diffusely positive				SQCC	NSCLC, favour SQCC
Negative		Any one of above focally positive				LCC-unclear#	NSCLC-NOS
Negative		Negative	Negative	Negative		LCC-null***	NSCLC-NOS
No stains available		No stains available	No stains available	No stains available		LCC with no additional stains	NSCLC-NOS (no stains available)

*Napsin may be used as an alternative to TTF-1. Although a sensitive marker, CK7 is not recommended as a marker of adenocarcinomatous differentiation due to a lack of specificity.
** Positive for mucin is defined as (5 or more droplets in 2 consecutive high power fields in resections {2004 WHO book} and mucin droplets in two or more cells within a biopsy). Fewer positive cells are regarded as negative.
*** Sarcomatoid carcinoma and neuroendocrine tumours should be excluded (i.e. undifferentiated morphology with no spindle/giant cells).
# Negativity for TTF1 and focal positivity for p63/p40/CK5-6 point to adenocarcinoma cell lineage once neuroendocrine tumours are excluded

Adapted from:

Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285



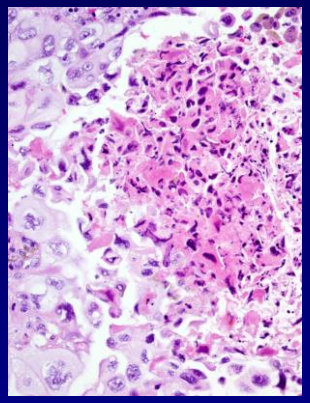


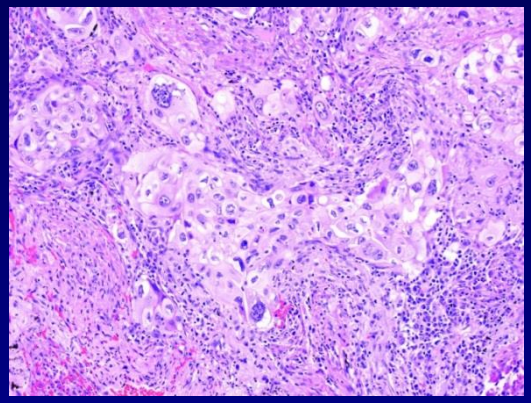
Putting into practice…

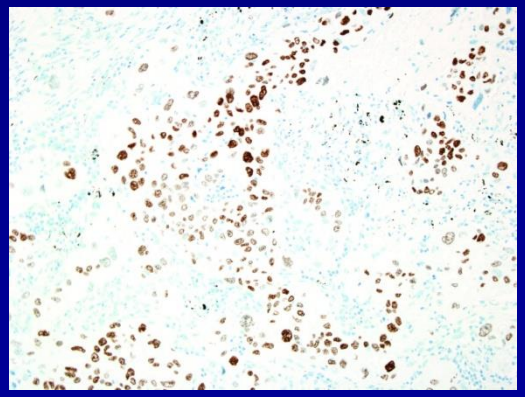
Beware of pitfalls….

“Pseudosquamoid” solid ADC

Rekhtman N et al. Clin Cancer Res 2012;18:1167-1176





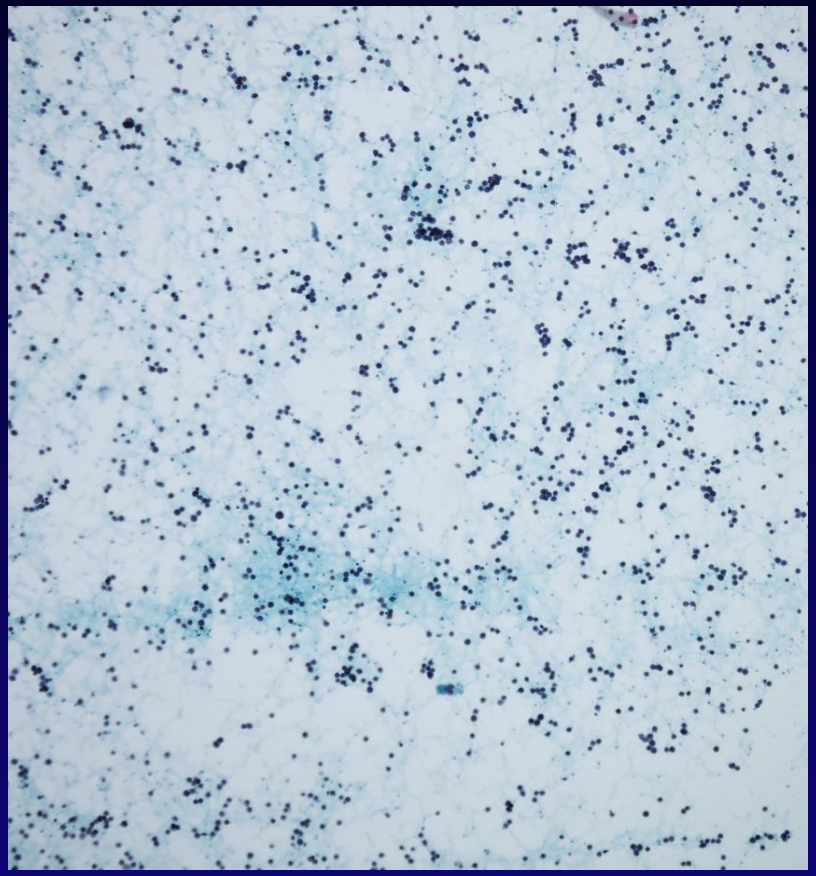


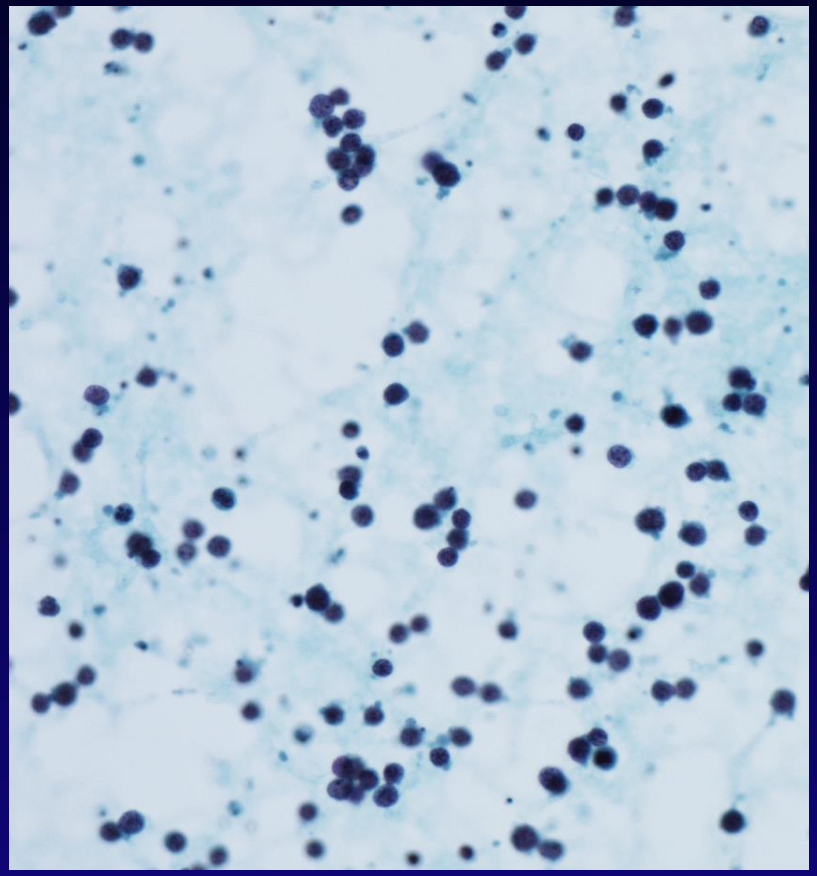
TTF-1

Table 5. Summary of reassessment of 16 *EGFR/KRAS*-mutant SQCCs identified by routine clinical genotyping

Characteristics[a]	*N* (%)
Specimen type	
Small specimen (biopsy or cytology)	12 (75)
Surgical resection	4 (25)
Tumor site	
Lung primary	8 (50)
Metastasis (lymph node, adrenal, bone, skin)	6 (38)
Recurrence	2 (11)
Interpretation after morphologic and immunohistochemical reassessment	
Reclassified as AD-SQC[b]	10 (63)
Reclassified as solid adenocarcinoma by IHC	5 (31)
Indeterminate	1 (6)
Smoking status by mutation	
EGFR-mutant "SQCC"	10 (63)
Never	7
Current or former	3
KRAS-mutant "SQCC"	6 (37)
Never	1
Current or former	5

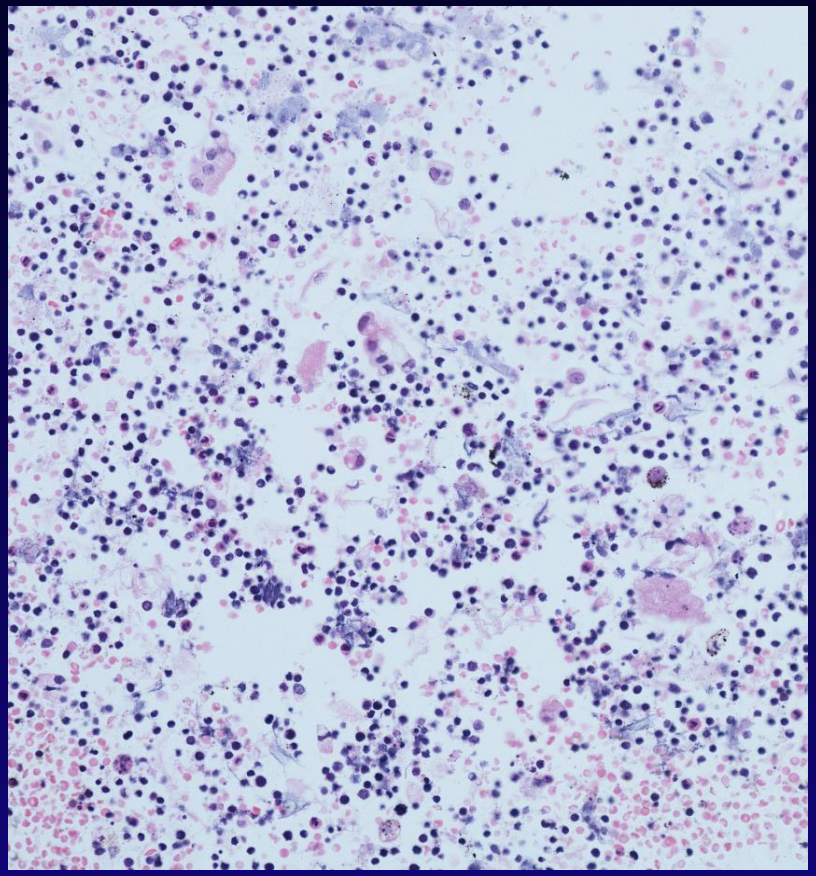
TBNA lymph node aspirate….



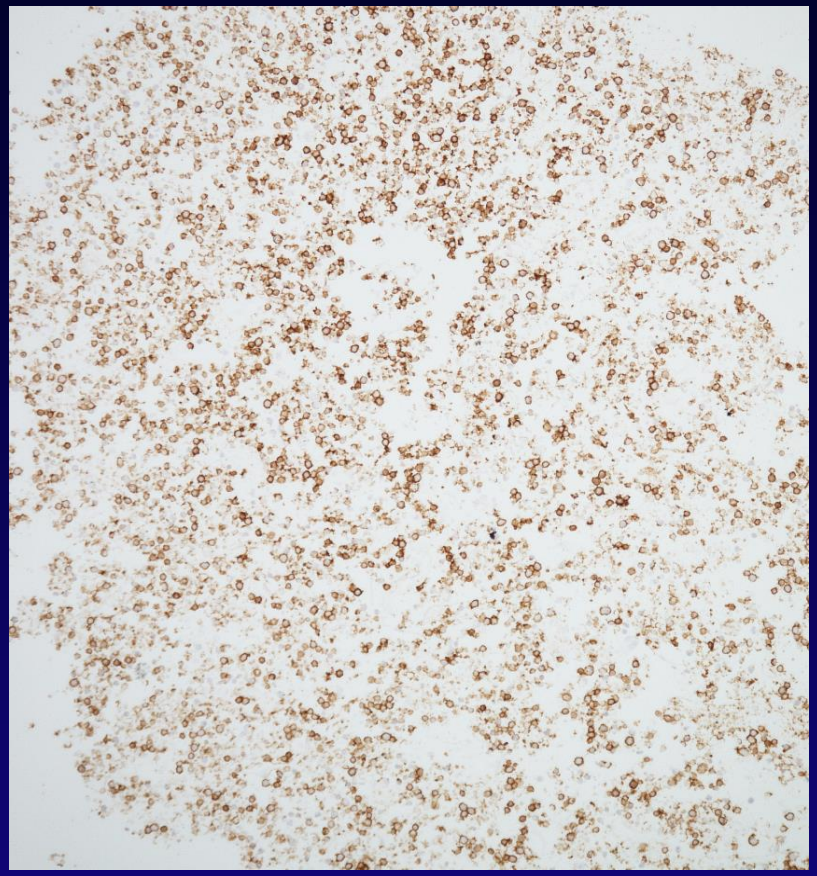


Originally reported as negative, lymphocytes

Metastatic small cell carcinoma

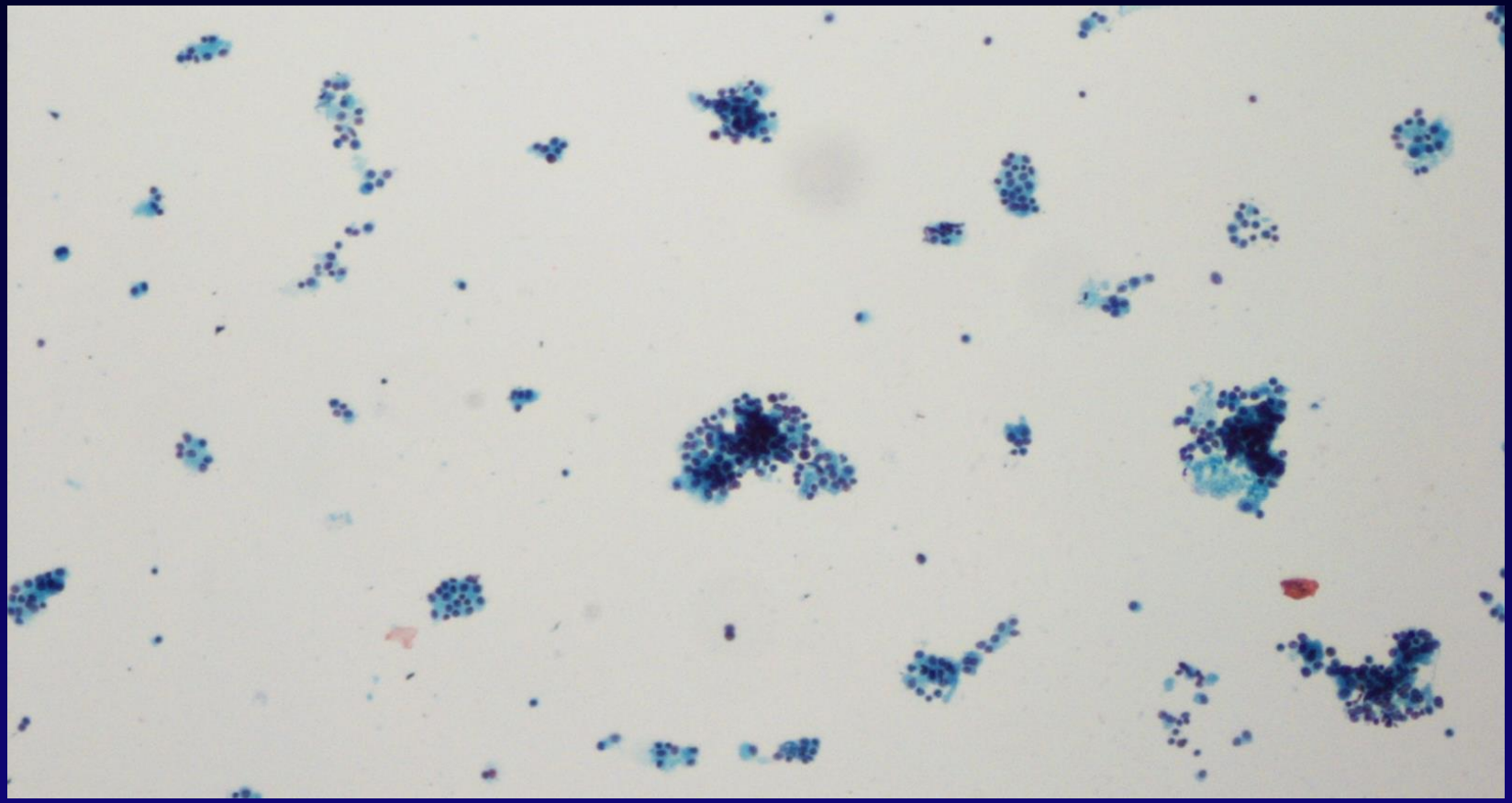


Cell pellet



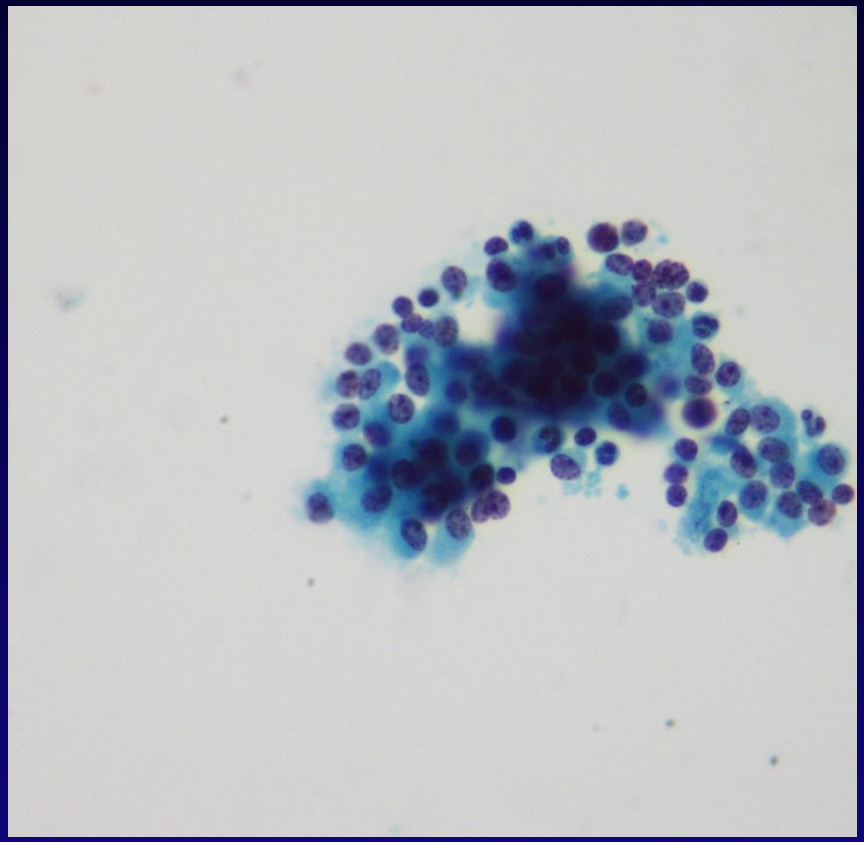
CD56

EBUS TBNA parabronchial mass "low grade epithelioid tumour"

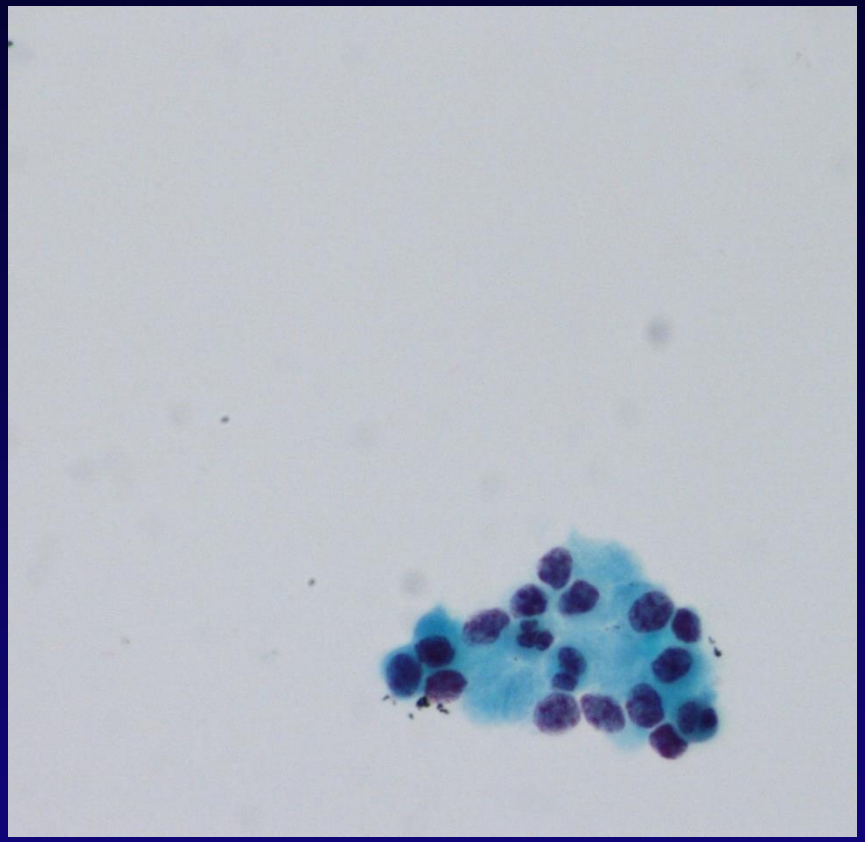


Carcinoid tumour

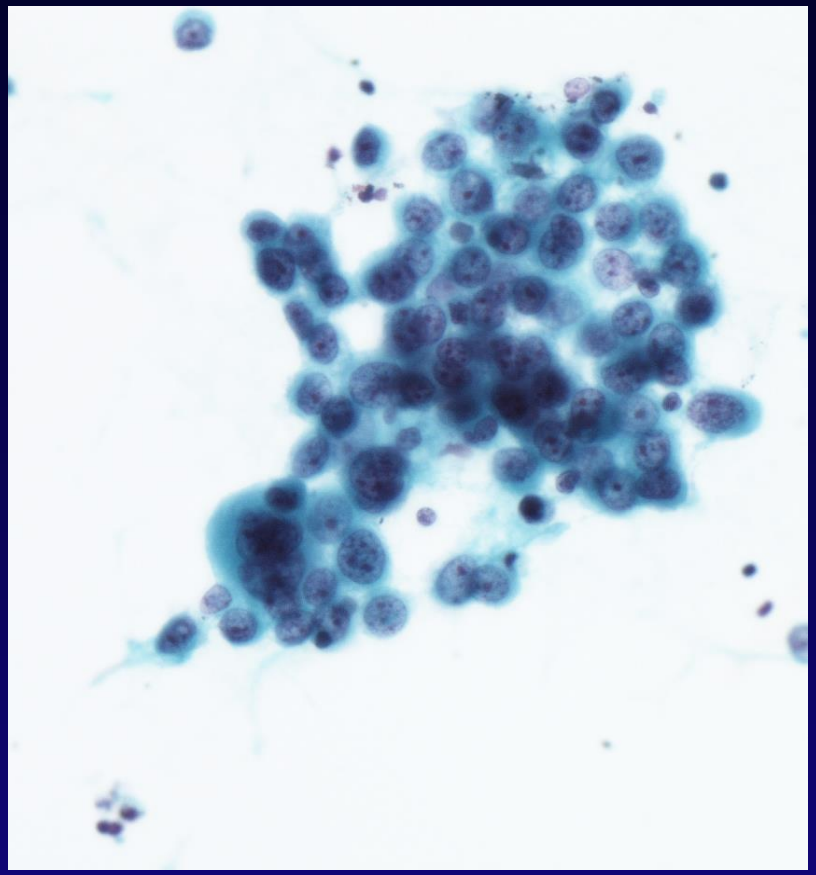
Bland plasmacytoid cells

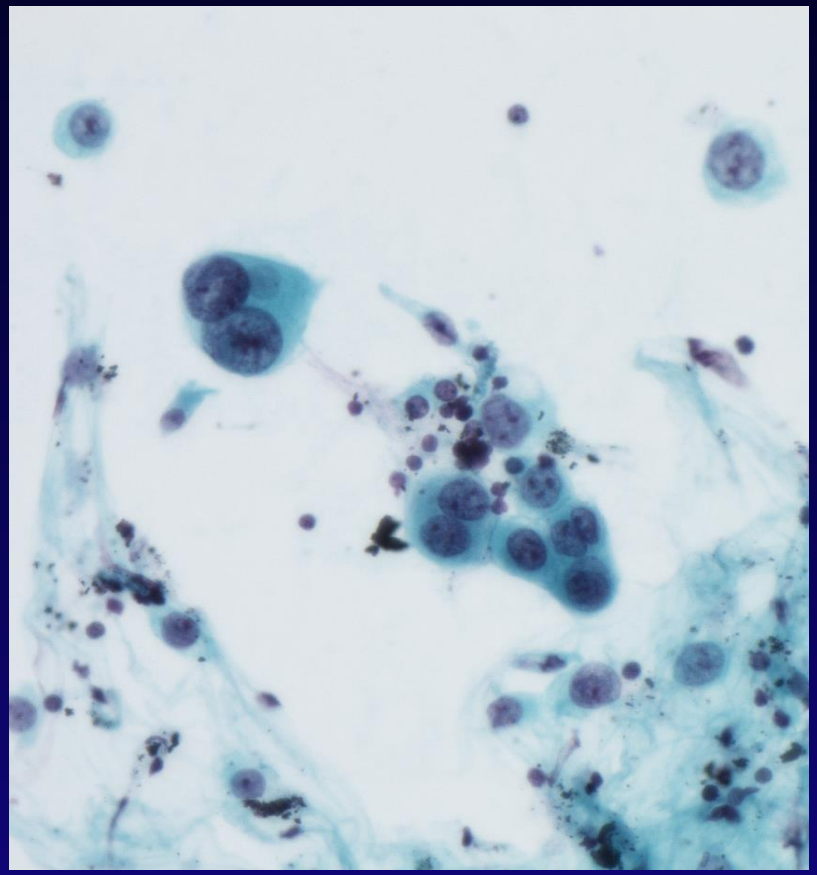


Rosettes

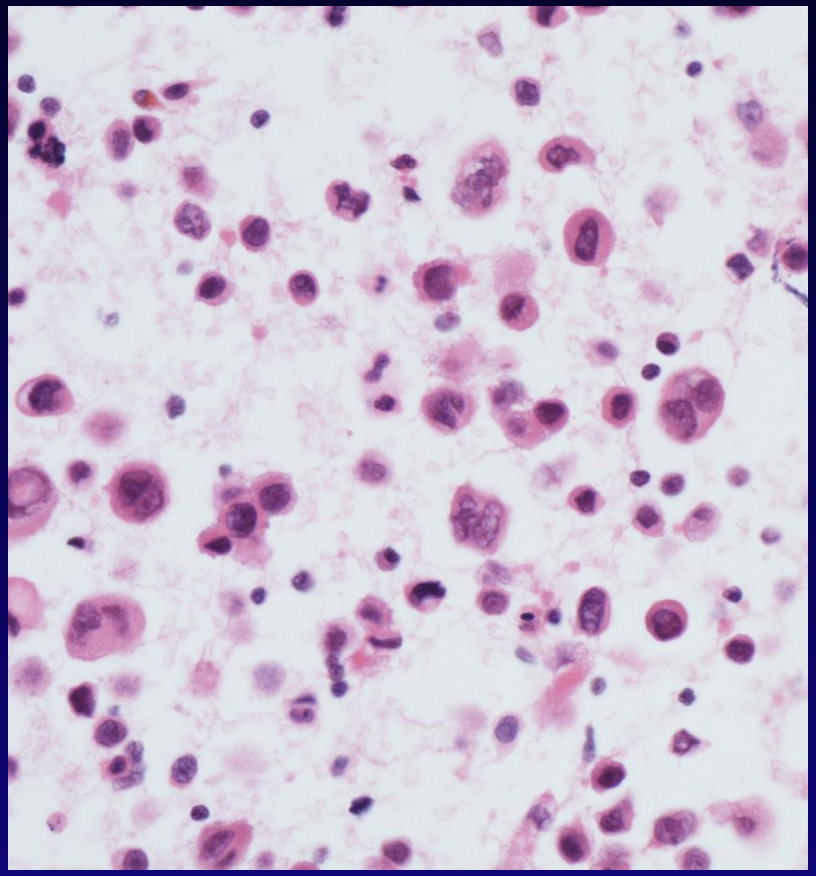


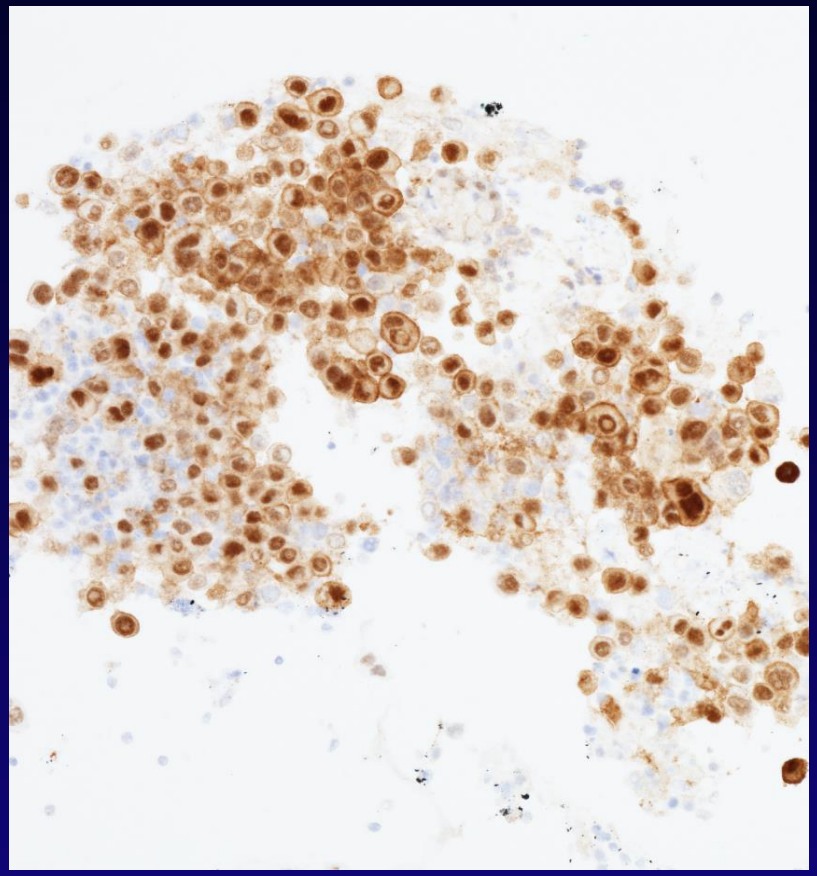
“Metastatic non-small cell carcinoma/epithelioid tumour”





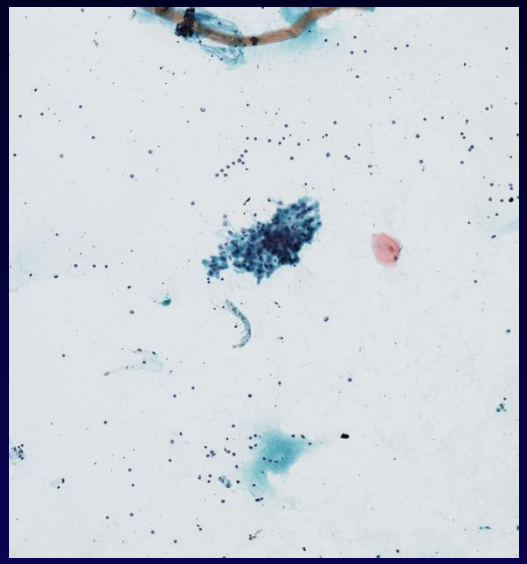
Metastatic melanoma

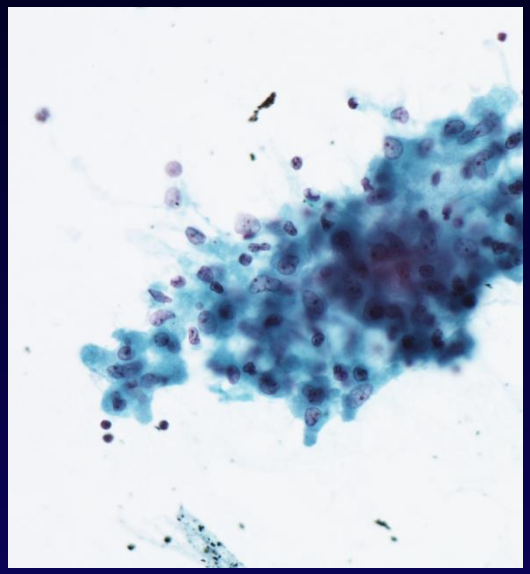


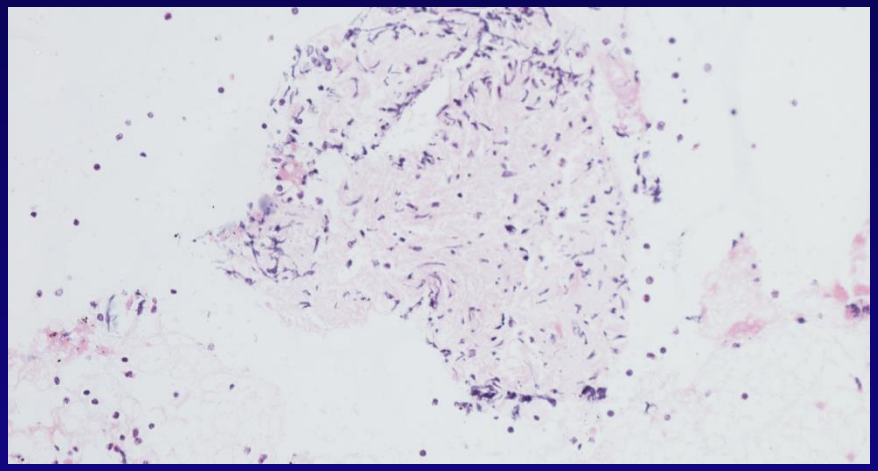


S100

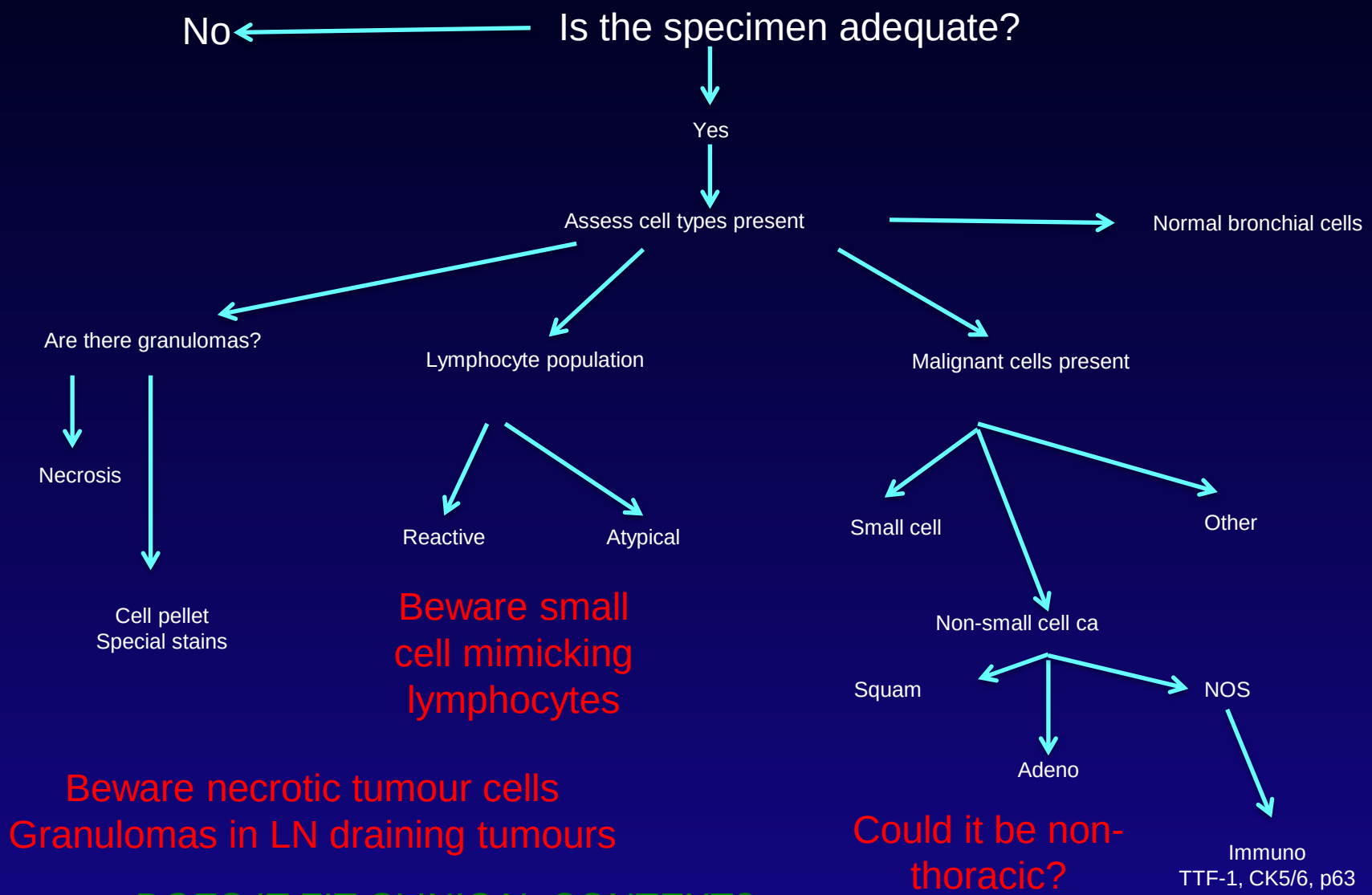
Non-neoplastic pathology







Diagnostic Algorithm for EBUS TBNA



Tissue Handling

Separate embedding of multiple cores

“Diagnostic” core

“Molecular” core

Memorial Sloan Kettering Cancer Center

Slide provided by Natasha Rekhtman

Molecular testing on cytology: smears vs cell blocks

- **Smears:**
  - Pros:
    - N
    - FI
  - Cons:
    - D
      C
    - IH
    - Sc
- **Cell blo**
  - Pros:
    - O
    - N
  - Cons:
    - …

Arch Pathol Lab Med 2013

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

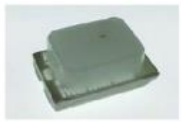
Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

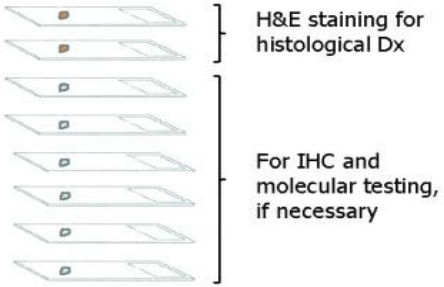
Neal I. Lindeman, MD; Philip T. Cagle, MD; Mary Beth Beasley, MD; Dhananjay Arun Chitale, MD; Sanja Dacic, MD, PhD; Giuseppe Giaccone, MD, PhD; Robert Brian Jenkins, MD, PhD; David J. Kwiatkowski, MD, PhD; Juan-Sebastian Saldivar, MD; Jeremy Squire, PhD; Erik Thunnissen, MD, PhD; Marc Ladanyi, MD

"4.2: Expert Consensus Opinion.
- Cytologic samples are suitable for EGFR and ALK testing, with cell blocks being preferred over smear preparations."

Tissue Handling

Step 1. In the initial block sectioning, sufficient unstained spares should be prepared for potential IHC and molecular testing, the necessity of latter which should be determined with discussion with clinicians.





Step 2. According to the histological status, further procedures should be followed.

Clear morphology (ADC, SQCC, SCLC) -> Diagnosis
NSCLC, NOS: Examined with a panel of at least one but no more than two ADC-specific (e.g. TTF-1, CK7) and SQCC-specific (e.g. p40 and CK5/6) marker using the u/s sections
Looks like SCLC: Be confirmed by a panel of cytokeartin, CD56 and TTF-1 if required, using the unstained sections
Looks like NSCLC with NE morphology: Be confirmed by a panel of CD56 and/or chromogranin and/or synaptophysin.
If there is no evidence of tumour on initial levels, Undertake further sectioning
If tumour is only present in the first two levels, Discuss with clinician and molecular biologist about what testing may be needed and what is feasible on the sections should be undertaken. Re-biopsy may be required

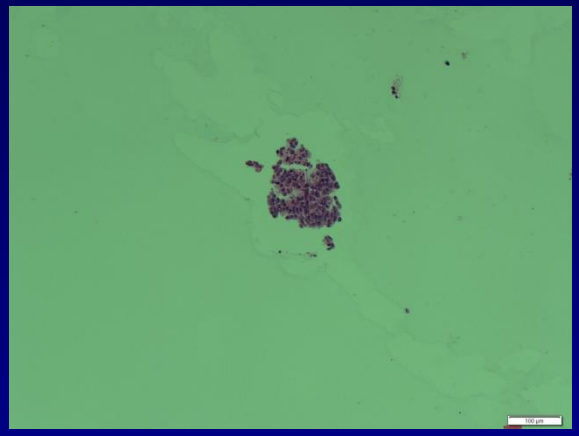
Step 3. When molecular testing is needed, the adequacy of specimens for molecular testing in terms of cancer cell content and DNA quantity and quality should be accessed.

Failure and cellularity (CRUK):

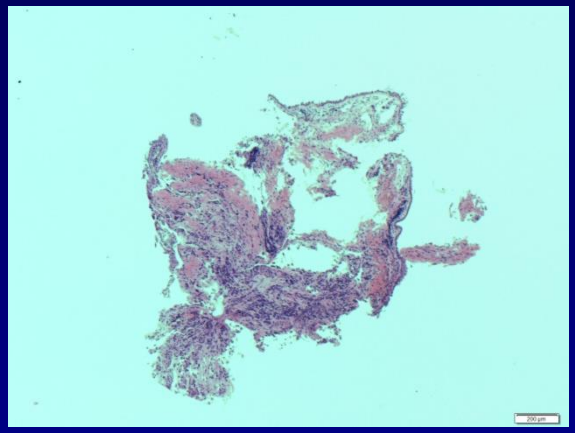
Category	Number of cells
v low	<100
v low - low	100-700
low	~1,000
low-intermediate	1,500-4,000
Intermediate	4,000-10,000
High	>10,000
v high	>50,000

ASSESSMENT CATEGORIES:

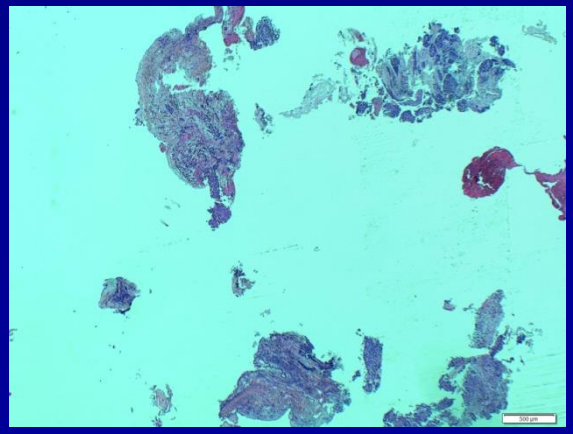
14_1002 100x VERY LOW <0.01ng/uL NGS FAIL



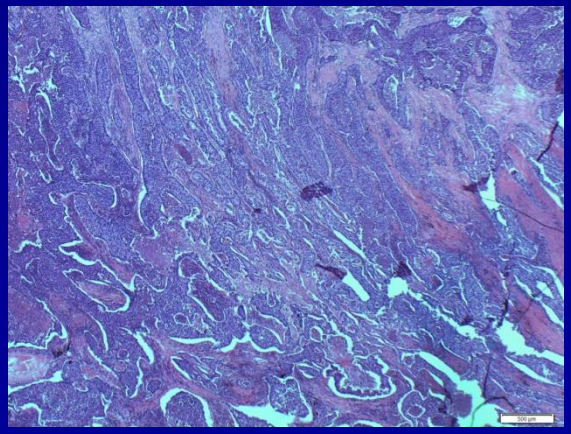
14_1010 40x LOW <0.01ng/uL NGS FAIL



14_1039 20x INTERMEDIATE 5.3ng/uL NGS PASS



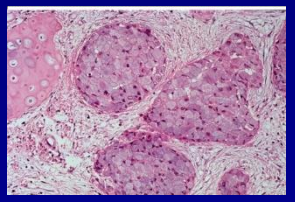
14_1026 20x HIGH 47.5ng/uL NGS PASS



Courtesy of CRUK

Best Practice for Usage of Tissue – Everyone has a Role to Play!

- Pre-examination phase
  - Identify those who you would consider for targeted therapy
  - Handle tissue appropriately (right media, timely fixation etc)
  - Put core biopsies in separate pots
- Examination phase ("judicious use of tissue")
  - Consider separate blocks for different cores
  - Cut into the tissue carefully (if cutting levels, take spare sections)
  - Selection for testing based on histology
    - ADC versus SQCC
    - Apply immunohistochemistry appropriately (ideally only once)
    - Specific antibodies (ALK)
      - ALK IHC correlates with gene rearrangement



Boland JM et al. *Hum Pathol.* 2009;40(8):1152-1158; Conklin CM et al. *J Thorac Oncol.* 2013;8(1):45-51.

- Post-examination phase
  - Provide data on tumour load in the sample
  - Enhance tumour load by microdissection

1-1D Molecular testing for treatment selection in lung cancer

Guidelines for the good use of tissue for molecular studies (from WHO 2015: chapter 1-1D)
Tissue specimens should be managed not only for diagnosis, but also to maximise the amount of tissue available for molecular studies.
Cell blocks should be prepared for cytology samples (including pleural fluids) when positive lung cancer, as it is not possible to predict whether other material is suitable for IHC or molecular analysis.
To guide therapy of patients with advanced lung cancer, each institution should have multidisciplinary team that coordinates the optimal approach to using tissue for molecular studies.
The pathology department should ensure that all molecular results become part of the records each individual specimen.

- Issues in 2015
  - Integrating next generation sequencing in to clinical practice
  - Prioritisation of which test first
  - Competition for IHC based tests (PD-L1, ALK IHC).
  - Getting complex results into the pathology report in understandable and timely fashion….

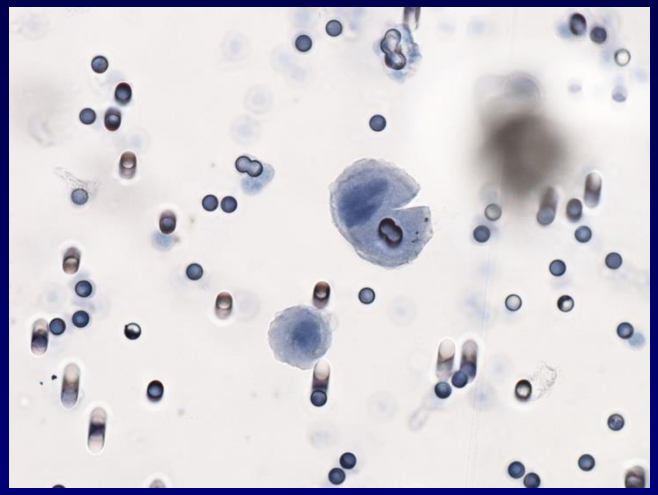
Sampling and analysis

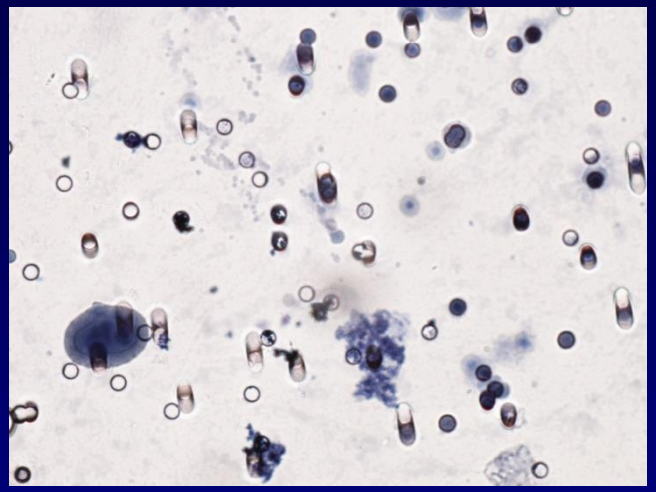
1994	2015	**2020-30**
• Sputum	• Washings	• Washings
• Brushings, Washings	• Biopsies	• Biopsies
• Biopsies	• Core needle	• Core needle
• Core needle	• TBNA (cytology)	• TBNA (biopsy)
• Mediastinoscopy	• VATS/open resection	• VATS/open resection
• Open resections	• Systematic nodal resection	• Systematic nodal resection
	• No tissue (Cyber knife/RFA)	• Circulating tumour cells
		• Blood
		• Breath
		• No tissue (Cyber knife/RFA)

Samples are getting smaller….

At some point, will there be a rate limiting size?
Will there be a rate limiting number of samples (heterogeneity)

Circulating tumour cells.....





Circulating Tumor Cell as a Diagnostic Marker in Primary Lung Cancer

Fumihiro Tanaka,[1] Kazue Yoneda,[1] Nobuyuki Kondo,[1] Masaki Hashimoto,[1] Teruhisa Takuwa,[1] Seiji Matsumoto,[1] Yoshitomo Okumura,[1] Shakibur Rahman,[1] Noriaki Tsubota,[2] Tohru Tsujimura,[3] Kozo Kuribayashi,[4] Kazuya Fukuoka,[4] Takashi Nakano,[4] and Seiki Hasegawa[1]

CTCs were first described in 1869

Ashworth, T. R (1869). "A case of cancer in which cells similar to those in the tumours were seen in the blood after death". Australian Medical Journal 14: 146–7

As of 2013, only one system has FDA clearance for clinical usage.

Overview of Applications of Molecular Diagnostics in Current Practice: Lung

- Accurate and consistent classification using the WHO 2015 terminology for biopsies and cytology

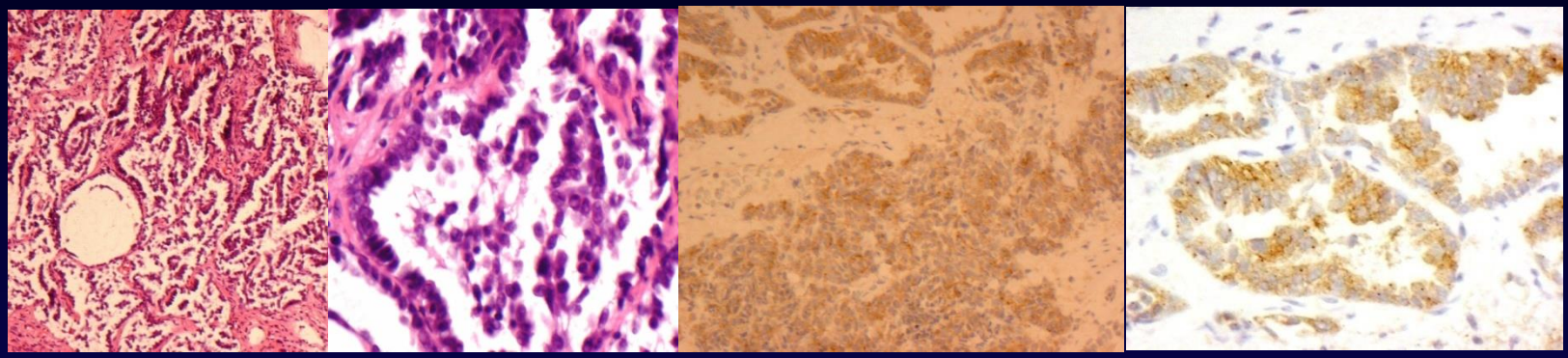
- Beware pitfalls
  - Dispersed population tumour cells
  - Small cell carcinoma vs lymphocytes
  - Metastatic carcinoma from extrathoracic malignancies
  - Rare tumours
  - Low cellularity & necrosis
  - Review at high power, beware cellular necrosisReactive bronchial epithelial cells, goblet cells and seromucinous glands

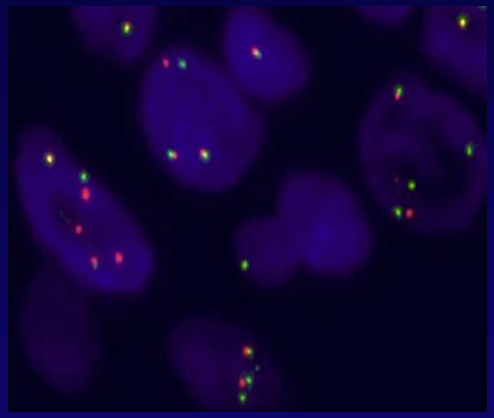
- **Appropriate** use of immunohistochemistry will reduce error rate and rate of NSCLC-NOS
- **Do not use IHC indiscriminately as it wastes tissue that may be needed for molecular studies**

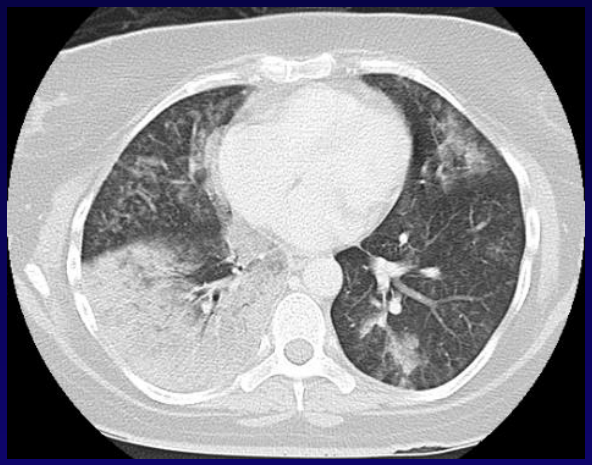
- Tissue availability – prioritising for best practice
  - All clinical staff should be thinking about it!
  - Standardisation of specimen handling

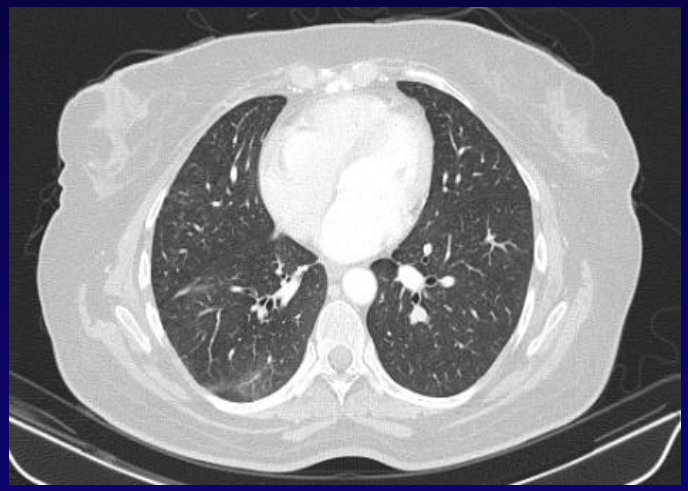
- Molecular diagnostics
  - More targets will appear leading to ever increasing competition for less tissue

Pathology in practice…
ADC with an ALK translocation









JULY 2011

MARCH 2012

Courtesy of Dr S Popat, RMH