

Undifferentiated Carcinomas: What are the issues

Keith M Kerr

Department of Pathology

Aberdeen University Medical School

Aberdeen, UK

Large Cell Carcinoma and Sarcomatoid Carcinomas

2004 WHO Classification	2015 WHO Classification
Squamous Cell Carcinoma	Adenocarcinoma
Small Cell Carcinoma	Squamous Cell Carcinoma
Adenocarcinoma	Neuroendocrine tumours
Large cell carcinoma	Large Cell Carcinoma
Adenosquamous carcinoma	Adenosquamous carcinoma
Sarcomatoid carcinoma	Sarcomatoid carcinomas
Carcinoid tumour	Other and Unclassified carcinomas
Salivary gland tumours	Salivary gland tumours

Undifferentiated carcinomas: Context

- Surgically resected tumours
 - Undifferentiated carcinomas **without** evidence of severe pleomorphism, tumour giant cells or spindle cells: Large Cell Carcinoma
 - Undifferentiated carcinoma **with** evidence of severe pleomorphism, tumour giant cells or spindle cells: Sarcomatoid Carcinomas
- This discussion excludes consideration of undifferentiated carcinoma in the context of a small biopsy or cytology samples: NSCLC-NOS. In the majority of these cases, **the tumour IS differentiated**, only the differentiated components have not been sampled.

Large Cell Carcinoma: 2004 definition

Definition

Large cell carcinoma is an undifferentiated non-small cell carcinoma (NSCC) that lacks the cytological (and architectural) features of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma. The diagnosis requires a thoroughly sampled resected tumour, and cannot be made on non-resection or cytology specimens.

A green oval callout with a slight gradient and shadow, containing the text '~10% of cases?' in white.

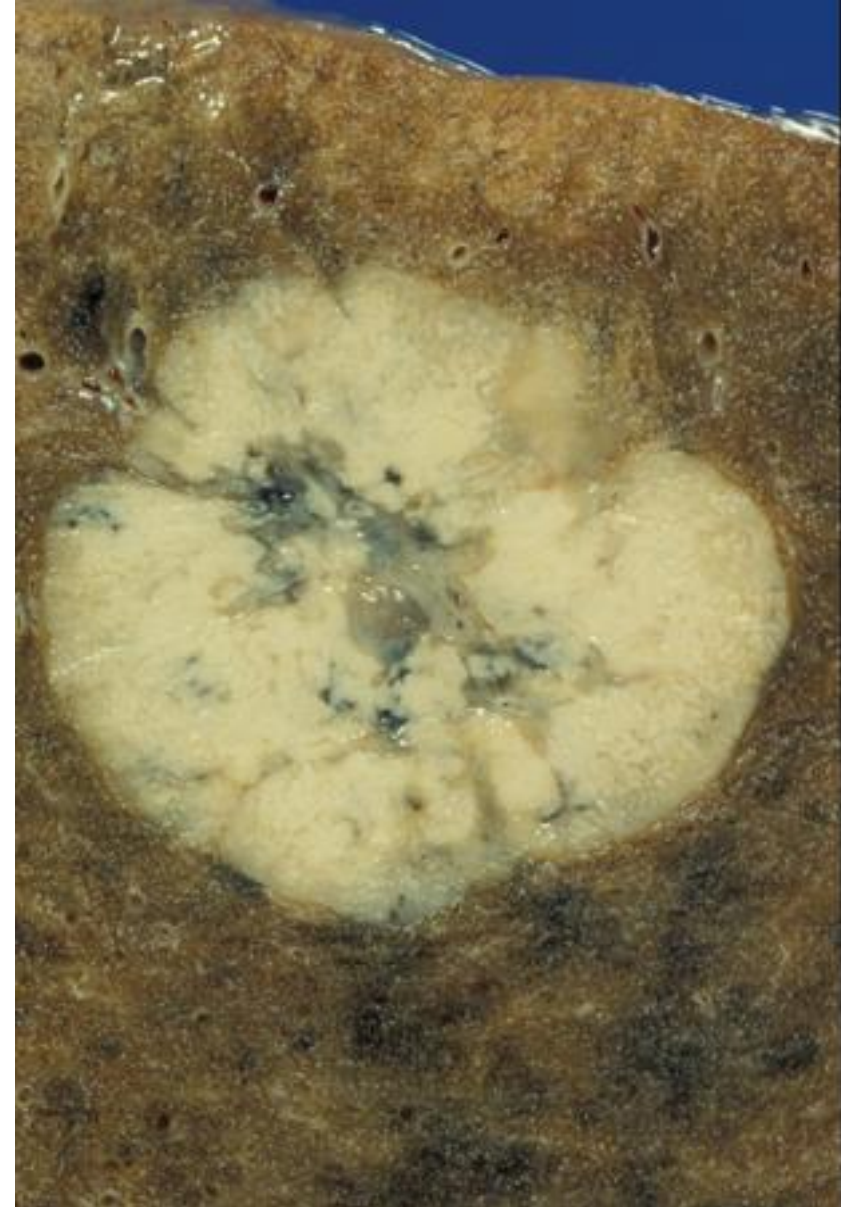
~10% of
cases?

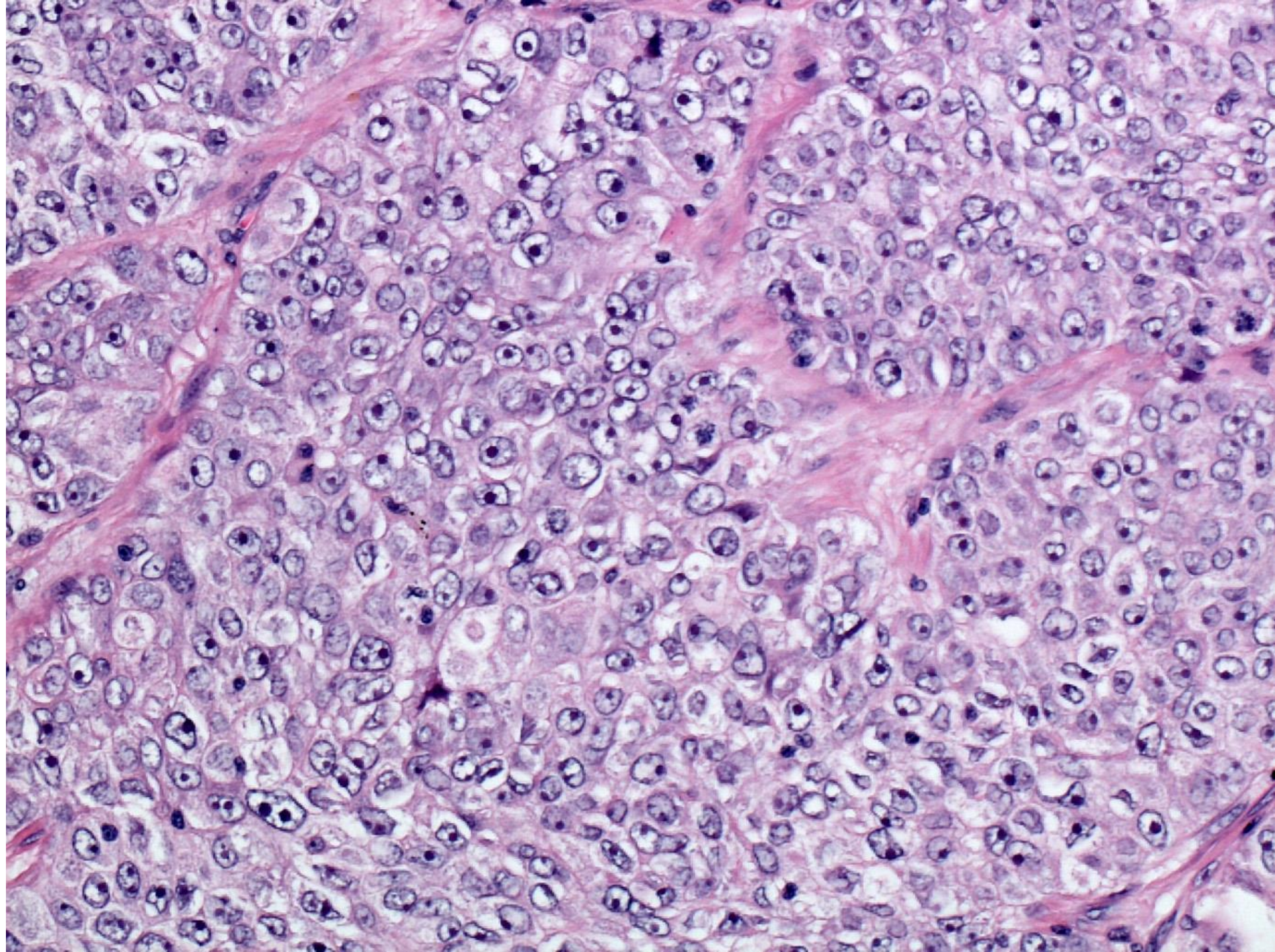
Large Cell Carcinomas: 2004

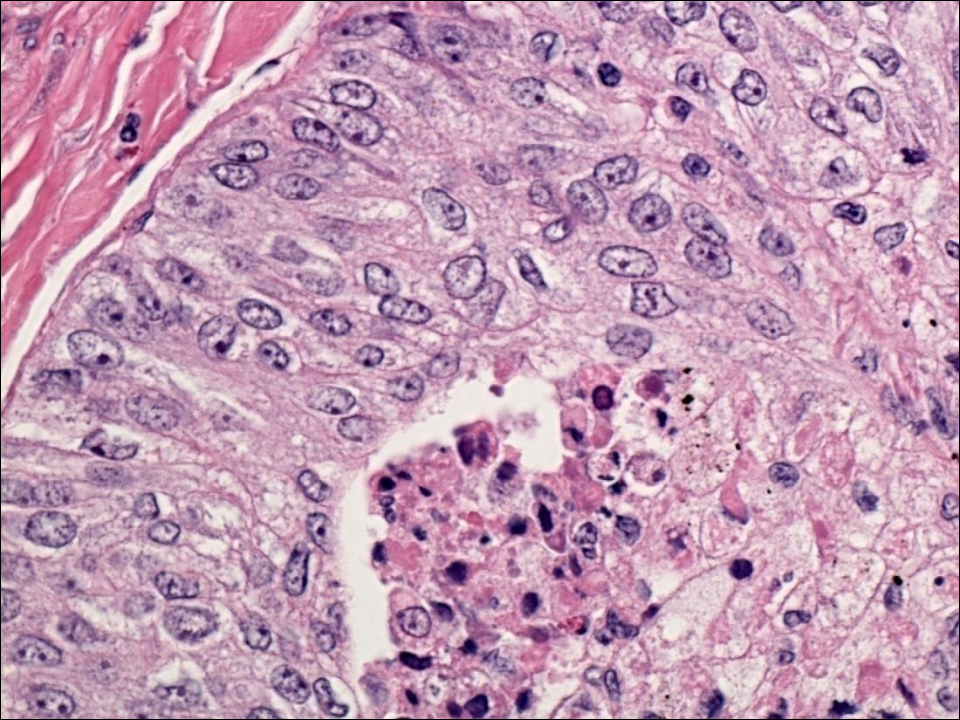
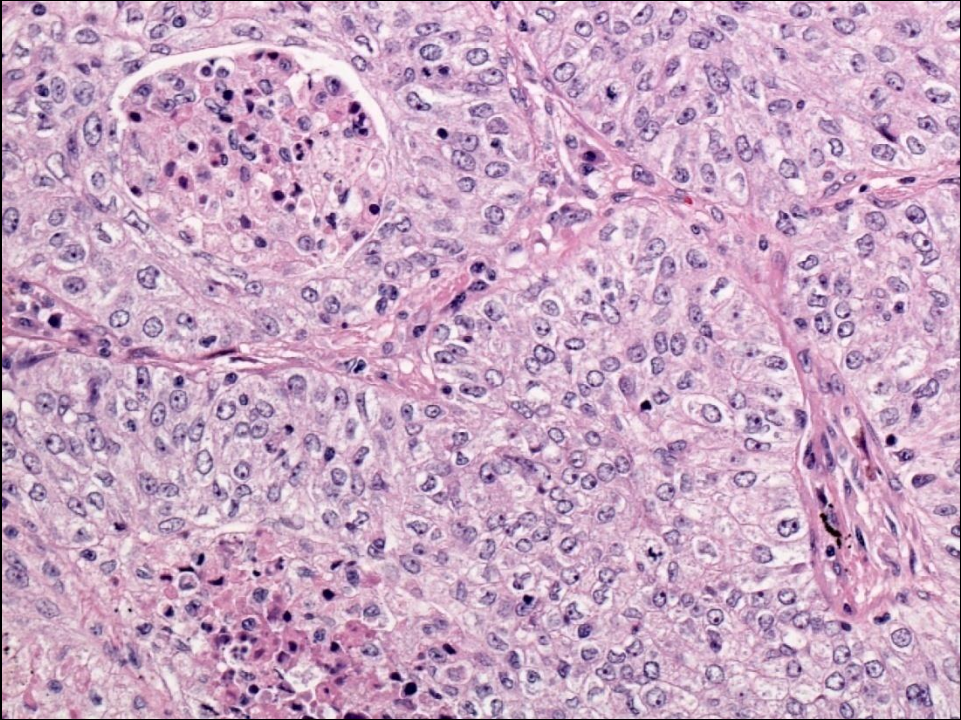
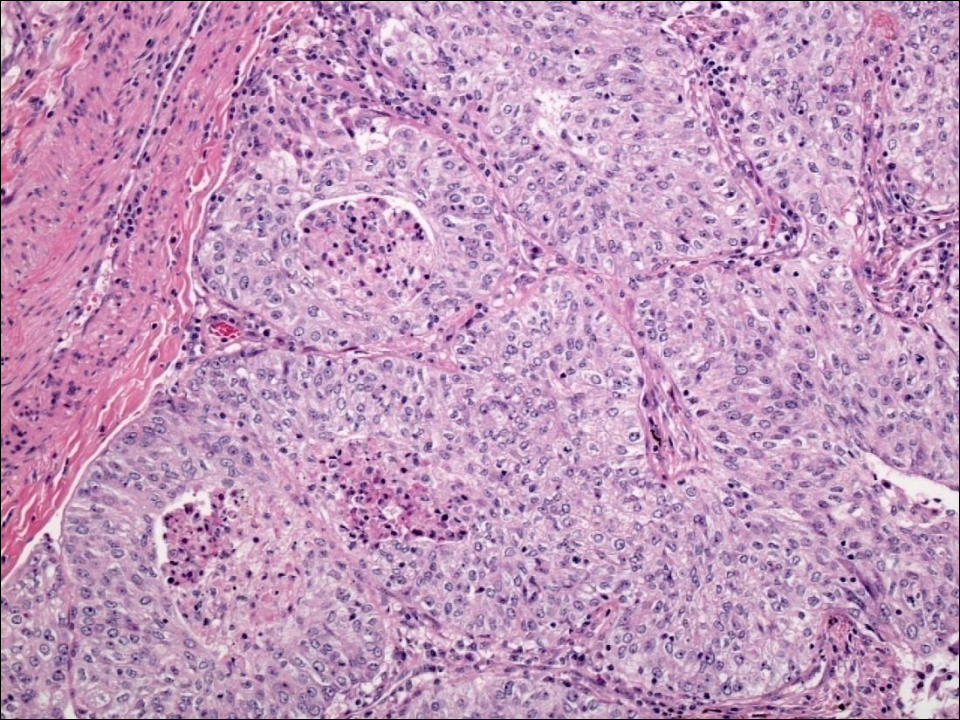
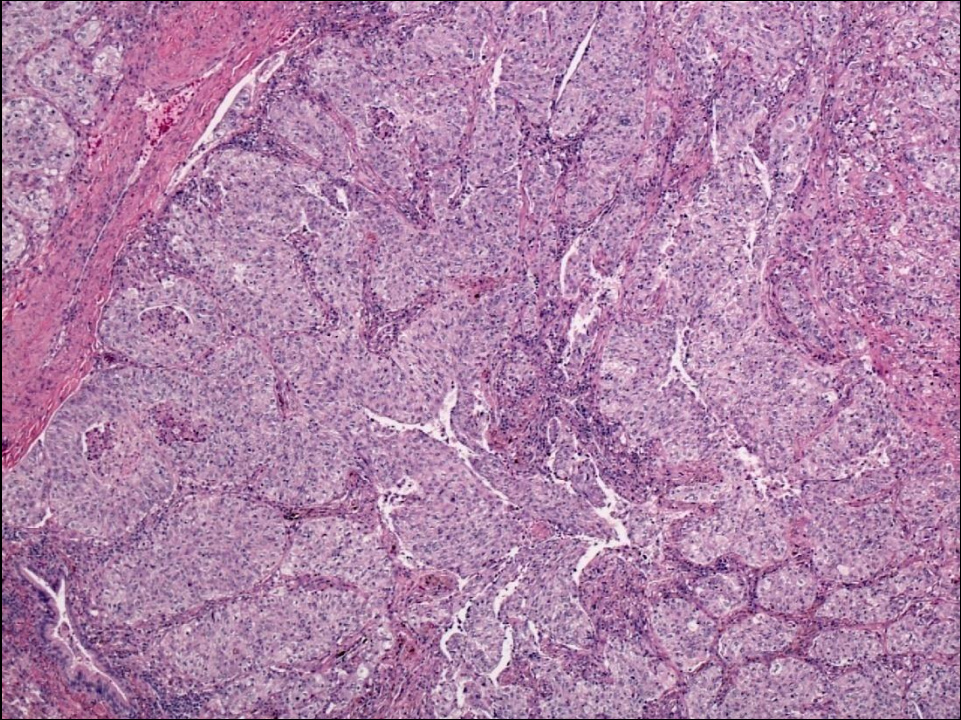
- Non-variant Large Cell Carcinoma, NOS
- Variant Large Cell Carcinomas
 - Basaloid Carcinomas
 - Large Cell Neuroendocrine Carcinomas
 - Lymphoepithelioma-like Carcinomas
 - Clear Cell Carcinoma
 - Large Cell carcinoma with Rhabdoid phenotype

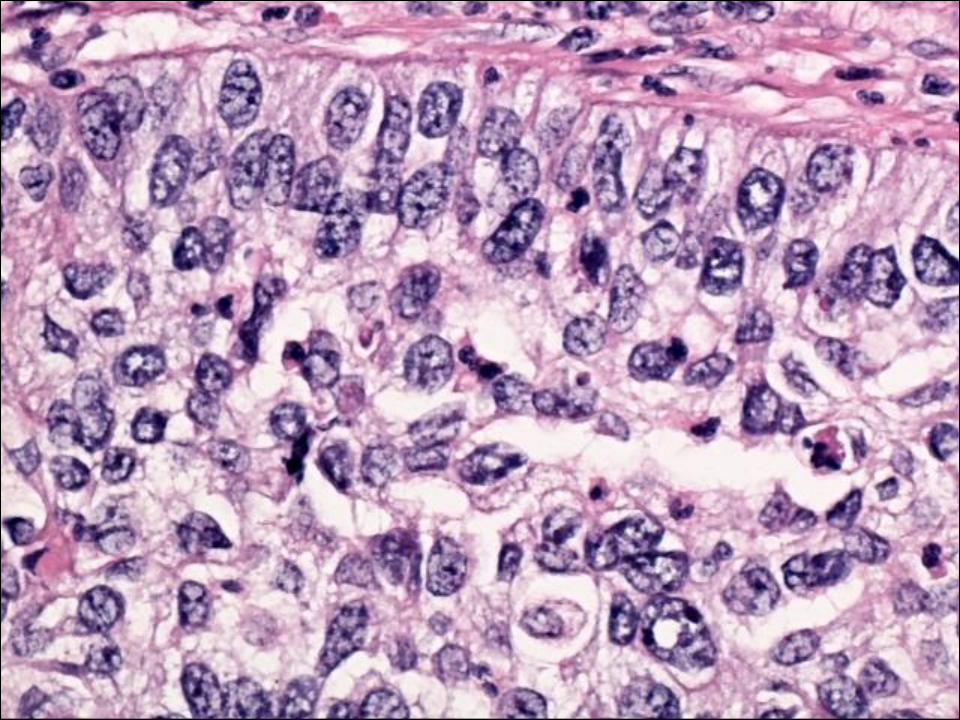
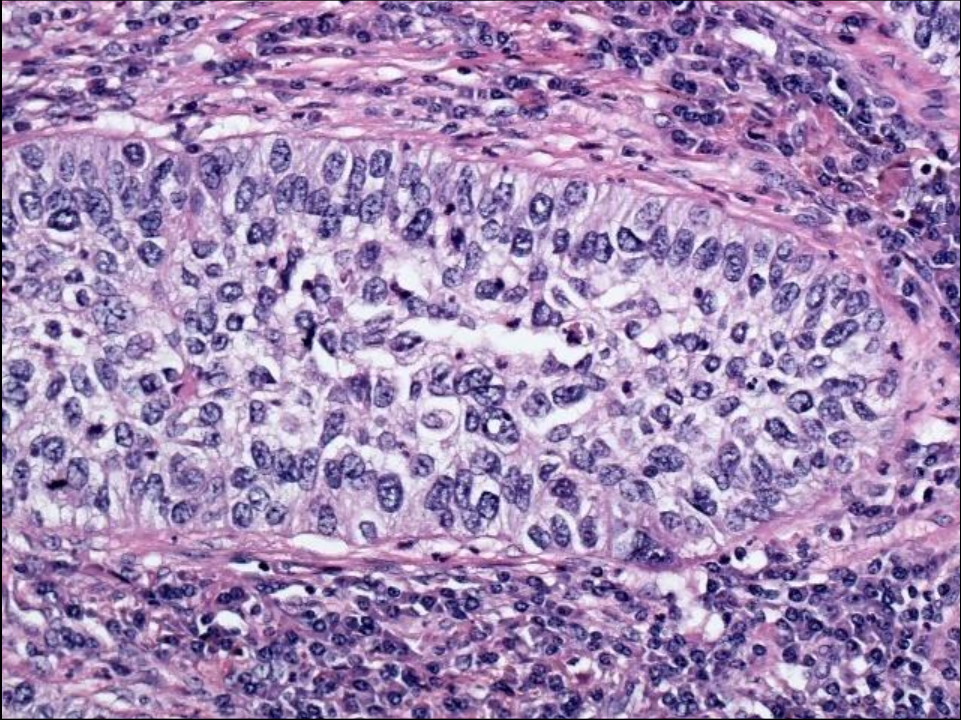
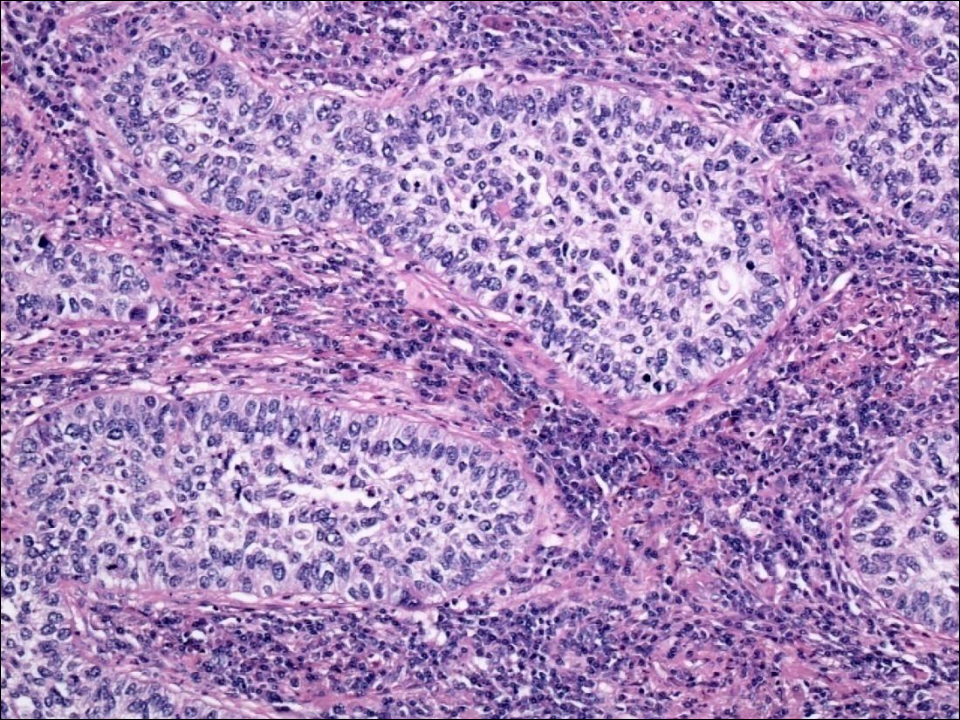
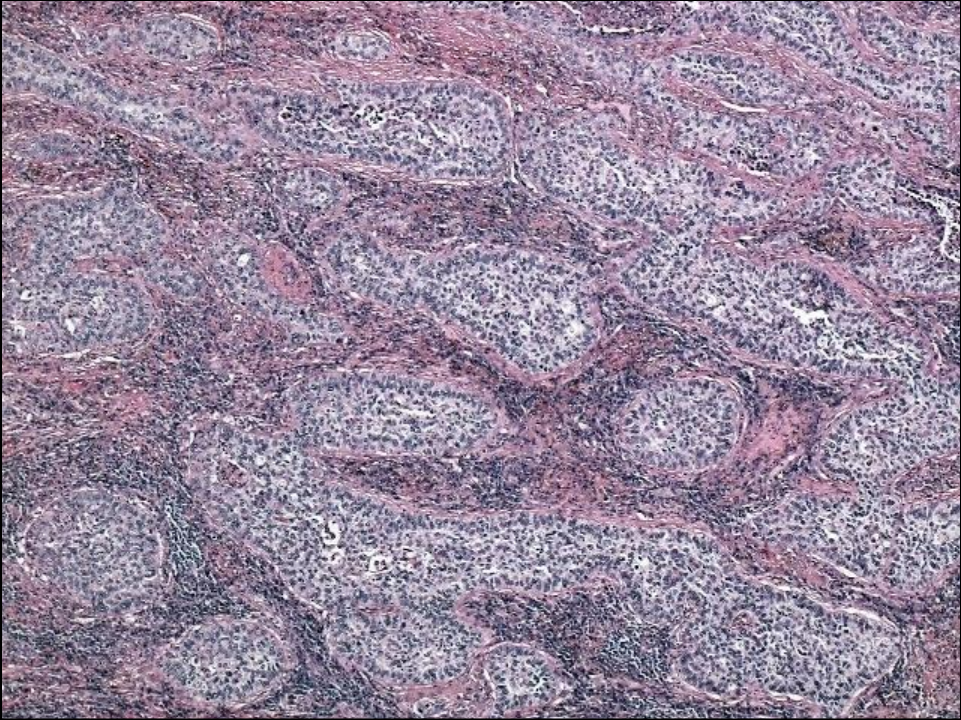
Large Cell Carcinoma – NOS

- Clinically and radiologically similar to other NSCLCs
- Males, smoking related
- Tend to be more peripheral, large masses, but not always
- Pleural and Chest wall invasion common
- Usual metastatic sites









Tumour progression and de-differentiation



Well Differentiated
Squamous Cell Ca

Poorly Differentiated
Squamous Cell Ca

Morphologically
Large Cell
Carcinoma

Well Differentiated
Adenocarcinoma

Poorly Differentiated
Adenocarcinoma

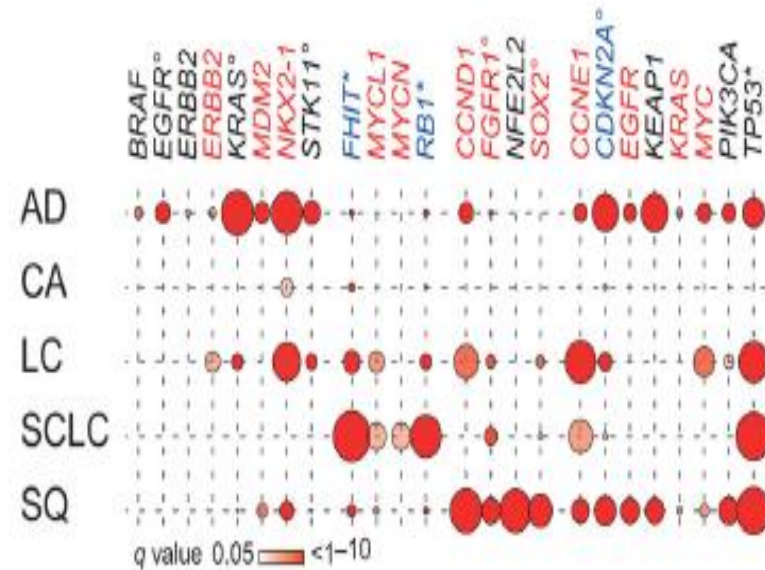
Pathologists will differ in
how they call marginal cases

A Genomics-Based Classification of Human Lung Tumors

The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM)

Sci Transl Med. 2013 October 30; 5(209): 209ra153. doi:10.1126/scitranslmed.3006802.

B



A

Histology
original

Prediction

AD
 $n = 393$

91.4%

AD

LC
incl LCNEC
 $n = 80$

48%

LC

LCNEC

SCLC
 $n = 48$

81%

SCLC

SQ
 $n = 245$

79%

SQ

Large Cell Carcinomas - Mutations

N =	Country	EGFR	KRAS	ALK	BRAF	PIK3CA	MEK
31	Italy	0	0	-	-	-	-
6	Italy	0	50%	-	-	-	-
18	Japan	0	6%	-	-	-	-
72	Scotland	0*	8.3%	0	1	0	-
102	USA	1	29%	3	2	1	1
20	Italy	1	40%	1	-	-	-
57	USA	1	43%	-	-	-	-

Overall prevalence 1% 25% 2%

Mutations largely matched IHC lineage, where data are available

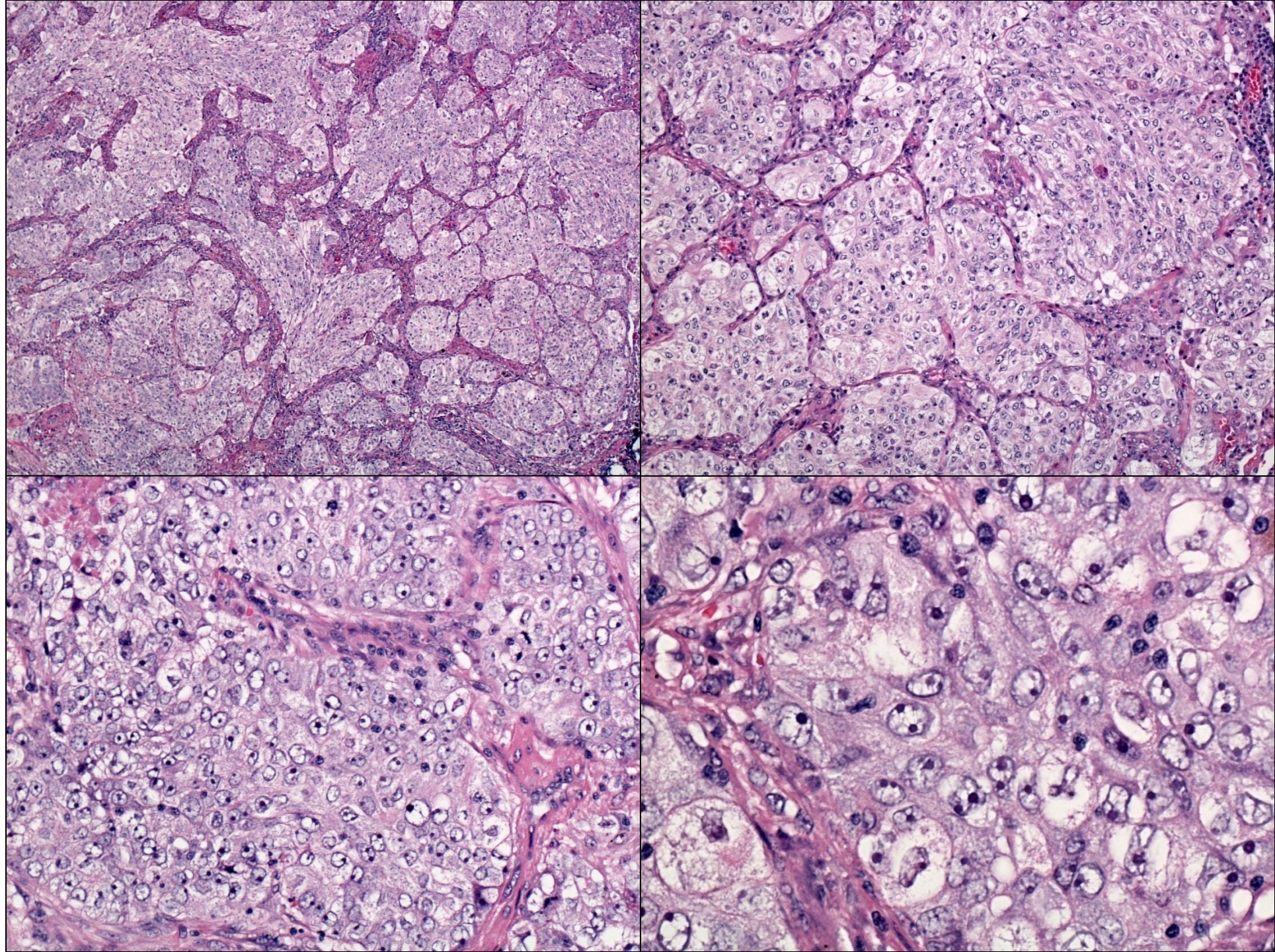
* EGFR c.2508C>T;p. R836R (SNP) in a Basaloid Ca

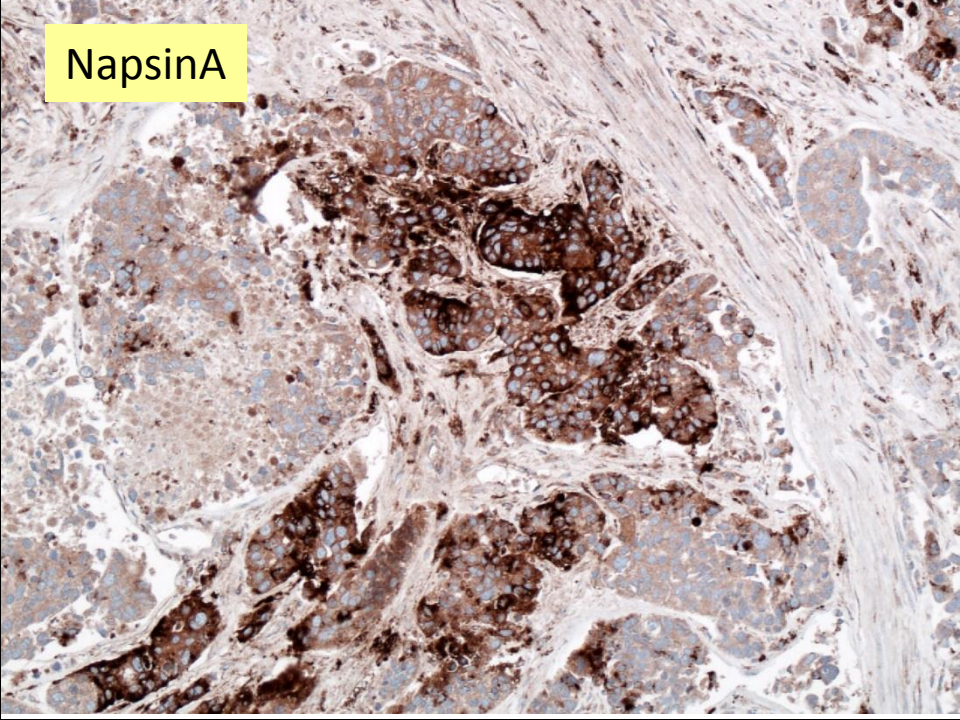
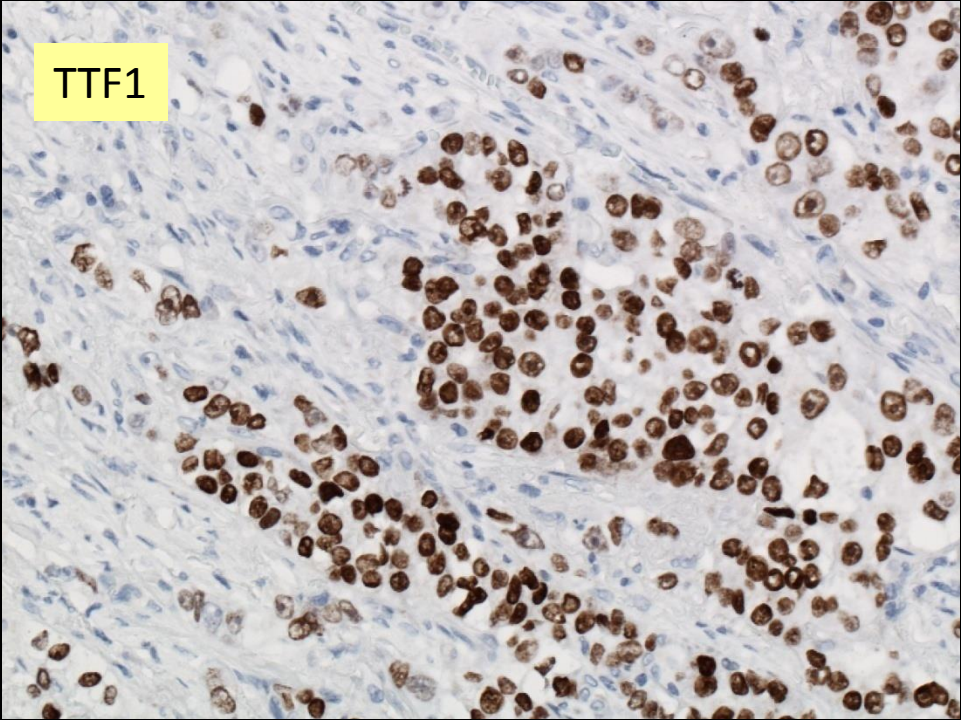
Marchetti A et al. J Clin Oncol 2005
 Sartori G et al. Am J Clin Pathol 2009
 Takeuchi et al, J Clin Oncol 2006
 Kerr KM et al, Lung Cancer 2012
 Rekhtman N et al. Mon Pathol 2013
 Rossi G et al, Virch Arch 2014
 Hwang D et al, Arch Path Lab Med 2014

Large Cell Carcinoma: 2015 definition

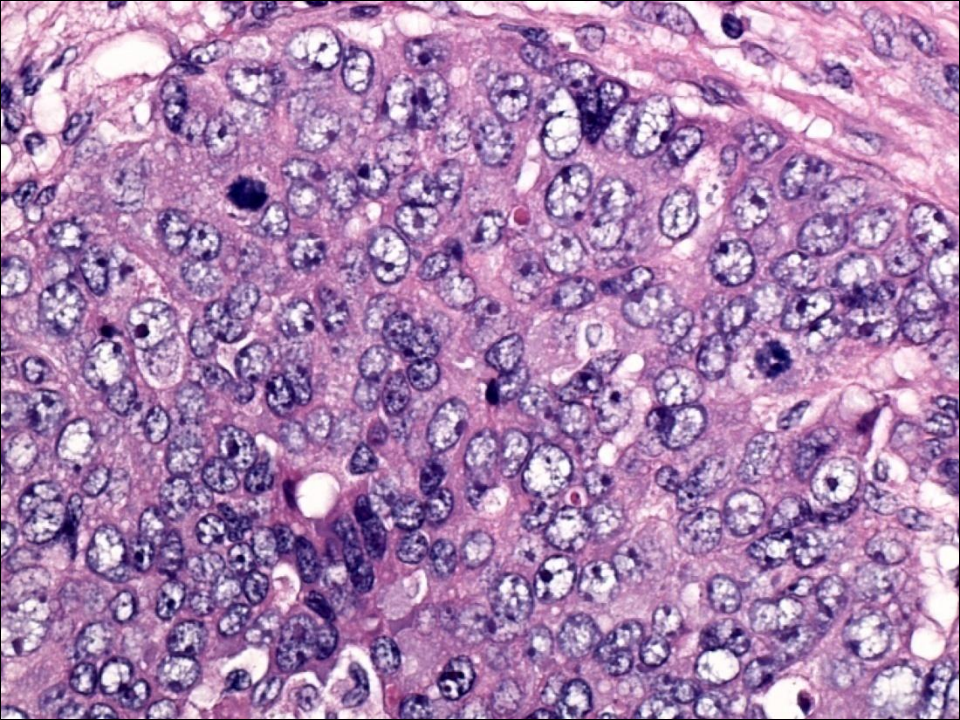
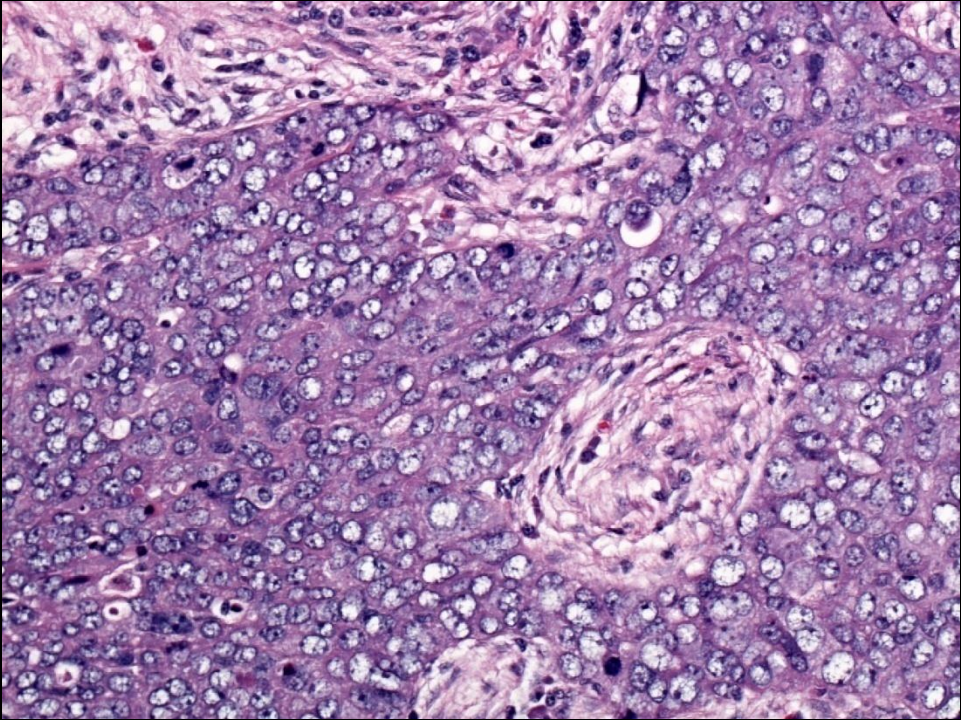
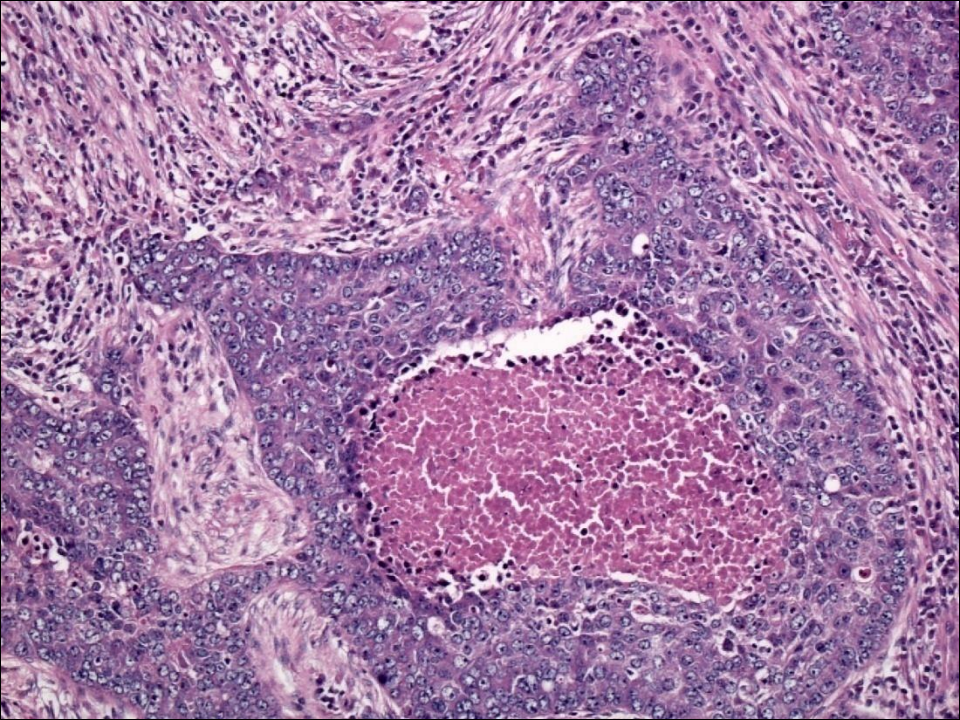
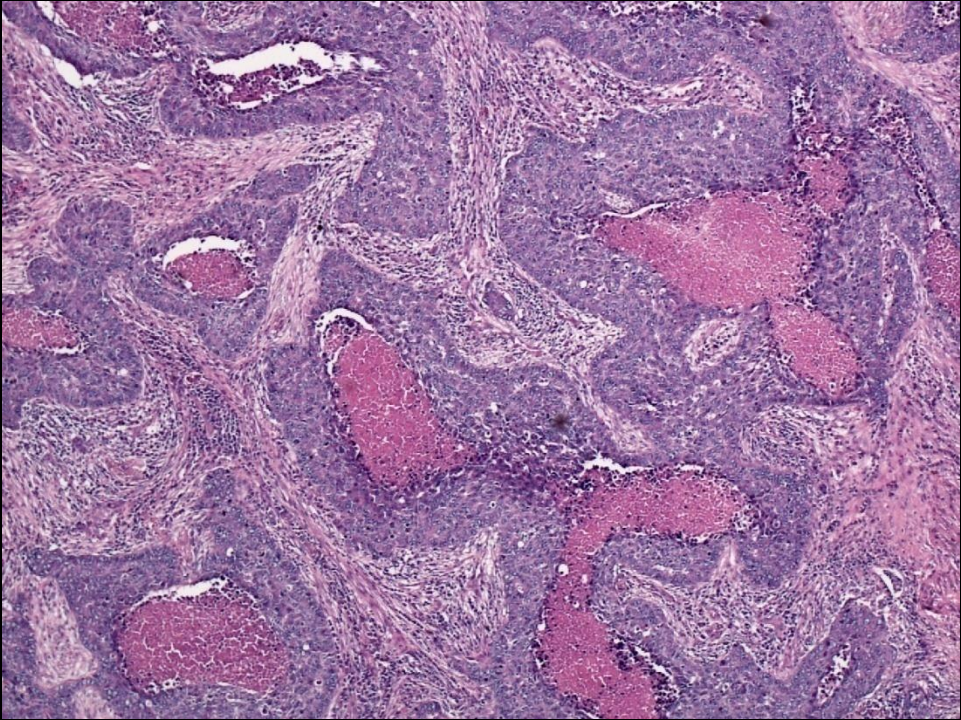
Definition

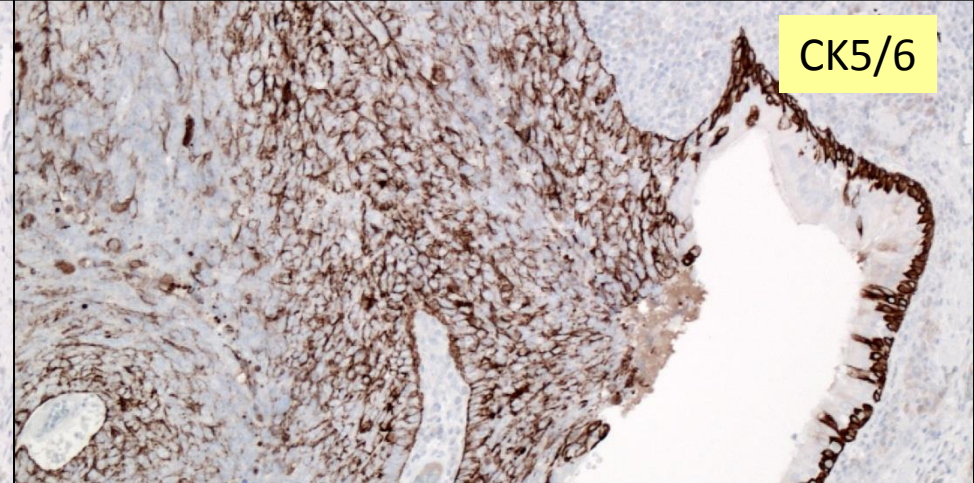
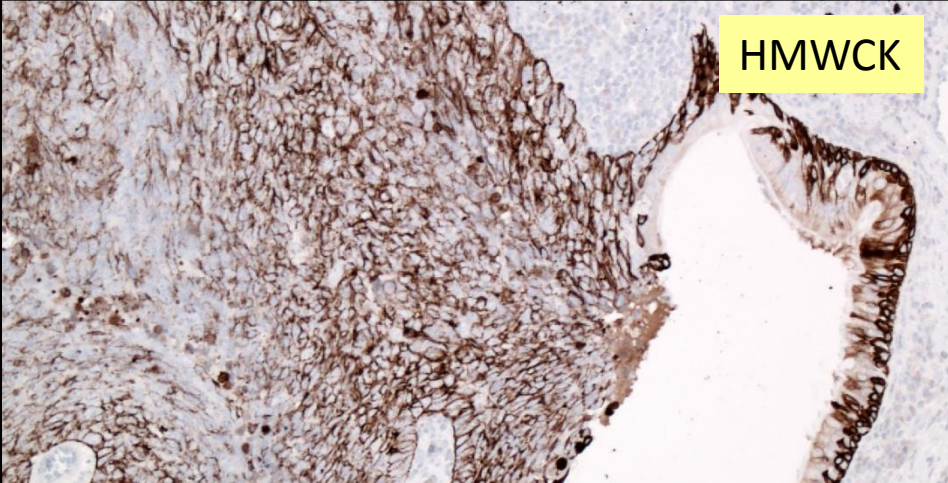
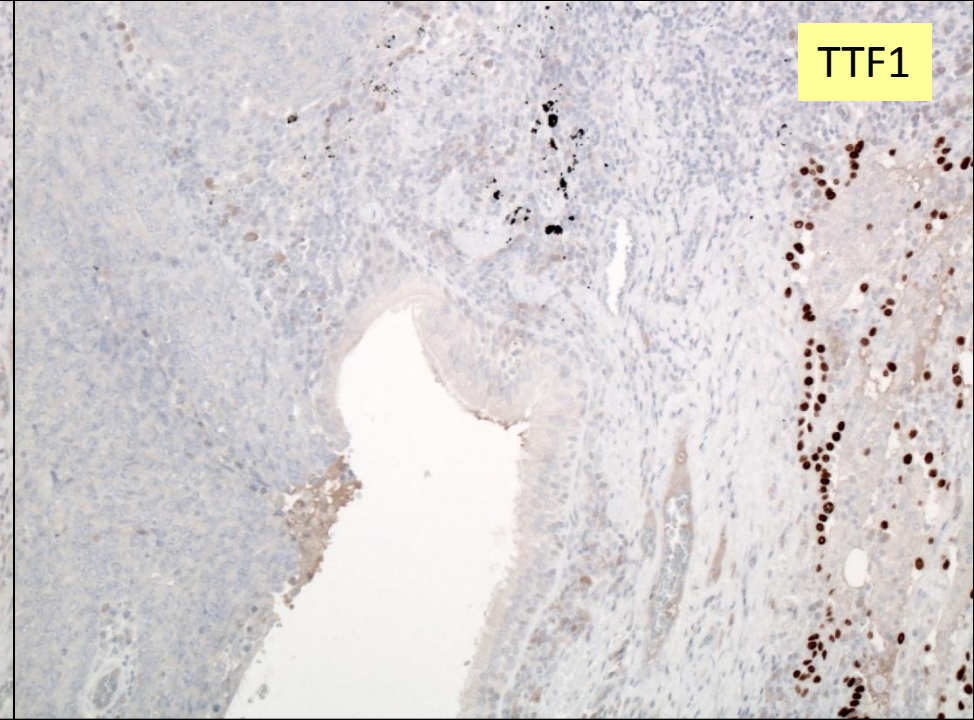
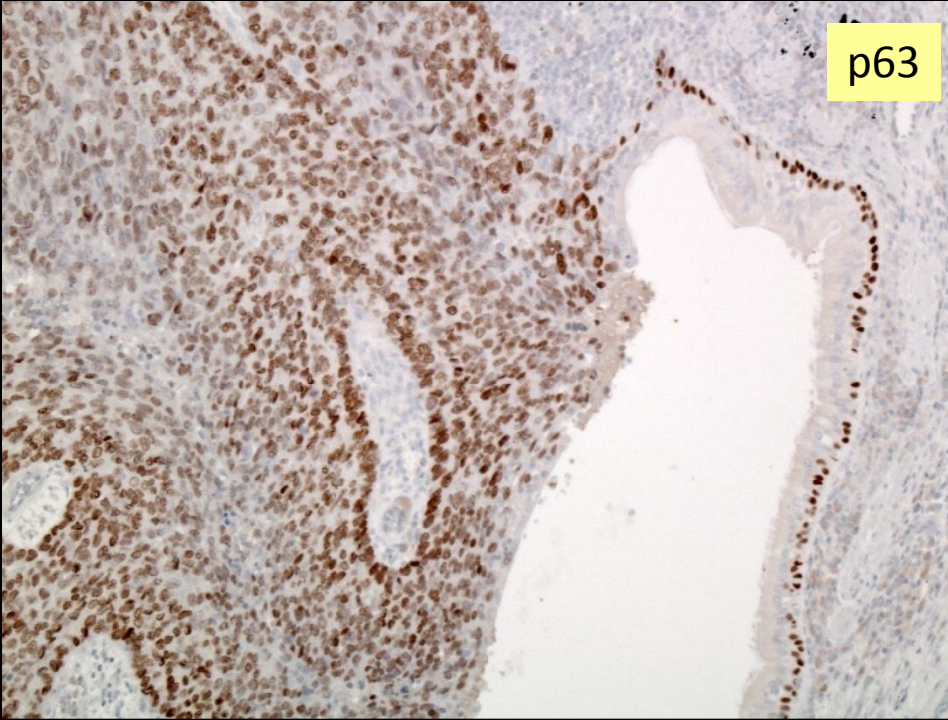
Large cell carcinoma is an undifferentiated non-small cell carcinoma (NSCC) that lacks the cytological, architectural **and immunohistochemical** features of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma. The diagnosis requires a thoroughly sampled resected tumour, and cannot be made on non-resection or cytology specimens.





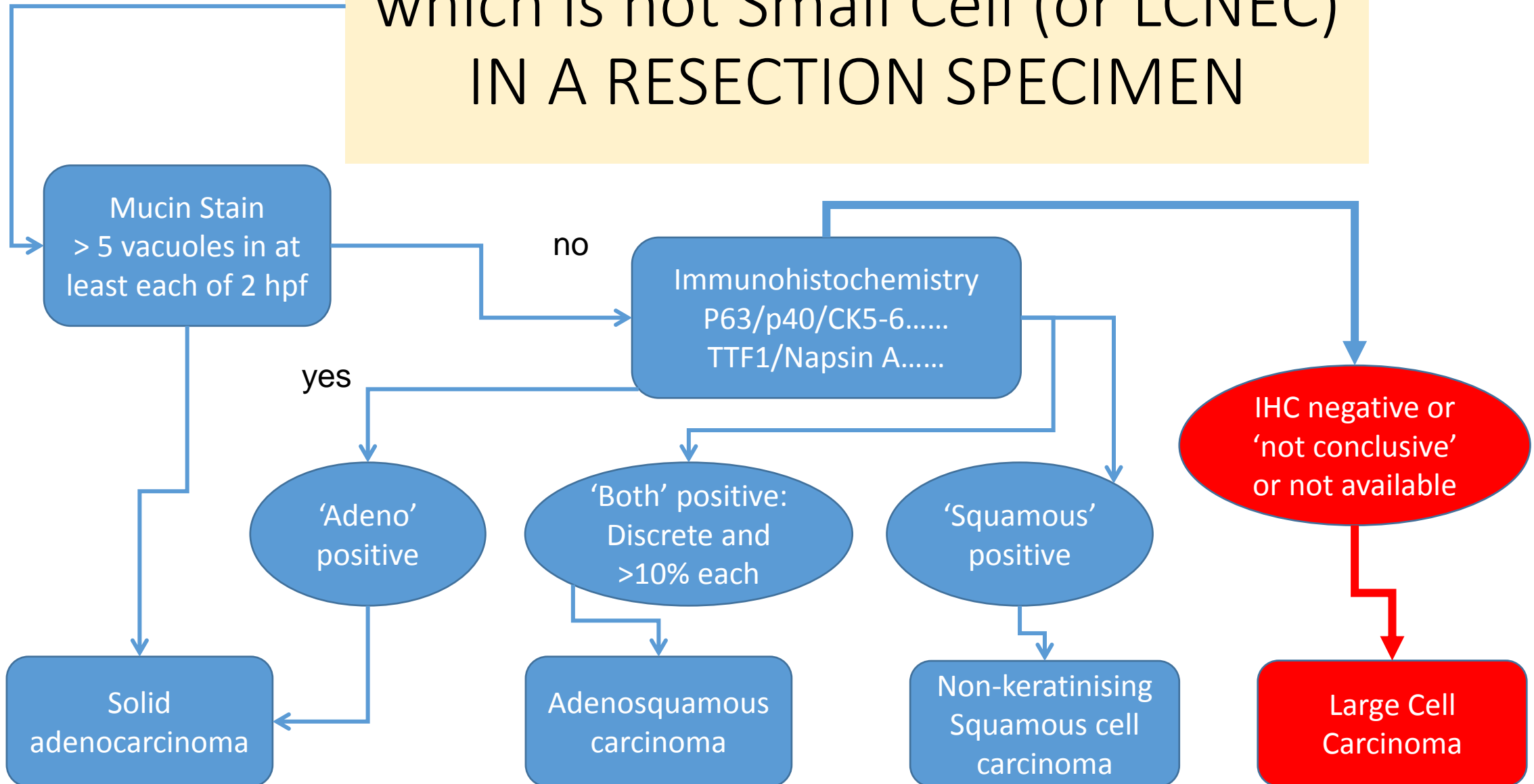
2015:
Adenocarcinoma: Solid subtype





2015:
Non-keratinizing Squamous Cell Carcinoma

Undifferentiated carcinoma which is not Small Cell (or LCNEC) IN A RESECTION SPECIMEN



ICD-O code Large cell carcinoma 8012/3

Based on their immunohistochemical profiles, three subtypes of large cell carcinoma can be distinguished

- Large cell carcinoma with **null** immunohistochemical features
- Large cell carcinoma with **unclear** immunohistochemical features
- Large cell carcinoma with **no** additional stains



30% of former
cohort remains?

Tumour progression and de-differentiation

The diagram illustrates the progression of two types of cancer: Squamous Cell Carcinoma (Ca) and Adenocarcinoma. At the top, a grey arrow points right, labeled 'Tumour progression and de-differentiation'. Below this, two horizontal arrows represent the progression of each cancer type. The top arrow is blue and contains three stages: 'Well Differentiated Squamous Cell Ca', 'Poorly Differentiated Squamous Cell Ca', and 'Non-keratinising Squamous Cell Ca'. The bottom arrow is red and contains three stages: 'Well Differentiated Adenocarcinoma', 'Poorly Differentiated Adenocarcinoma', and 'Solid-pattern Adenocarcinoma'. Both arrows point towards a large purple arrow on the right, which is labeled 'Morphology & Immunohistochemistry Large Cell Carcinoma'. At the bottom, a text note states: 'Pathologists will still differ how they call marginal cases !!!!'.

Well Differentiated
Squamous Cell Ca

Poorly Differentiated
Squamous Cell Ca

Non-keratinising
Squamous Cell Ca

Morphology
&
Immunohistochemistry
Large Cell
Carcinoma

Well Differentiated
Adenocarcinoma

Poorly Differentiated
Adenocarcinoma

Solid-pattern
Adenocarcinoma

Pathologists will still differ
how they call marginal cases !!!!

Which markers and how much staining?

For Adenocarcinoma

- **TTF1**
- Napsin A
- Surfactant apoproteins
- CK7
- Definite staining but it can be weak and patchy
- Which clone?

For Squamous Cell Carcinoma

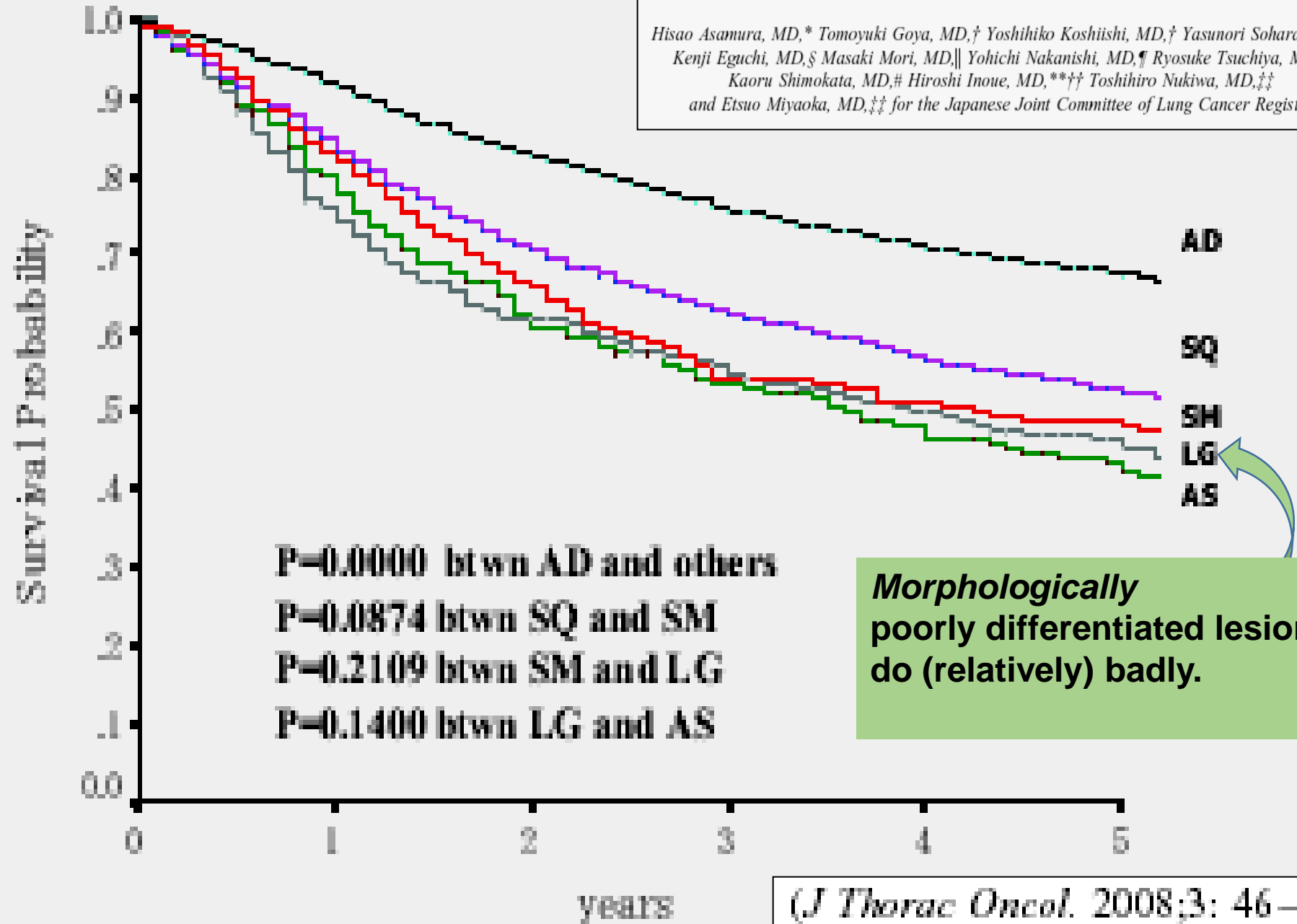
- **P63**
- **P40**
- **CK5/6**
- Desmocollin
- 34betaE12
- Strong and diffuse staining ONLY

Survival Function

A Japanese Lung Cancer Registry Study

Prognosis of 13,010 Resected Lung Cancers

Hisao Asamura, MD,* Tomoyuki Goya, MD,† Yoshihiko Koshiishi, MD,† Yasunori Sohara, MD,‡
Kenji Eguchi, MD,§ Masaki Mori, MD,|| Yohichi Nakanishi, MD,¶ Ryosuke Tsuchiya, MD,*
Kaoru Shimokata, MD,# Hiroshi Inoue, MD,**†† Toshihiro Nukiwa, MD,‡‡
and Etsuo Miyaoka, MD,‡‡ for the Japanese Joint Committee of Lung Cancer Registry



1-7: Sarcomatoid Carcinomas

1-7A Pleomorphic, Spindle cell and Giant cell carcinomas

1-7B Carcinosarcoma

1-7C Pulmonary Blastoma

No change to the definitions or categories.

IHC is not a feature of classification.

Pleomorphic, Spindle cell and Giant cell carcinomas

Definition

Pleomorphic carcinoma is a poorly differentiated non-small cell lung carcinoma that contains at least 10% spindle and/or giant cells, with the remainder of the tumour showing squamous cell carcinoma, adenocarcinoma, or undifferentiated non-small cell carcinoma.

Spindle cell carcinoma consists of an almost pure population of epithelial spindle cells, with no differentiated carcinomatous elements.

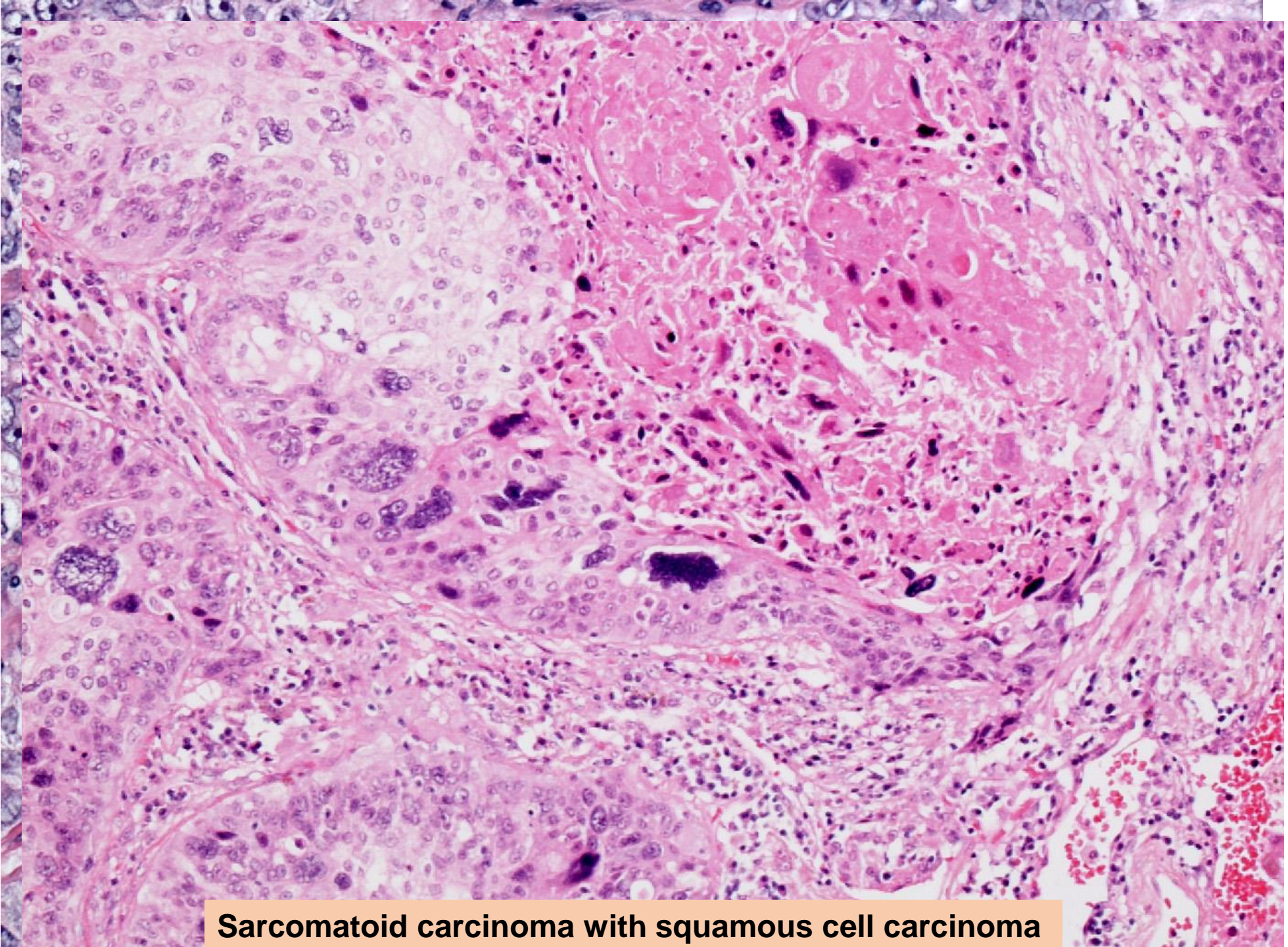
Giant cell carcinoma consists almost entirely of tumour giant cells (including multinucleated cells), with no differentiated carcinomatous elements.

Sarcomatoid Carcinomas

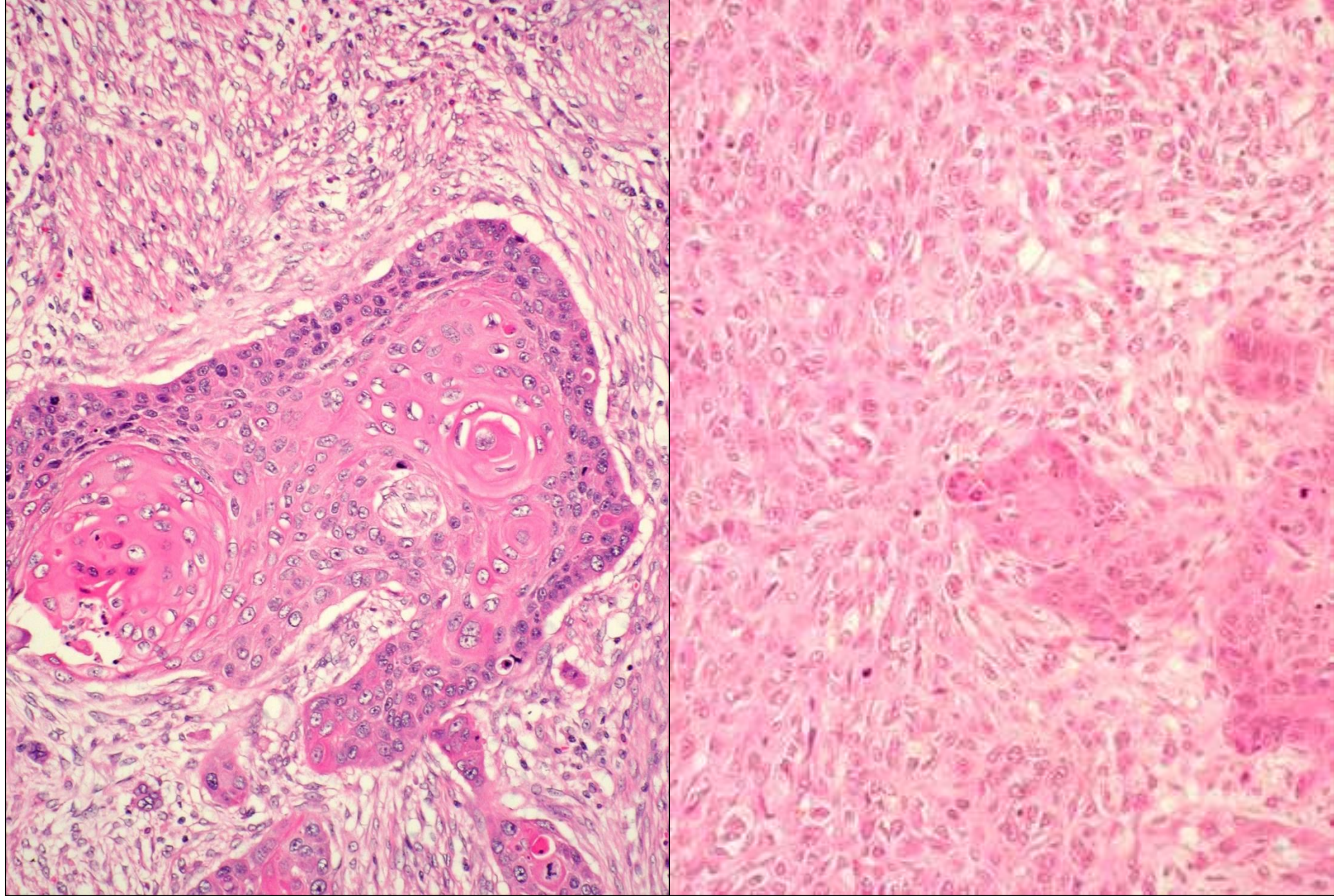
- Many are combined with 'standard' NSCLC elements
 - **Adenocarcinoma**
 - **Squamous cell carcinoma**
 - Large Cell carcinoma
- Pure forms are very rare
 - Giant cell carcinoma
 - Spindle cell carcinoma

1-3% of Lung Cancers

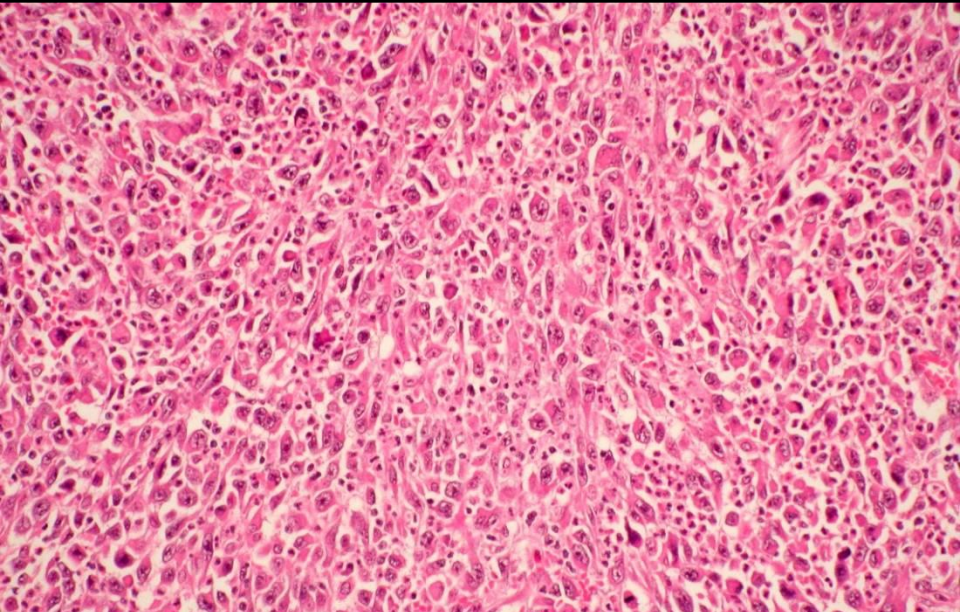
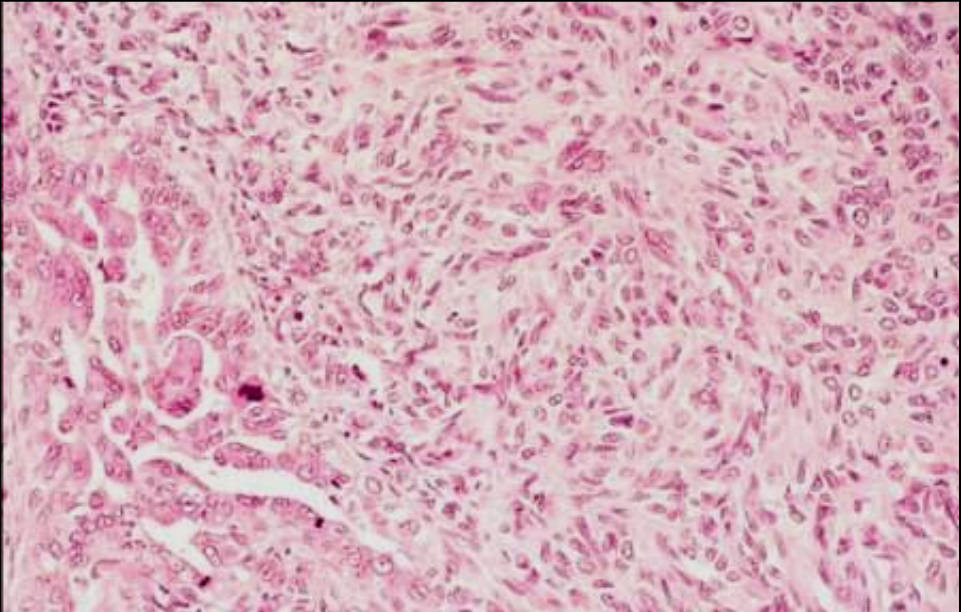
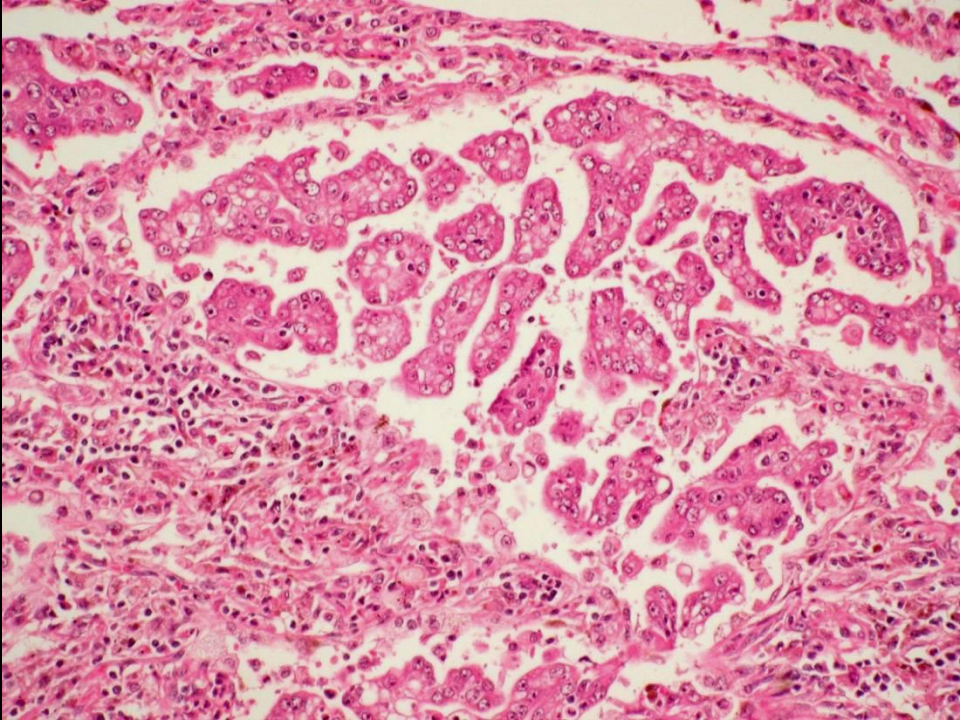
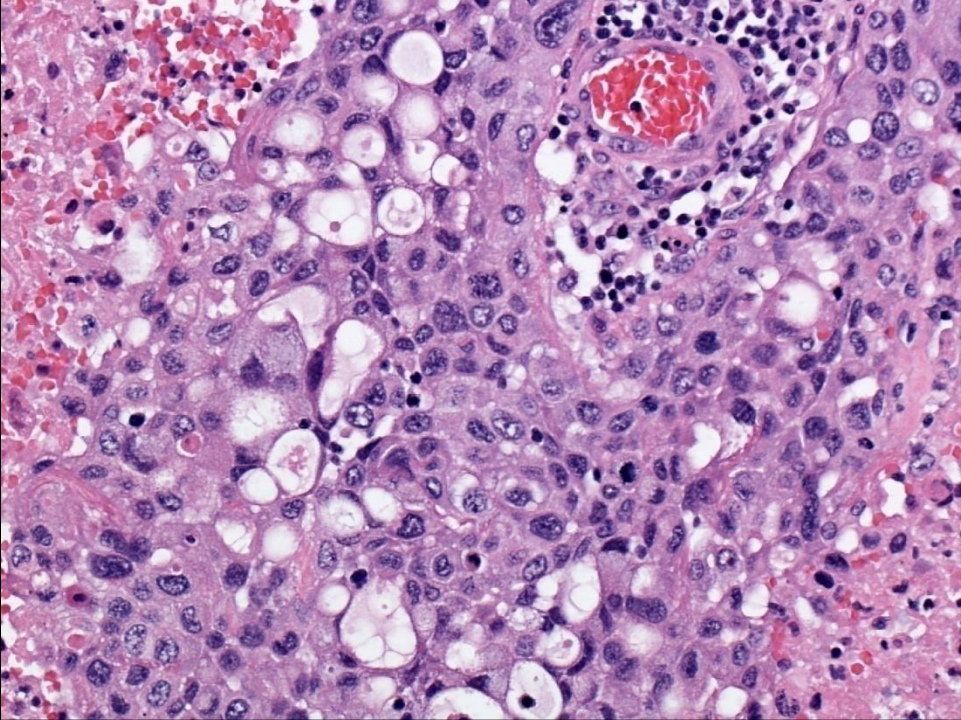
0.3% of Lung Cancers



Sarcomatoid carcinoma with squamous cell carcinoma

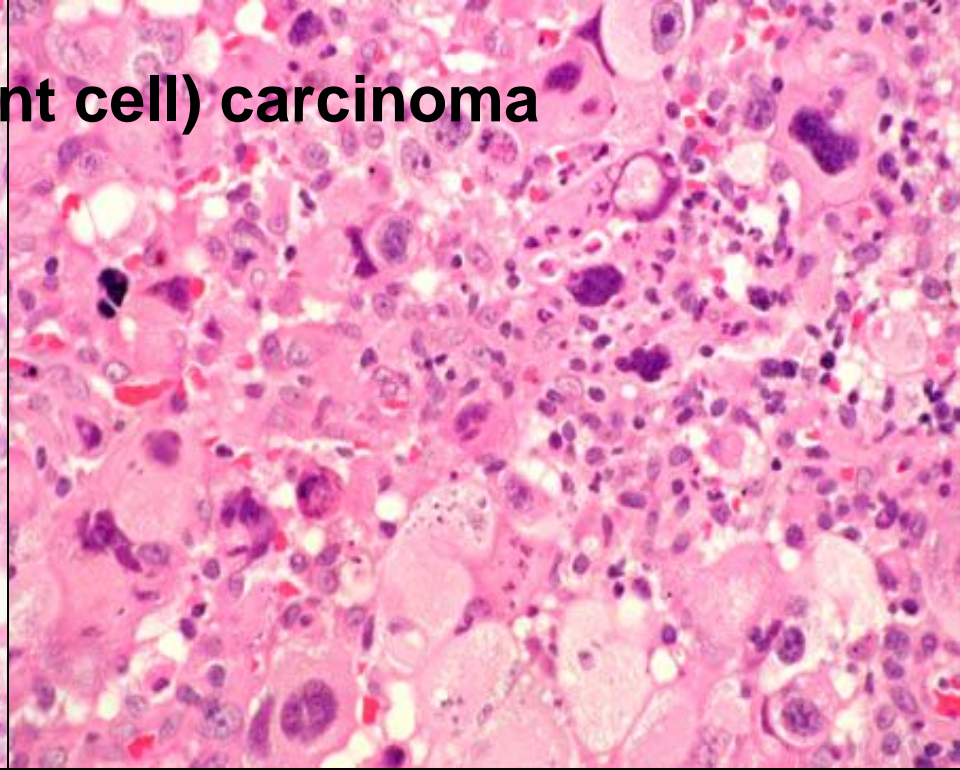
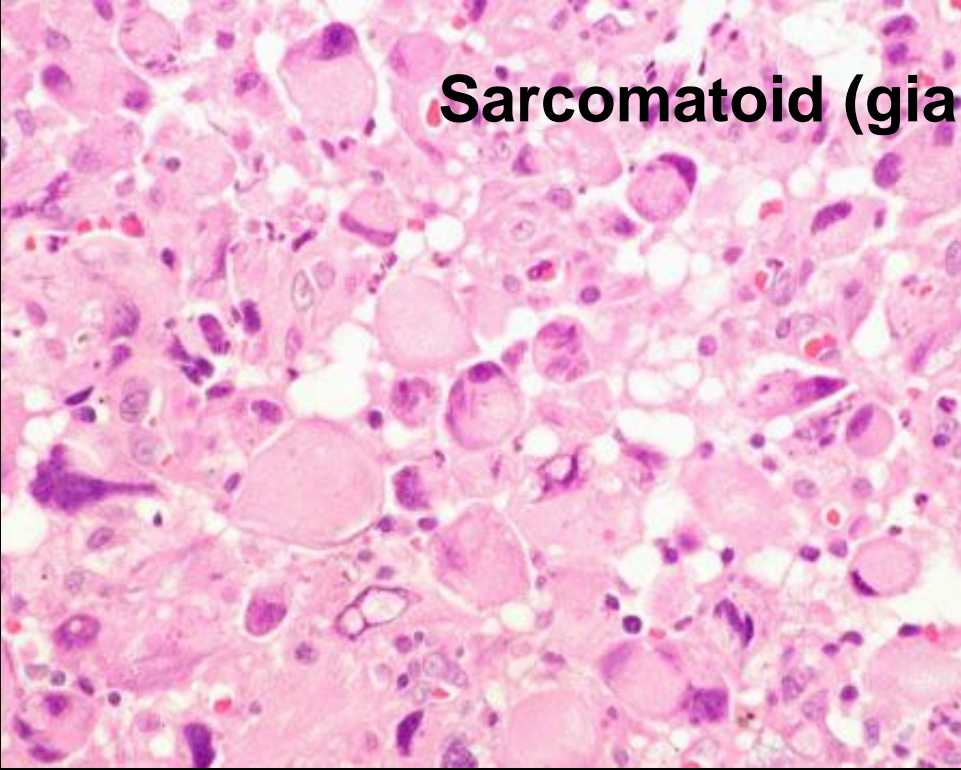


Sarcomatoid carcinoma with squamous cell carcinoma

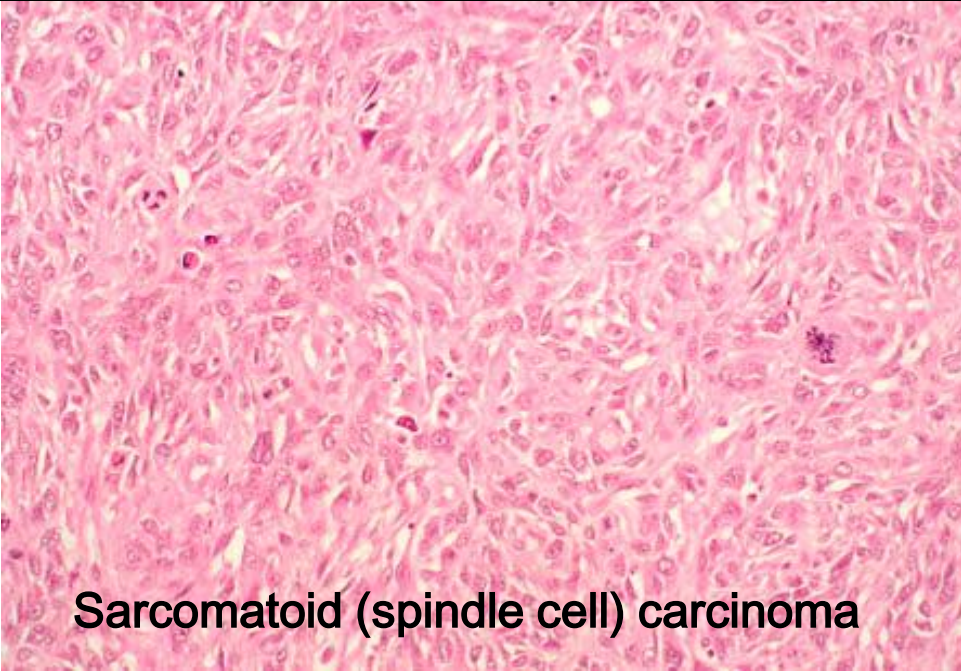


Sarcomatoid carcinoma with adenocarcinoma

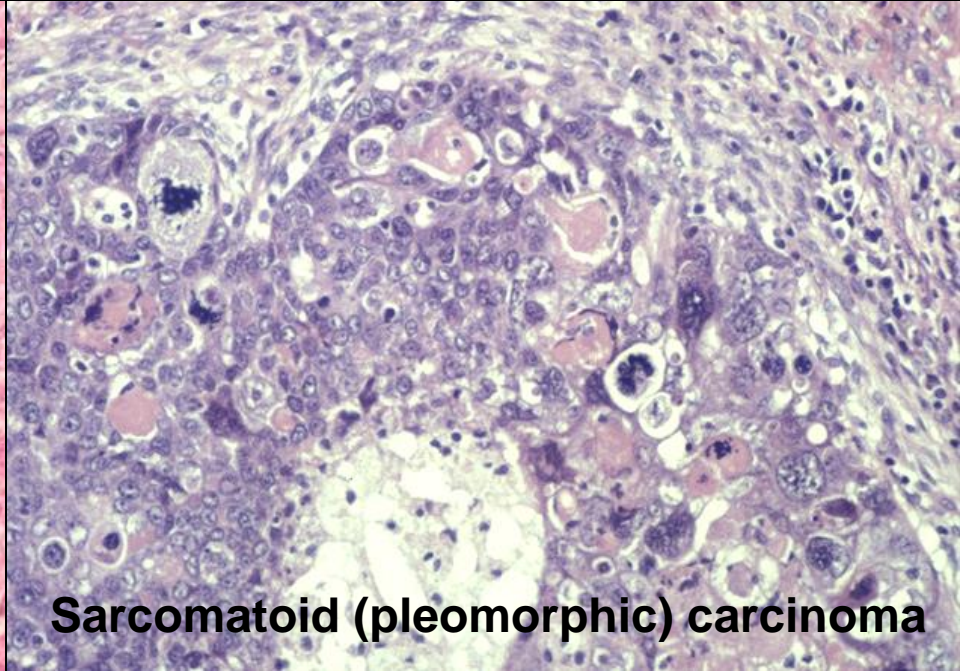
Sarcomatoid (giant cell) carcinoma

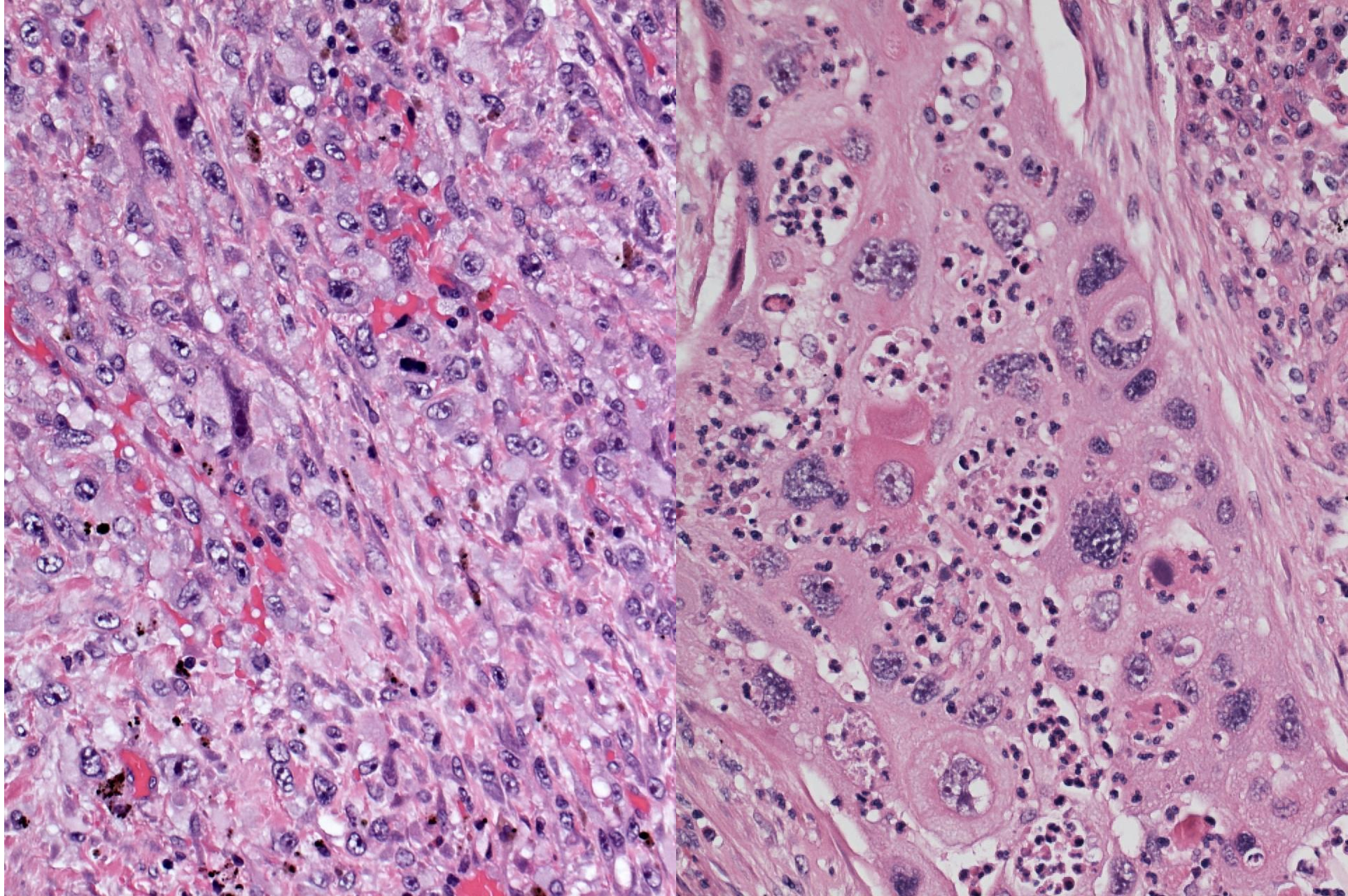


Sarcomatoid (spindle cell) carcinoma



Sarcomatoid (pleomorphic) carcinoma





‘Relatively’ Pure Spindle Cell and Giant Cell Carcinoma are extremely rare

Sarcomatoid Carcinomas - Mutations

No of Cases	Country	<i>EGFR</i> mutations	<i>KRAS</i> mutations	BRAF/ALK/PIK3CA
61	Korea	15% 89% exon19del 11% L858R exon21	10%	-
17	Japan	18% 67% exon19del 33% L858R exon21	-	-
13	Italy	0	37%	-
27	Italy	-	22%	-
35	Scotland	0	28.6%	0

Lee S et al. J Can Res Clin Oncol 2010
 Kaira K et al. J Thorac Oncol 2010
 Sartori et al. Am J Clin Pathol 2009
 Pelosi G et al. Mod Pathol 2004

Conclusions

- Undifferentiated carcinomas still exist!
- Expression of lineage markers may inform on biology
- Expression of lineage markers may correlate with mutation profile
- Mutation profiles are dominated by KRAS mutations

16TH WORLD CONFERENCE ON LUNG CANCER

IASLC



INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

WWW.IASLC.ORG



Abstract Submission Open	January 2015
Registration Open	January 2015
Abstract Submission Deadline	April 24, 2015
Abstract Notifications	June 22, 2015
Early Registration Deadline	June 26, 2015
Late Breaking Abstract Submission Deadline	July 10, 2015
Regular Registration Deadline	July 24, 2015

SEPTEMBER 6–10, 2015

→ DENVER, COLORADO, USA

CURE FOR LUNG CANCER