MTE02

UPDATE ON WHO CLASSIFICATION AND STAGING OF LUNG CANCER

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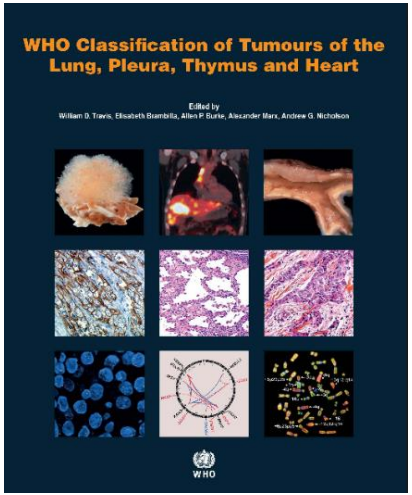
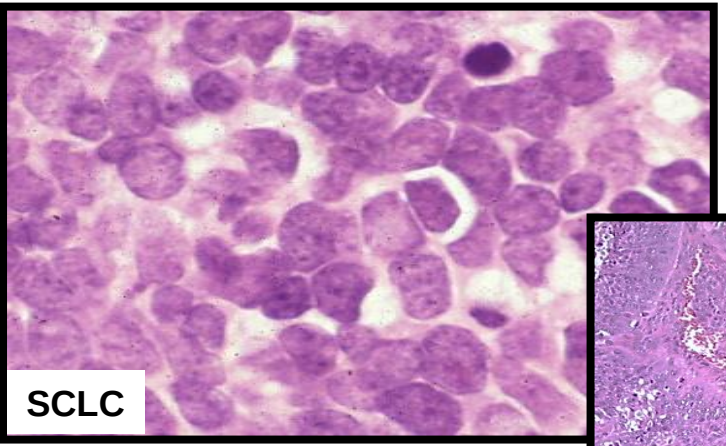
OUTLINE

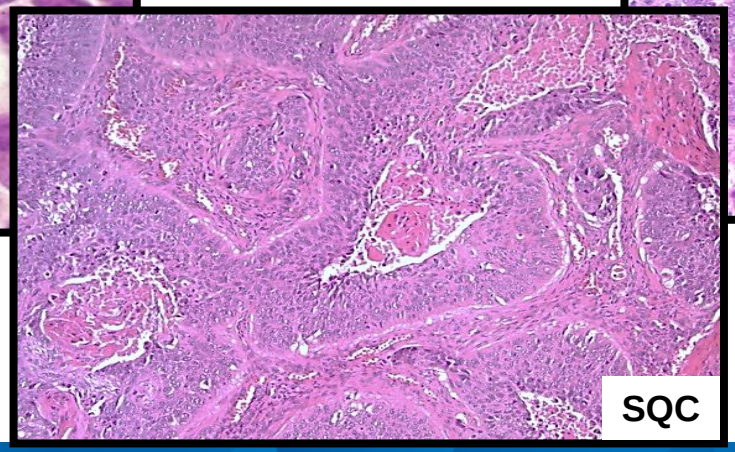
- Diagnosis of lung carcinoma on small specimens
- Diagnostic immunohistochemistry
- Molecular testing
- Adenocarcinoma classification and staging
- Large cell carcinoma

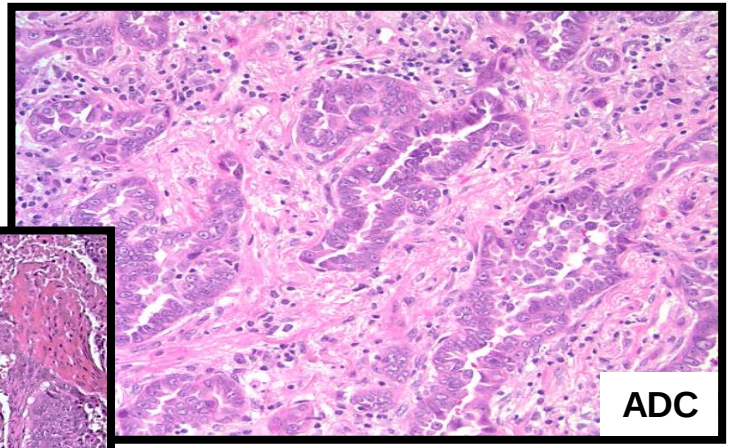


Consensus and Editorial meeting, IARC, Lyon , 24-26 April 2014

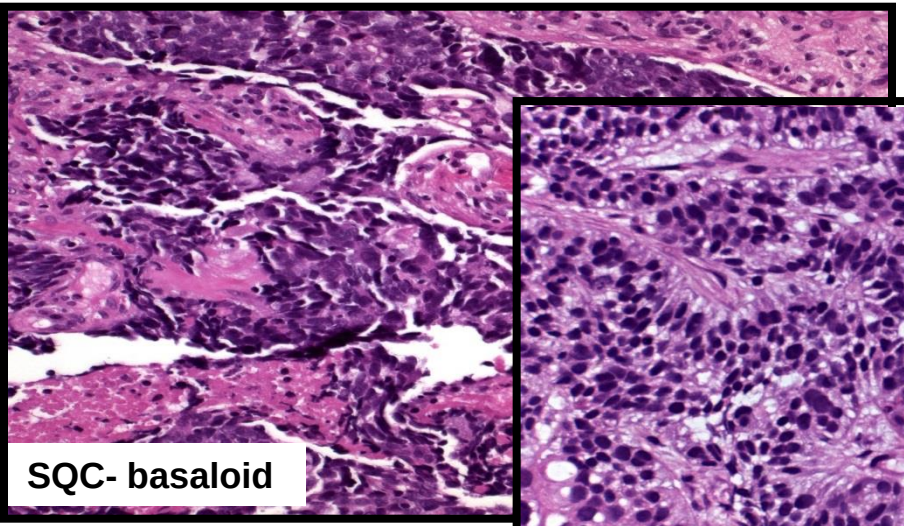
EASY CASES- MORPHOLOGY IS SUFFICIENT

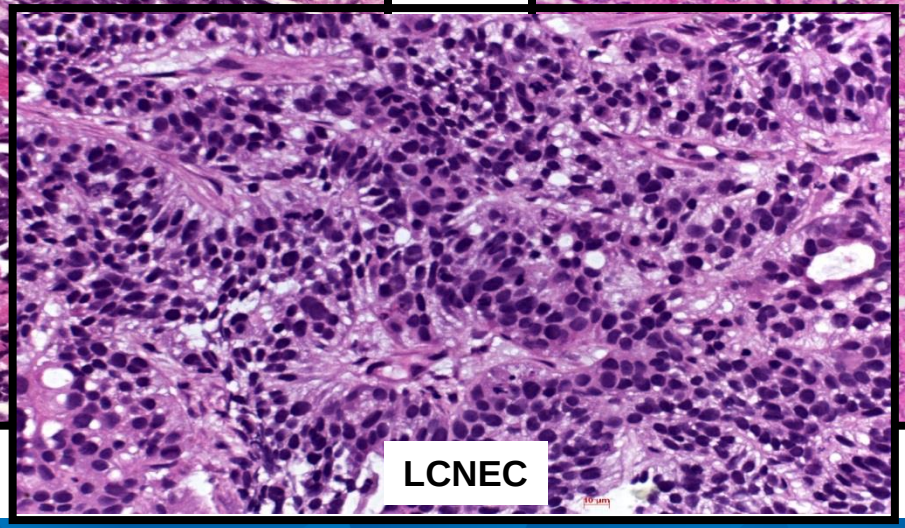


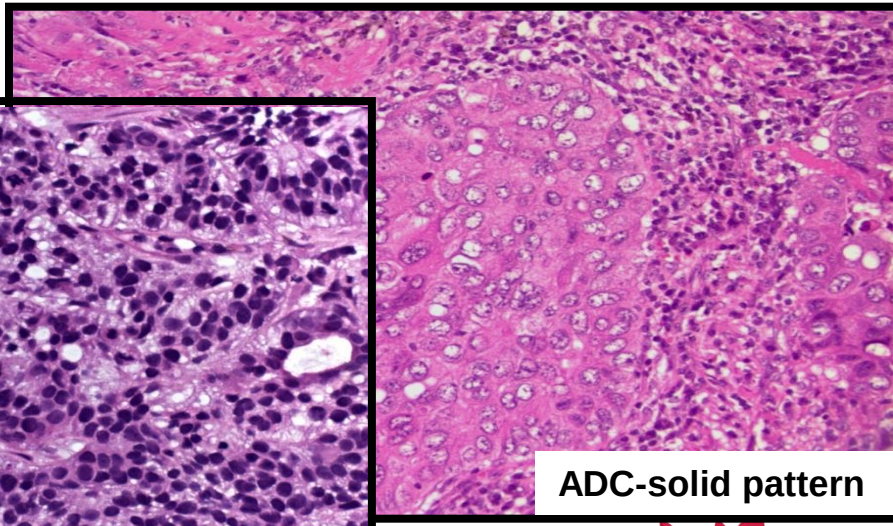




NOT SO EASY CASES- IMMUNOHISTOCHEMISTRY SHOULD HELP





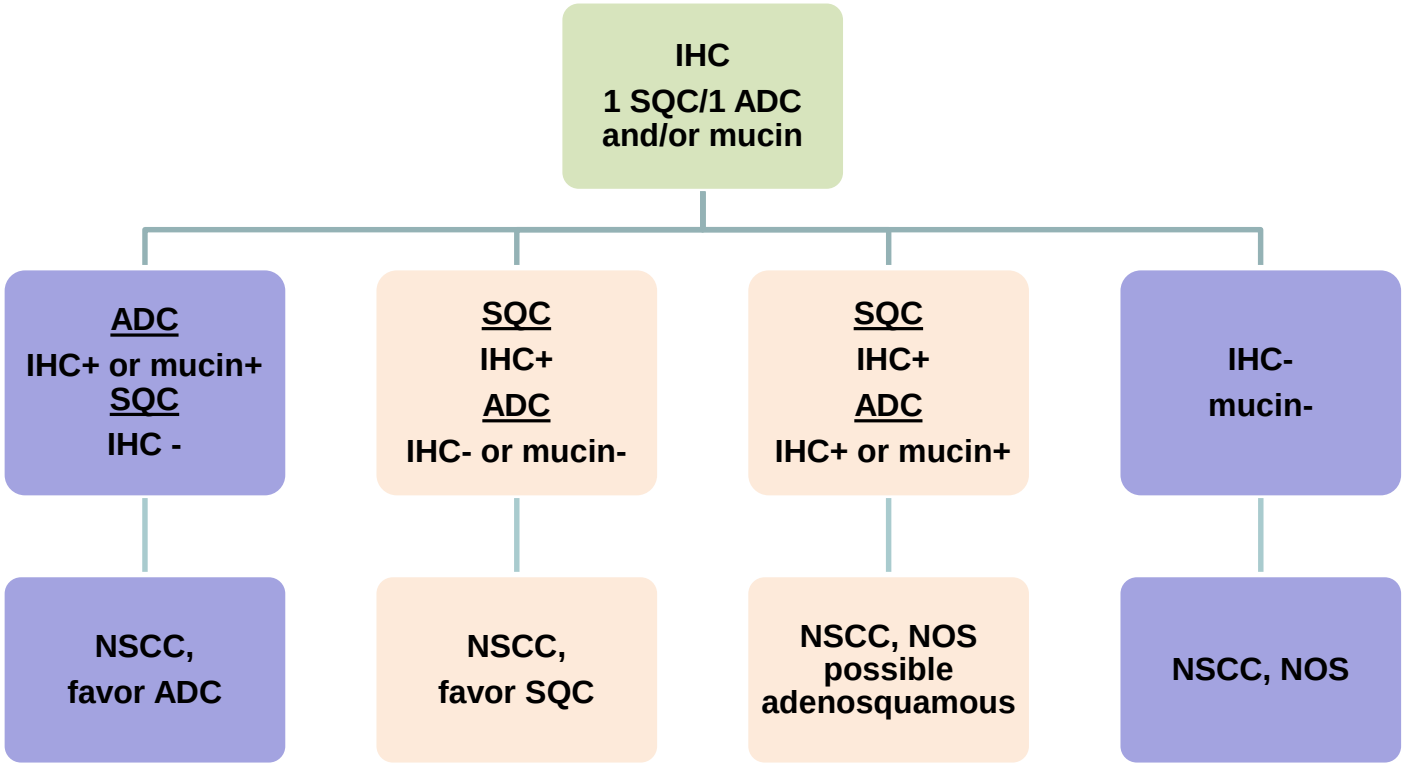


IMMUNOHISTOCHEMISTRY AND NSCLC

MARKER	ADENOCARCINOMA	SQUAMOUS CELL CARCINOMA
TTF-1	70-90	Almost never
P40	Almost never	~100
P63	10-20	~100
CK 7	~90	~20-30
CK5/6	10-20	~100

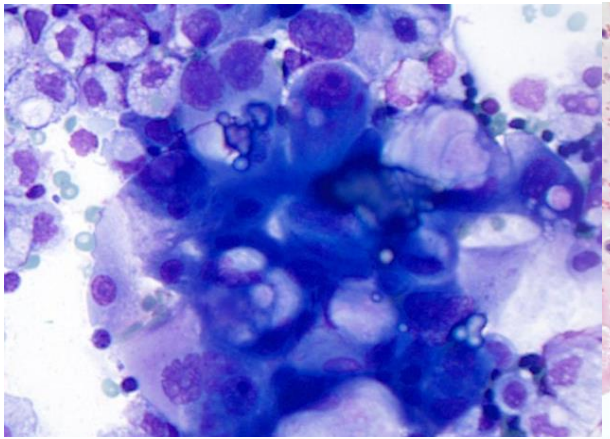
Cytokeratin 20, Napsin A, surfactant A, Ber-EP4, B72.3, synaptophysin, chromogranin, CD56, CEA

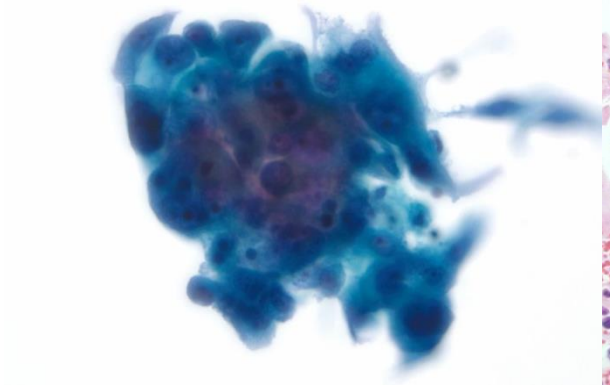
IMMUNOHISTOCHEMISTRY AND SMALL SPECIMENS WORK-UP AND REPORTING

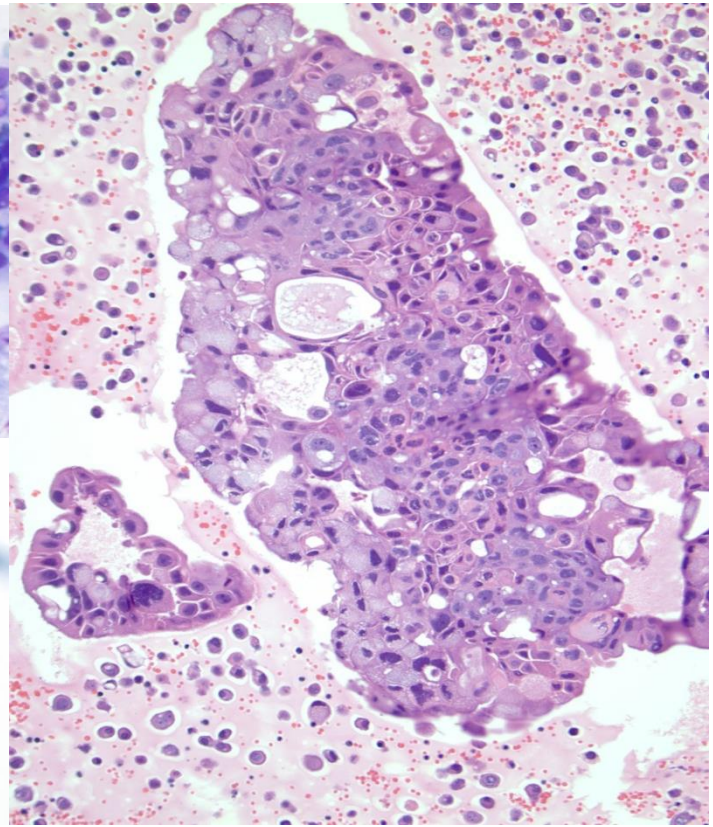


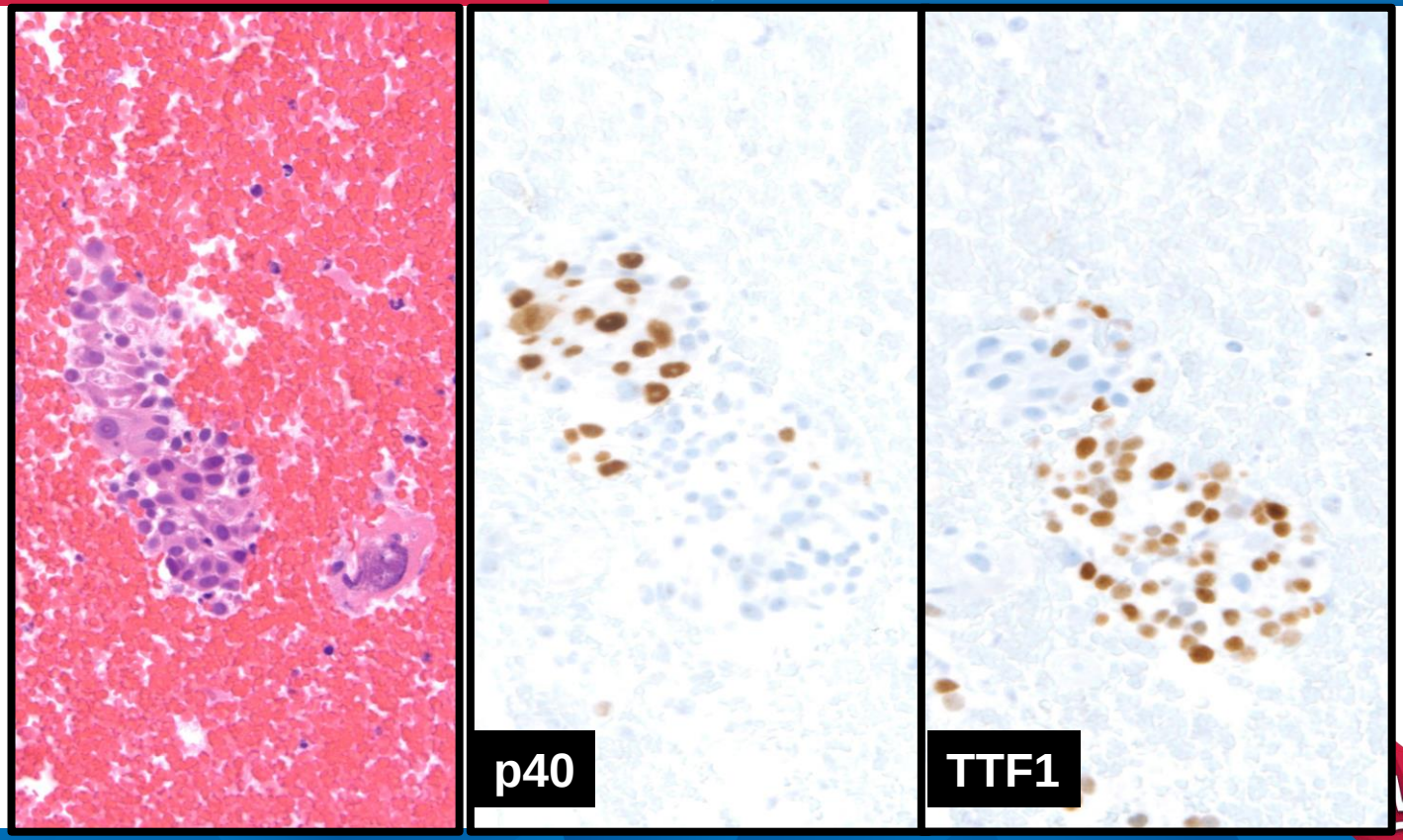
NOT ALL PATHOLOGY REPORTS WILL BE STRAIGHT FORWARD

- **PATHOLOGY REPORT:**
  - **non-small cell carcinoma with squamous and glandular features**
- **2015 WHO:**
  - **NSCC, NOS with a comment that this could represent adenosquamous carcinoma**







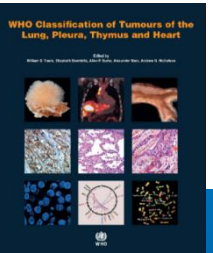

p40
TTF1

NOT ALL PATHOLOGY REPORTS WILL BE STRAIGHT FORWARD

- **ADENOCARCINOMA WITH NEUROENDOCRINE DIFFERENTIATION**

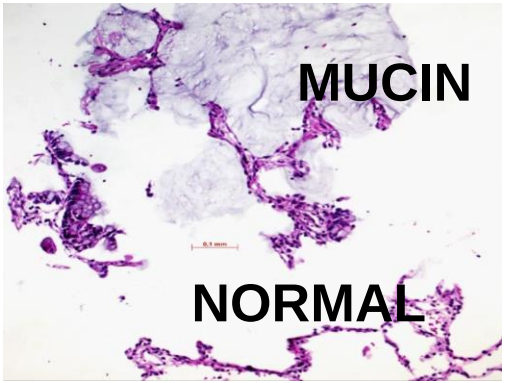
2015 WHO ABOUT NSCLC WITH NEUROENDOCRINE DIFFERENTIATION

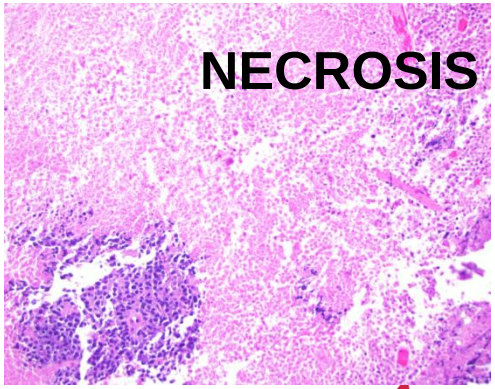
"…they should be classified as squamous, adenocarcinoma or large cell carcinoma with a comment about positive neuroendocrine markers. The clinical inference of this tumor category on survival and chemotherapy response is still unclear, so they are not recognized as specific entities. "



QUALITY OF TUMOR SAMPLE

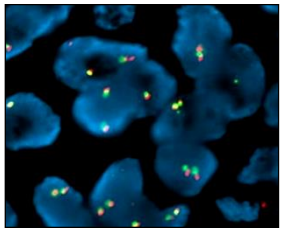
- Is there a homogenous tumor cell population?
- Are the tumor cells viable?
- Is there background necrosis or mucin?





QUANTITY OF TUMOR SAMPLE

- What is the overall cellularity?
  Are there sufficient tumor cells (sufficient DNA/RNA) for molecular studies?



FISH

100 cells

SINGLE GENE

300 cells

MULTIGENE

300 cells
10ng DNA

WHOLE GENOME

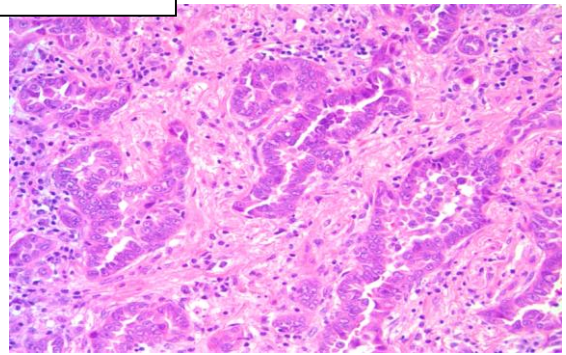
>500 cells
100ng DNA

WHO 2015 CLASSIFICATION OF LUNG ADENOCARCINOMA *FOR RESECTION SPECIMENS*

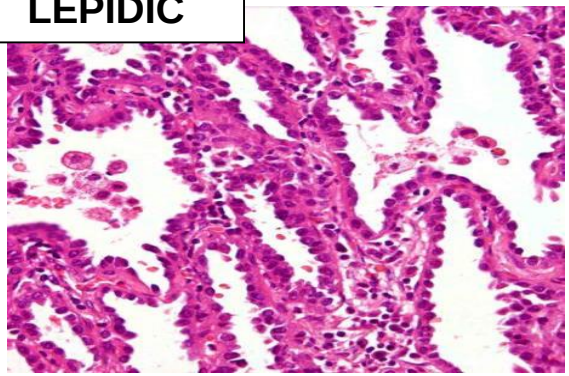
- **PREINVASIVE LESIONS**
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ (AIS) (formerly BAC)
  - Non-mucinous; mucinous
- **MINIMALLY INVASIVE ADENOCARCINOMA (MIA)**
  - A lepidic predominant tumor with ≤ 5 mm invasion
  - Non-mucinous; mucinous
- **INVASIVE ADENOCARCINOMA**

WHO 2015 CLASSIFICATION
INVASIVE ADENOCARCINOMA SUBTYPES

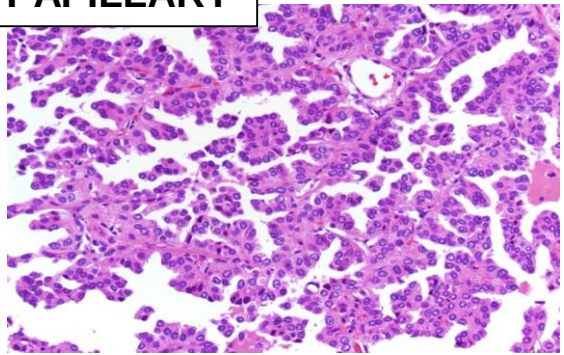
ACINAR



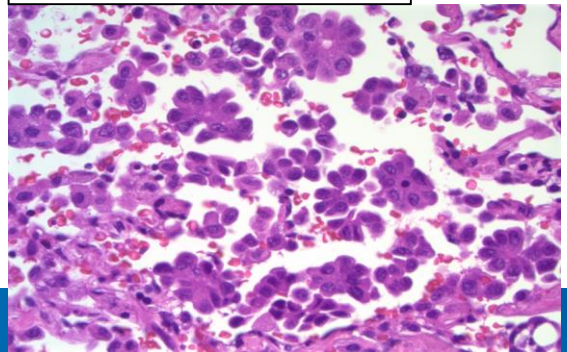
LEPIDIC



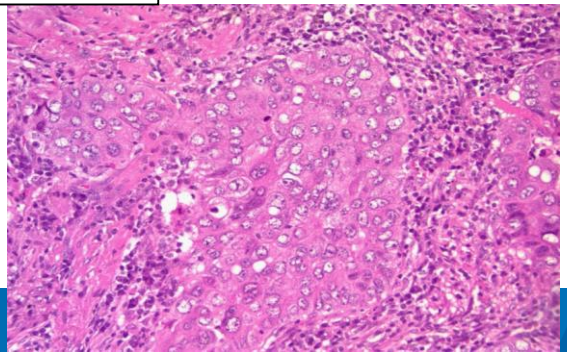
PAPILLARY



MICROPAPILLARY

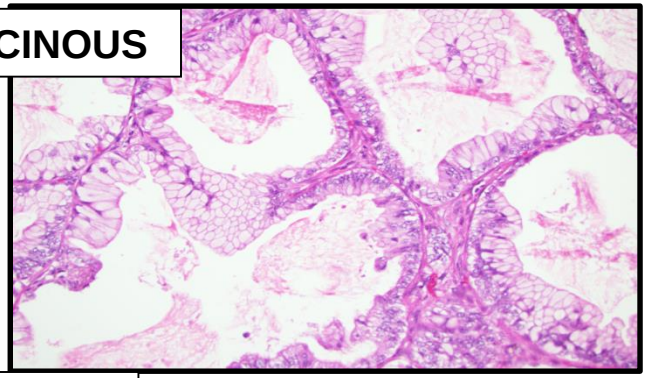


SOLID

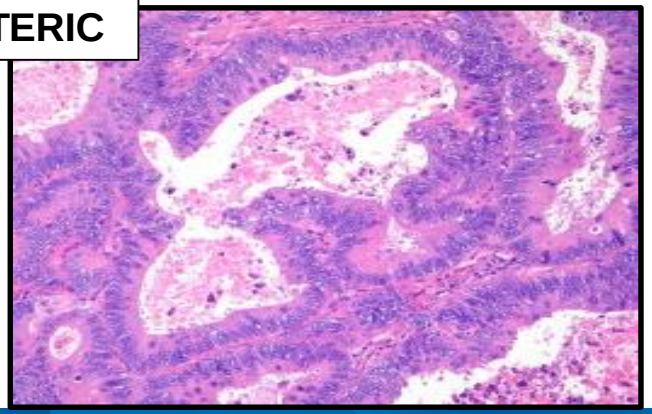


WHO 2015 CLASSIFICATION
INVASIVE ADENOCARCINOMA VARIANTS

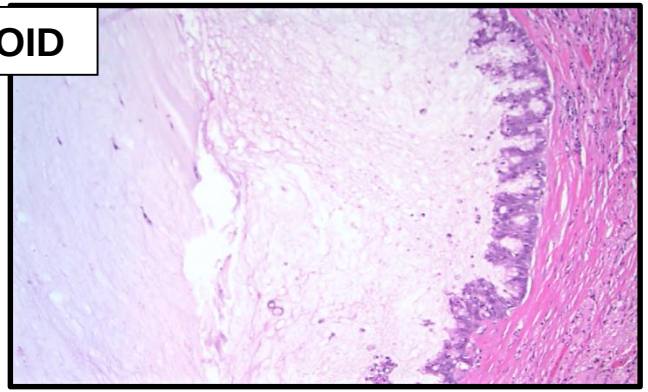
MUCINOUS



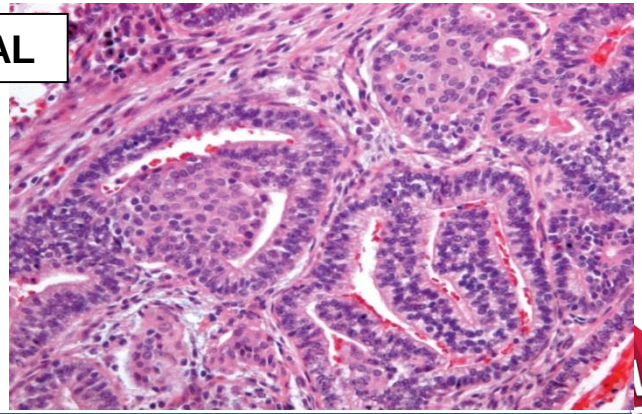
ENTERIC



COLLOID



FETAL

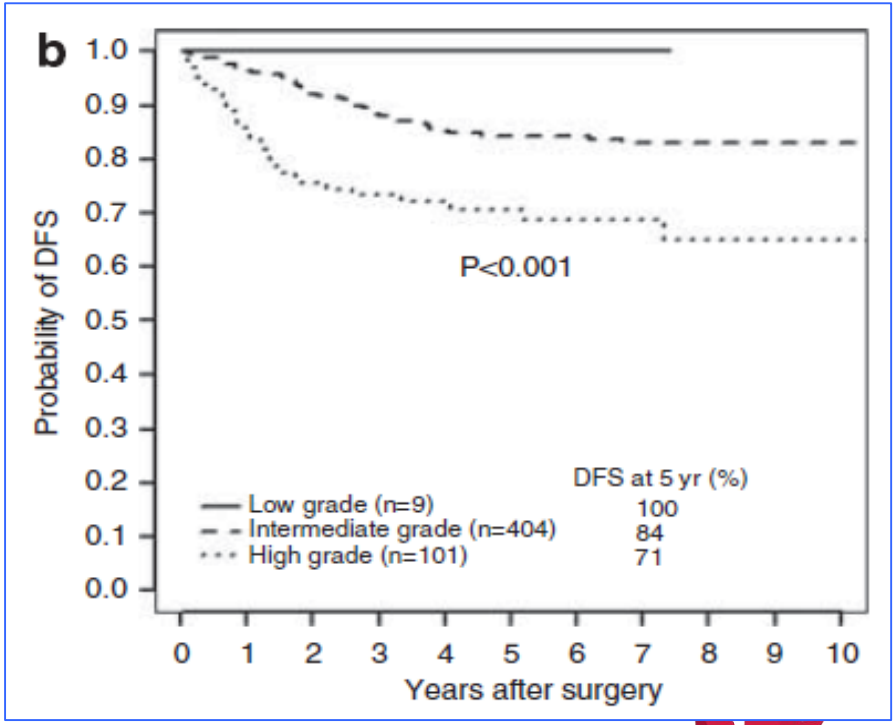


INVASIVE ADENOCARCINOMA

- Recording the percentages of the various histologic types in 5% increments (not just the most predominant type) in pathology reports
- No established histological or cytological grading criteria exists for lung adenocarcinoma

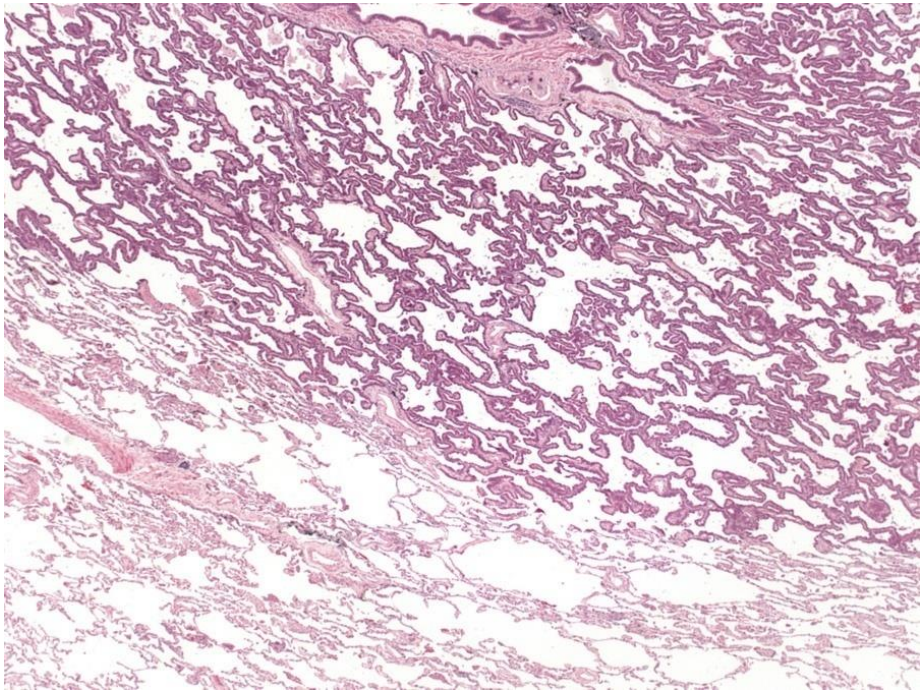
ADENOCARCINOMA SUBTYPING AND SURVIVAL

Classification subtypes	DFS at 5 yrs
Low Grade	
Adenocarcinoma in situ	100%
MIA, nonmucinous	100%
MIA, mixed	100%,
Intermediate Grade	
Lepidic predominant	90%
Acinar predominant	84%
Papillary predominant	83%
High Grade	
Micropapillary predominant	67%
Solid predominant	70%
Colloid predominant	71%
Invasive mucinous	76%



Yoshizava A et al. Mod Pathol 2011;24(5):653-64

How to separate AIS from MIA?



ADENOCARCINOMA IN SITU (AIS)

- A localized small (≤ 3.0 cm) ADC with growth restricted to neoplastic cells along pre-existing alveolar structures (lepidic growth) lacking stromal, vascular or pleural invasion
- 100% disease-free specific survival if completely resected
- pT stage: Tis(AIS)

MINIMALLY INVASIVE ADENOCARCINOMA (MIA)

- Solitary and discrete, ≤ 3.0 cm with a predominantly lepidic pattern and ≤ 5 mm invasion in <u>any one focus</u>
- 100% disease-free specific survival if completely resected
- pT stage:T1-mi

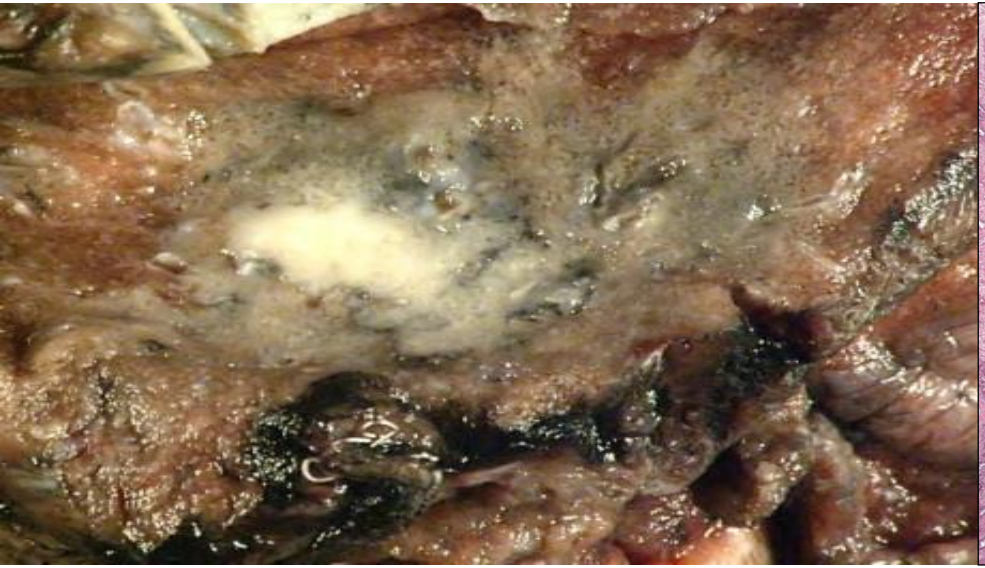
HOW TO MEASURE INVASION?

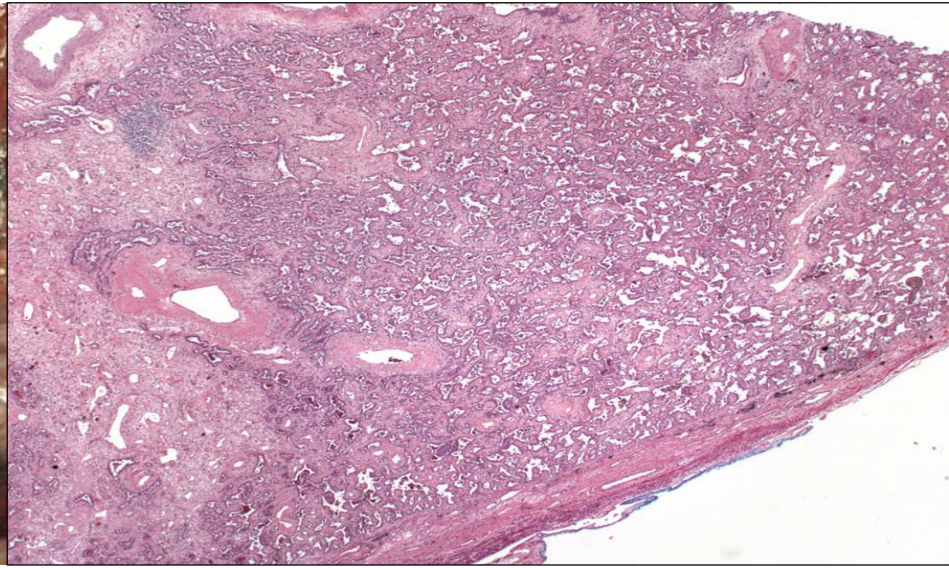
OR

INVASIVE SIZE = % OF INVASIVE COMPONENT x TUMOR DIAMETER

i.e. 2.0 cm tumor with 20% acinar and 80% lepidic
2.0 x 0.2 =0.4 cm

HOW TO STAGE INVASIVE LEPIDIC ADENOCARCINOMA?

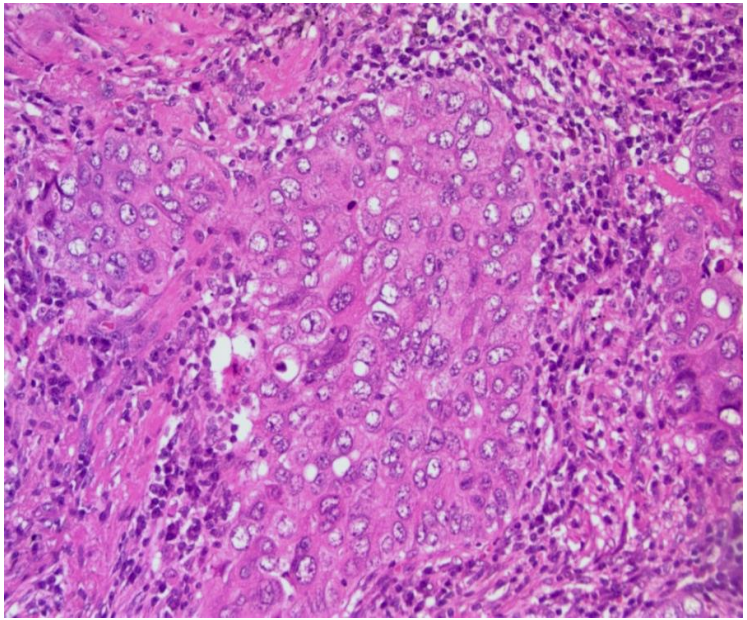




Total tumor size should be recorded, but only the invasive component used as a descriptor of the T-categories

- **pT stage: T1 any**

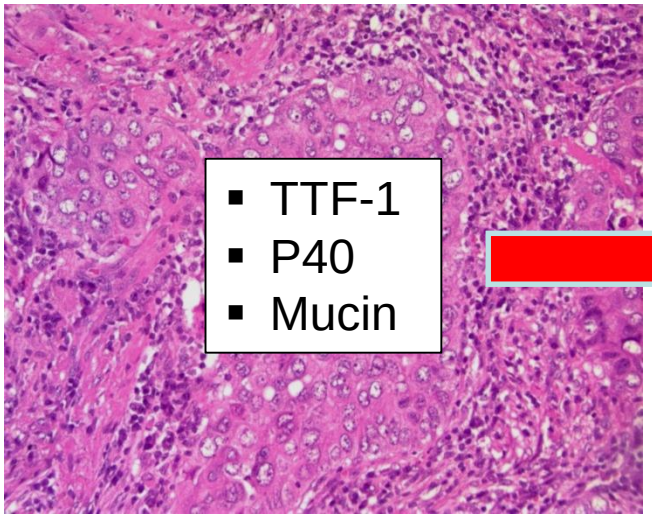
LARGE CELL CARCINOMA

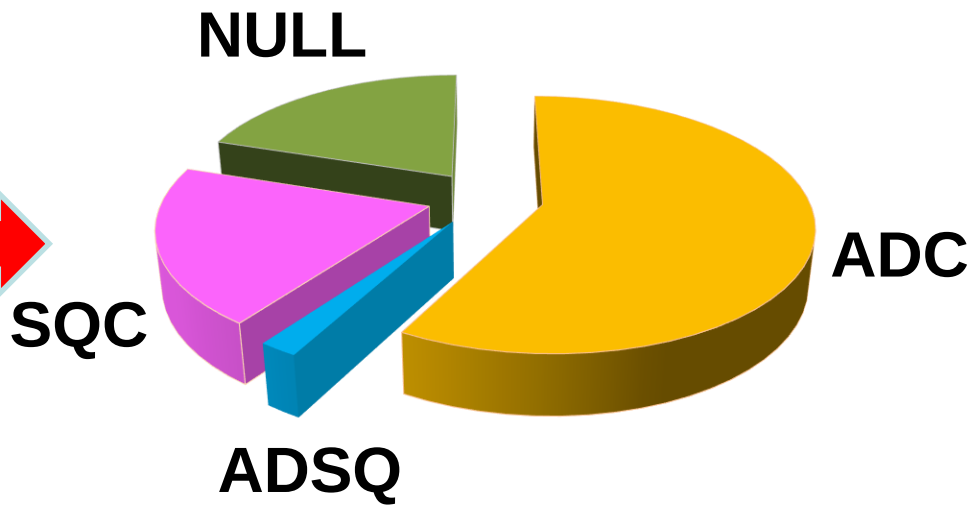


WHO 2004

- Poorly differentiated non-small cell carcinoma without morphologic evidence of squamous, glandular or neuroendocrine differentiation

LARGE CELL CARCINOMA





Rekhtman N et al. Mod Pathol. 2013 Apr;26(4):511-22; Rossi G et al. Virchows Arch. 2014 Jan;464(1):61-8

WHO 2015 LARGE CELL CARCINOMA

- 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 tumor, and cannot be made on non-resection or cytology specimen

TAKE HOME MESSAGE

- Precise lung carcinoma morphologic classification can be achieved on cytology/small biopsy specimens and with use of limited IHC panels (TTF,p40, NE marker)
- Tumor tissue should be spared for molecular testing
- Adoption of 2011 IASLC/ATS/ERS lung adenocarcinoma classification for resection specimens (AIS, MIA, invasive adenocarcinoma)
- 8th edition of AJCC establishes Tis for adenocarcinoma, T1-mi for MIA
- T stage of lepidic predominant adenocarcinoma is determined by the size of invasion, not the gross size

MTE02.02

Update on WHO Classification and Staging of Lung Cancer

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TAIWAN

OUTLINE

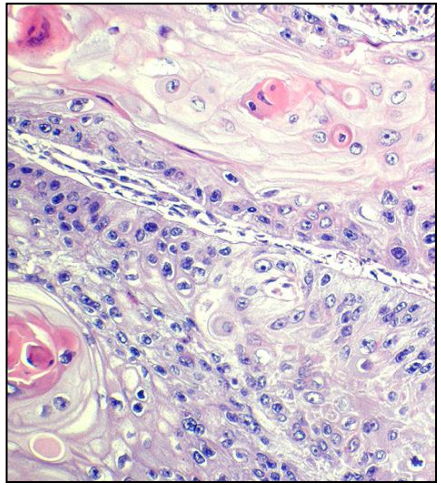
1. Squamous cell carcinoma
2. Neuroendocrine tumors
3. Adenosquamous carcinoma
4. Sarcomatoid carcinoma
5. Lymphoepithelioma-like carcinoma and NUT carcinoma

OUTLINE

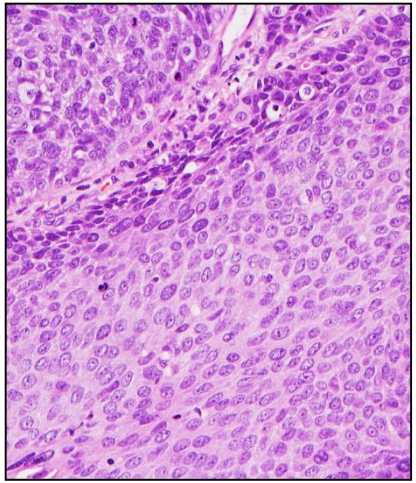
1. **Squamous cell carcinoma**
2. **Neuroendocrine tumors**
3. **Adenosquamous carcinoma**
4. **Sarcomatoid carcinoma**
5. **Lymphoepithelioma-like carcinoma and NUT carcinoma**

Squamous Cell Carcinoma (SqCC)

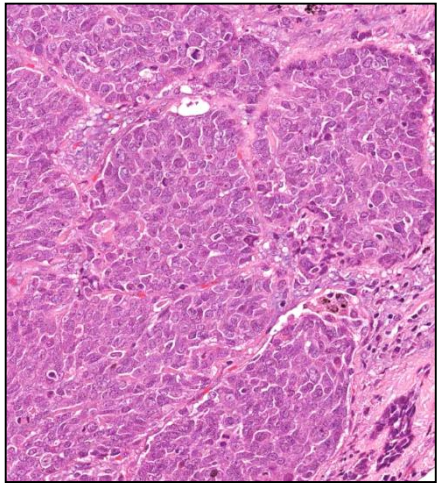
Keratinizing



Non-keratinizing



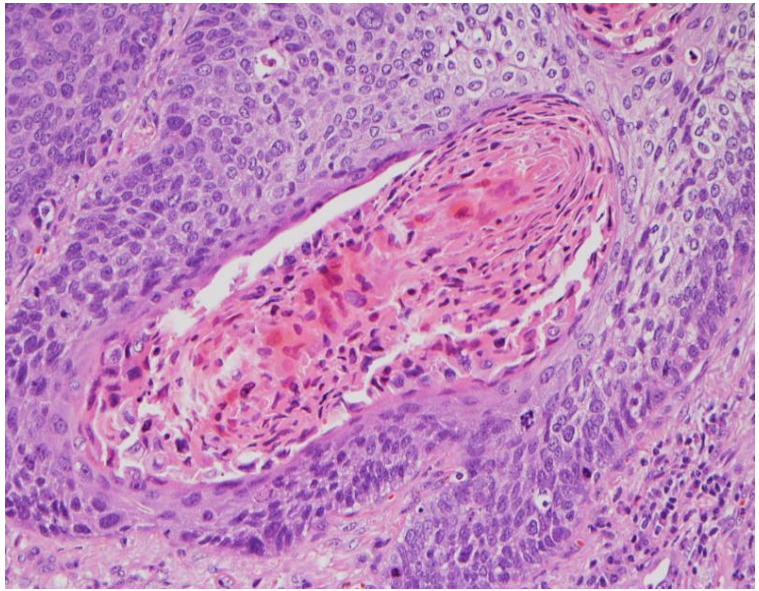
Basaloid



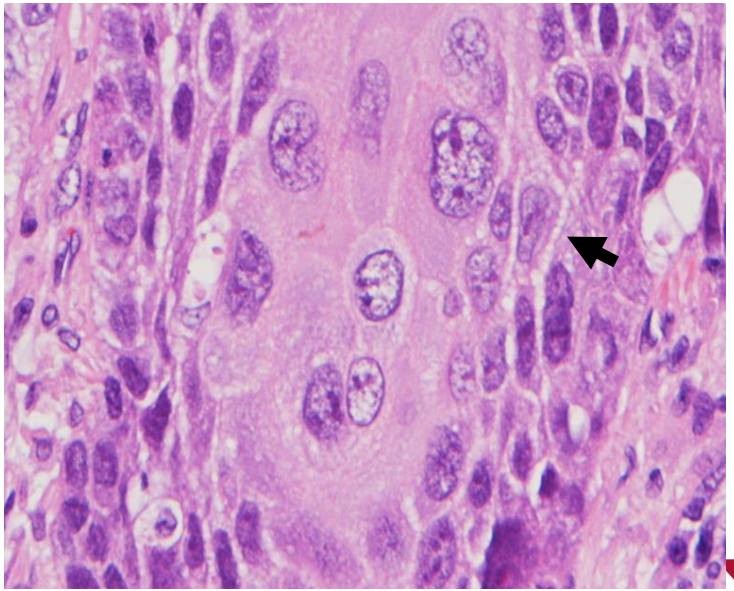
- **Prognostic differences → Controversial**
- **Clinical significance → Uncertain**

Keratinizing Squamous Cell Carcinoma

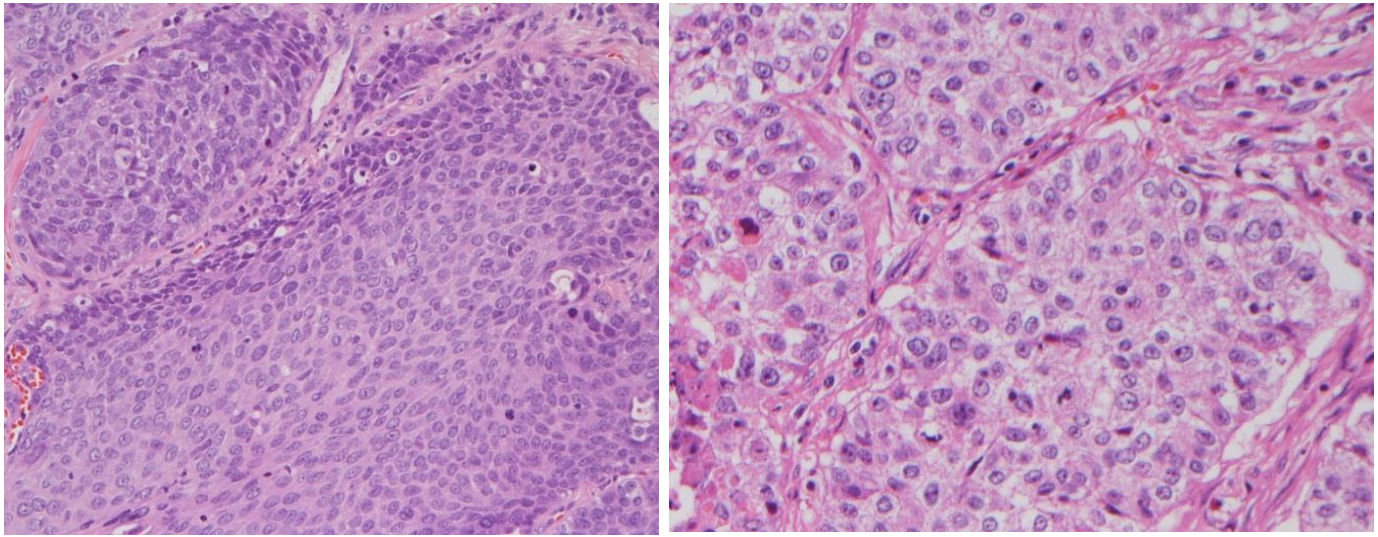
Keratinization



Intercellular Bridge

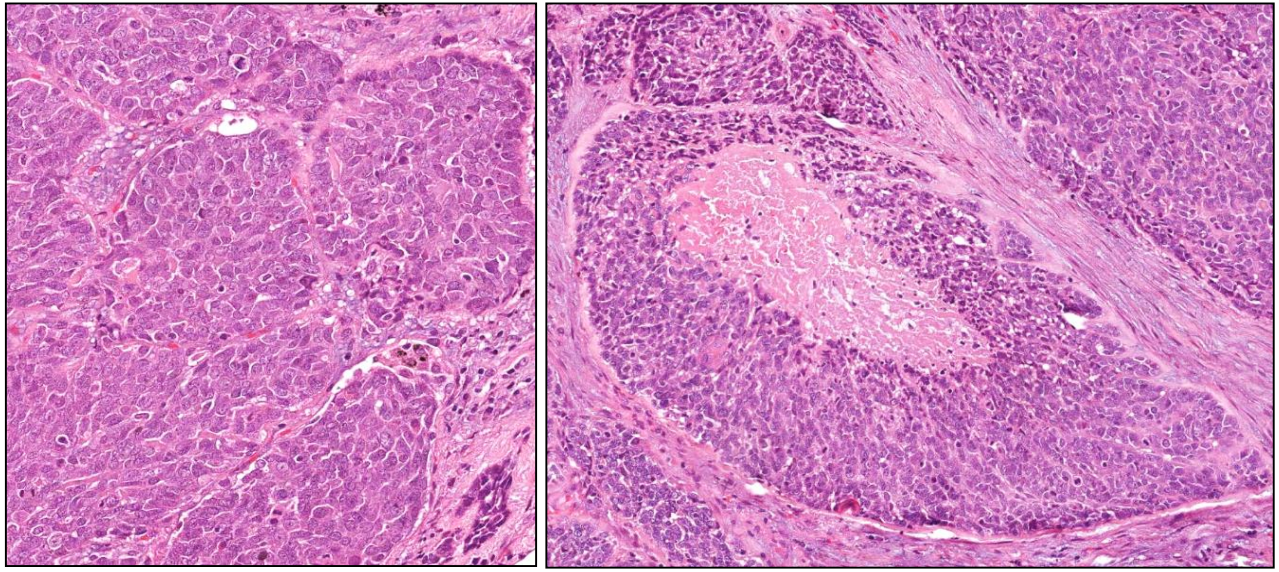


Non-Keratinizing SqCC

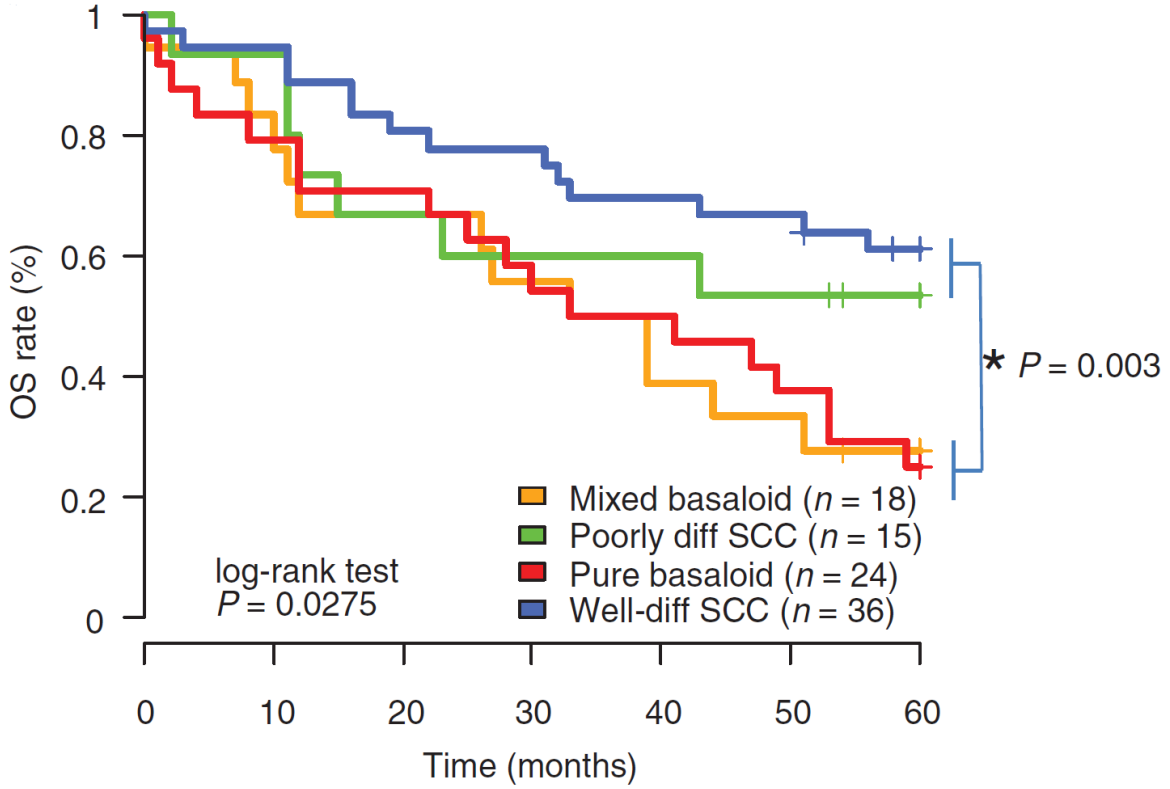


- Lack of keratinization and intercellular bridges
- Immunohistochemistry is required for diagnosis

Basaloid SqCC

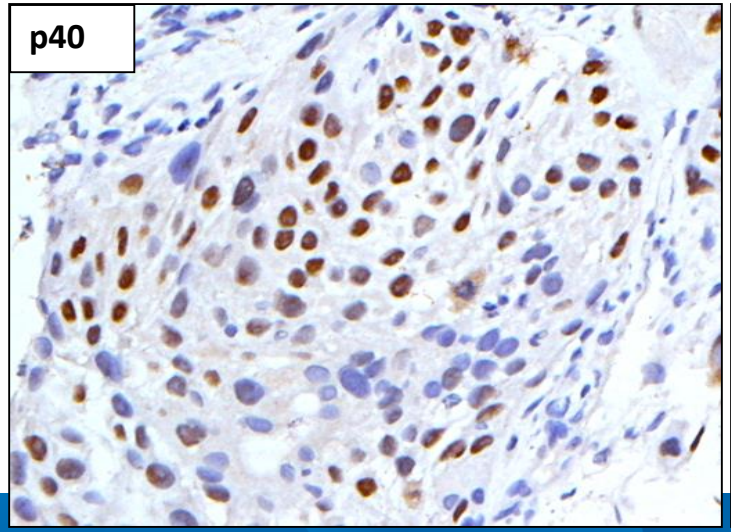


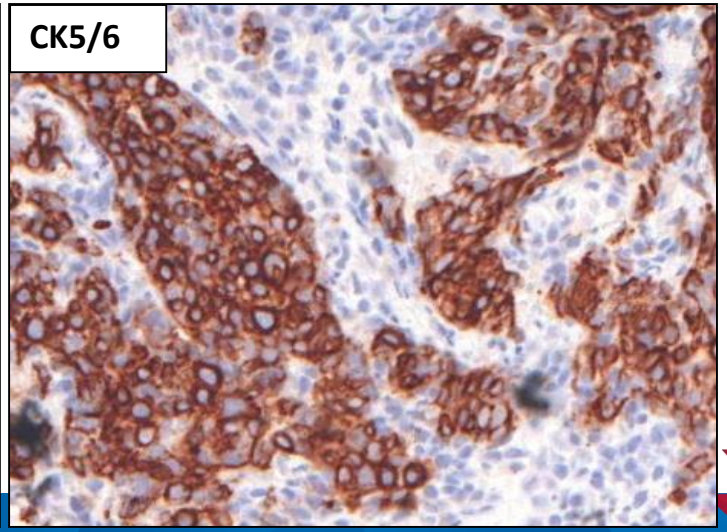
- Poorly differentiated tumor with small monotonous tumor cells
- Immunohistochemistry is required for diagnosis


OS rate (%)
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
Time (months)
log-rank test
P = 0.0275
Mixed basaloid (n = 18)
Poorly diff SCC (n = 15)
Pure basaloid (n = 24)
Well-diff SCC (n = 36)
* P = 0.003

Squamous Cell Carcinoma Markers

- **p40 (best): >95% sensitivity, but can be focally positive in adenocarcinoma**
- **p63, CK5/6, CK34βE12**





Proposed Grading System for Squamous Cell Carcinoma

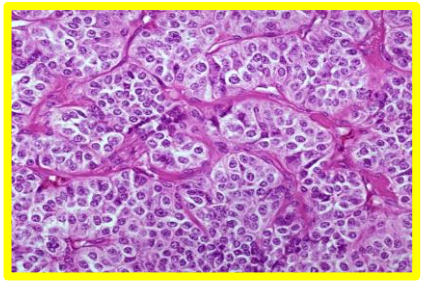
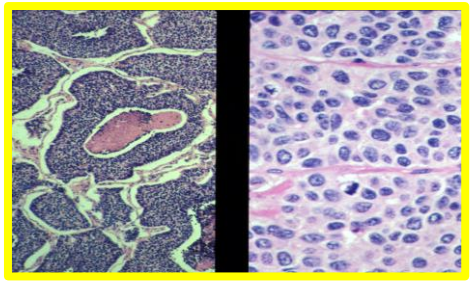
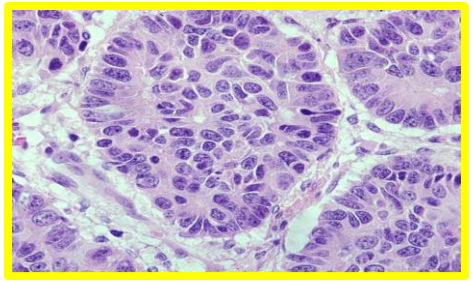
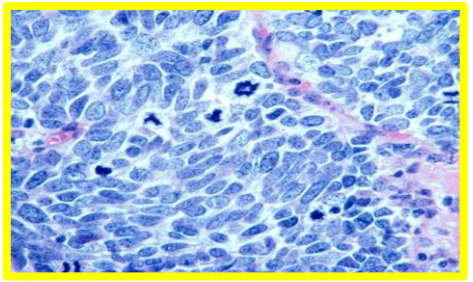
Pattern	Score	Mitosis (10 HPFs)	Score	Budding (10 HPFs)	Score	Cell nest size	Score	Grade	Score
SqCC in situ	0	N/A	0	N/A	0	N/A	0	0	SqCC in situ
All others	1	<15	1	Absent	0	Low (>15 cells per nest)	1	1	4-5
Basaloid	2	> 15	2	Low (< 15)	1	High (1-15 cells per nest)	2	2	6-7
				High (>= 15)	2	Single cell	3	3	8-9
								4	10-11

OUTLINE

1. Squamous cell carcinoma
2. Neuroendocrine tumors
3. Adenosquamous carcinoma
4. Sarcomatoid carcinoma
5. Lymphoepithelioma-like carcinoma and NUT carcinoma

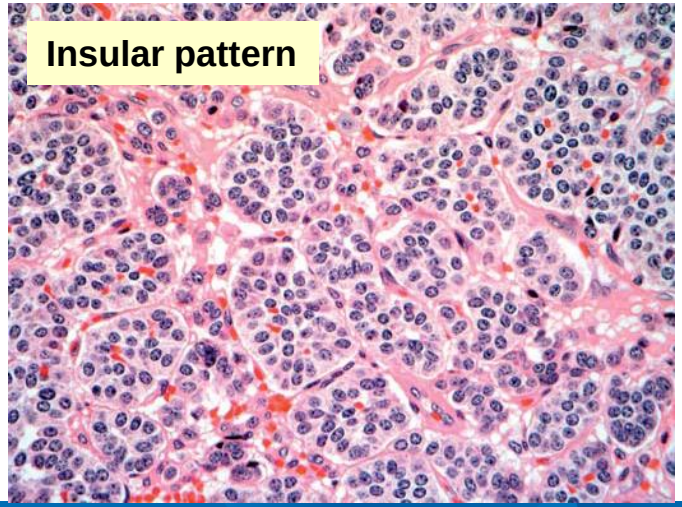
Neuroendocrine Tumors

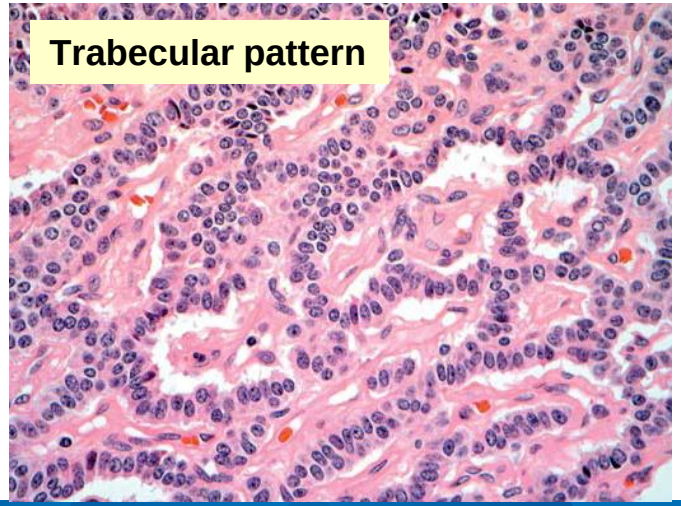
Typical carcinoid (Low grade)	Atypical carcinoid (Intermediate grade)	Large cell NE carcinoma (High grade)	Small cell carcinoma (High grade)

Typical Carcinoid (TC)

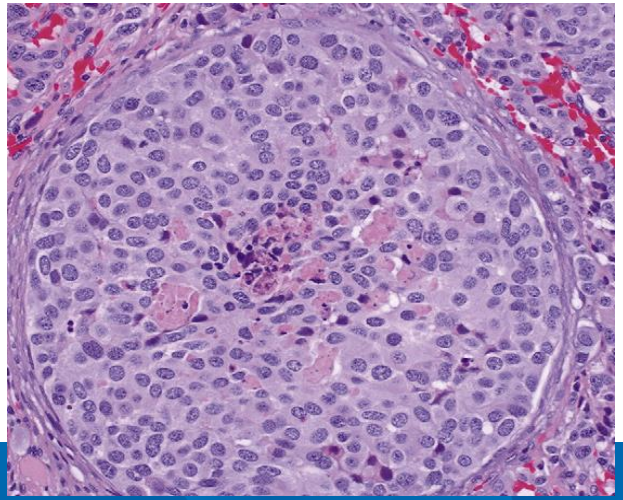
- Organized “neuroendocrine morphology”
- Mitosis: 0-1 per 2 mm^2
- Necrosis: (-)

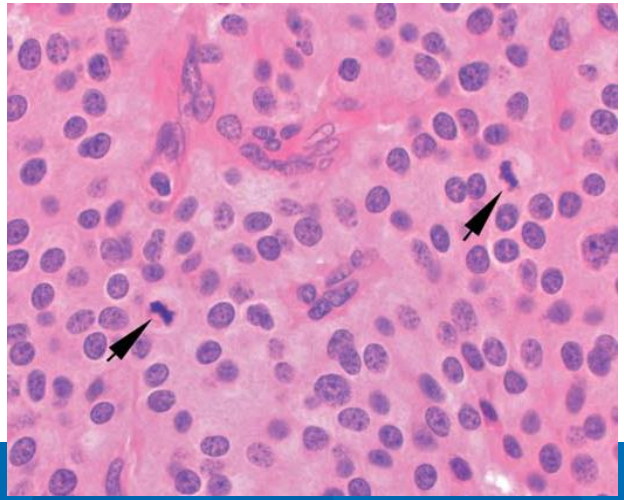




Atypical Carcinoid (AC)

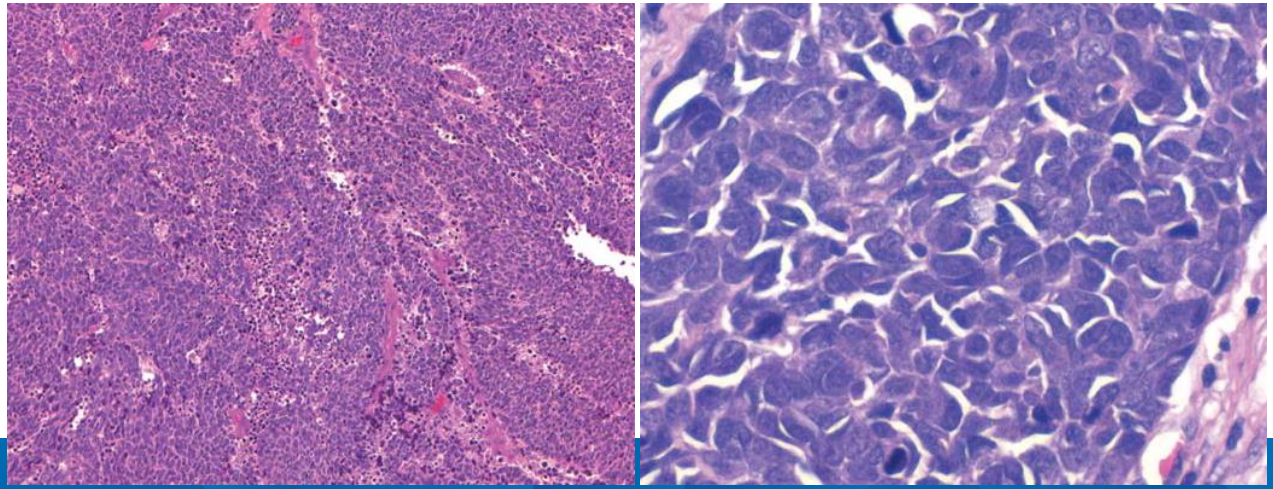
- Organized “neuroendocrine morphology”
- Mitosis: 2-10 per 2 mm^2
- Necrosis: may focally present
- May NOT be able to D/D from TC in biopsy specimen





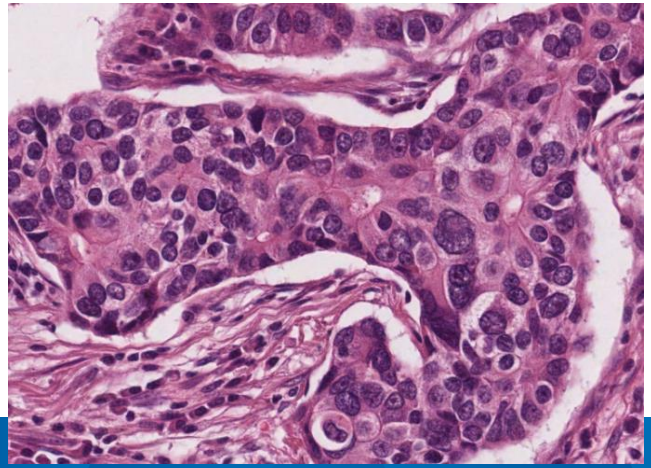
Small Cell Carcinoma (SCLC)

- Poorly organized structure
- Small tumor cells with scant cytoplasm
  - Fine chromatin, inconspicuous nucleoli
- Numerous mitosis, confluent necrosis



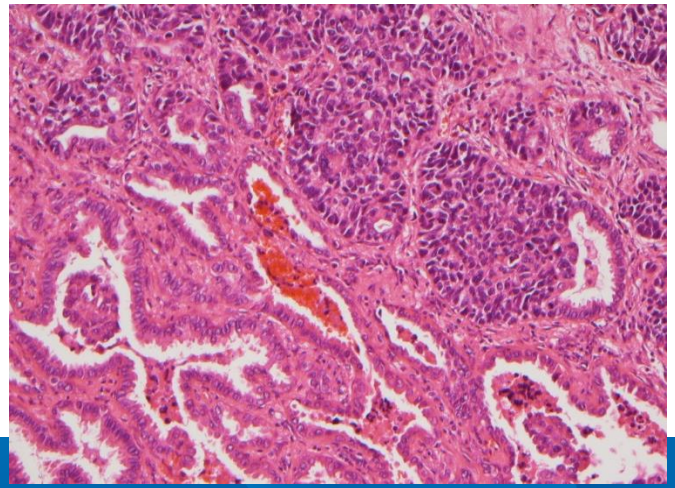
Large Cell NE Carcinoma (LCNEC)

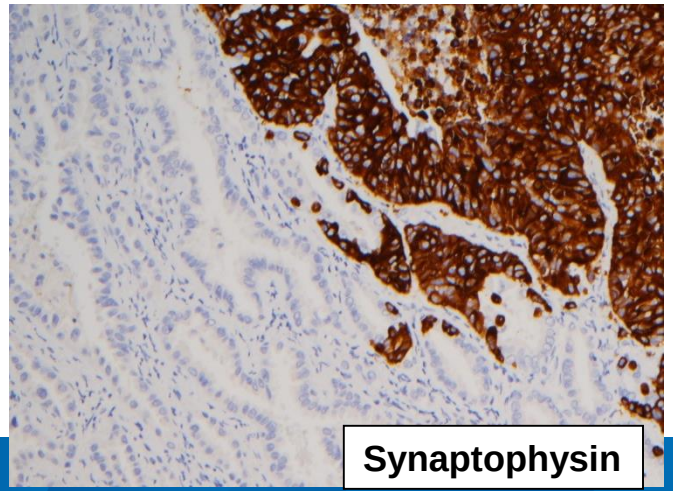
- Attenuated neuroendocrine morphology
- Large pleomorphic tumor cells
  - Vesicular nuclei, prominent nucleoli
- Numerous mitosis, confluent necrosis
- Immunohistochemistry is required for diagnosis



Combined Small Cell Carcinoma

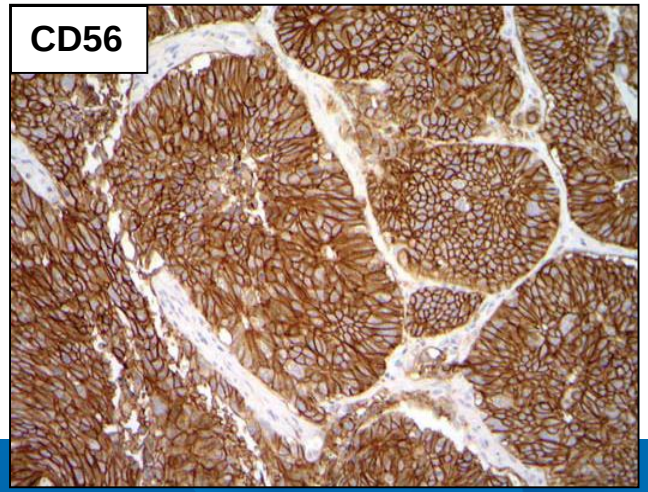
- Small cell carcinoma component + NSCLC component
- NSCLC component:
  - Squamous, adenocarcinoma, large cell carcinoma, …
  - Large cell neuroendocrine carcinoma

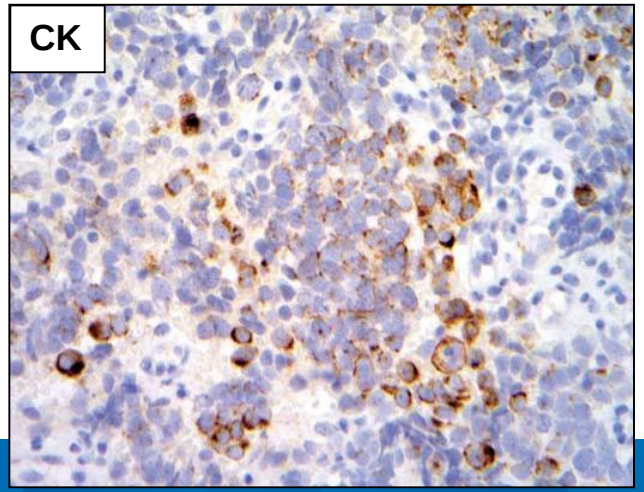


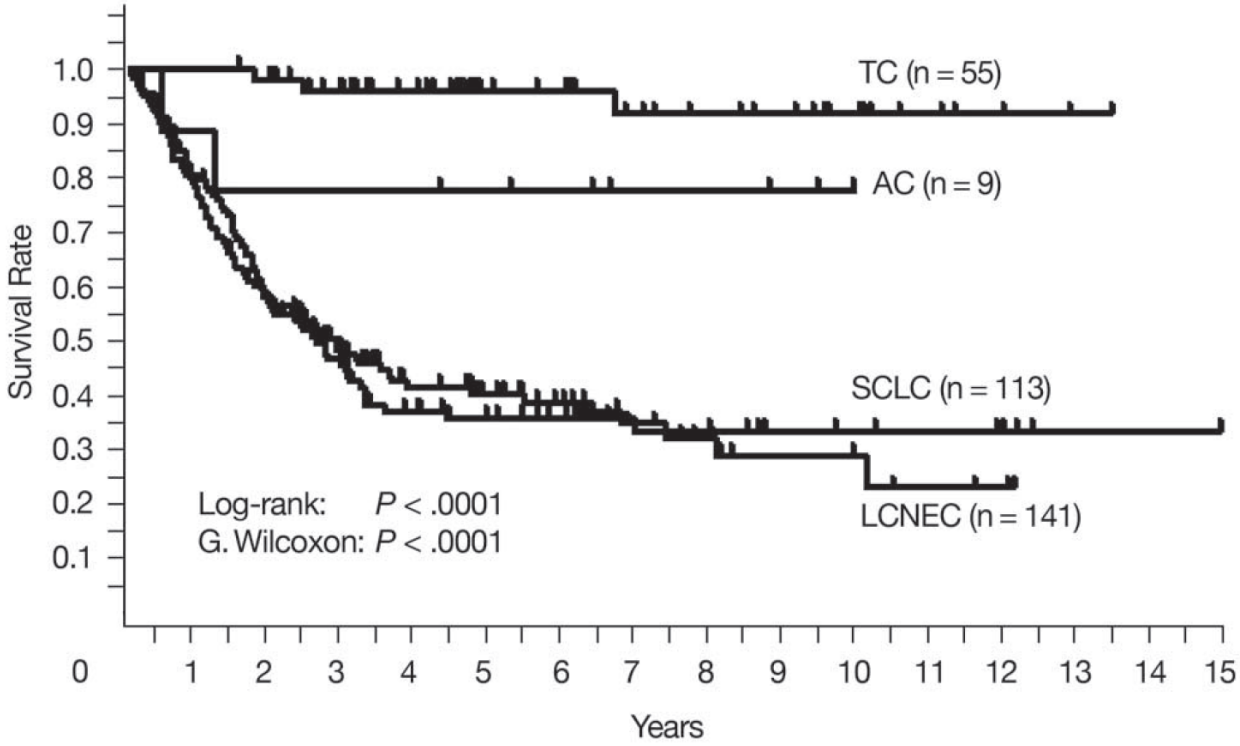


Neuroendocrine markers

- Chromogranin A, Synaptophysin, CD56
- Positive for at least one marker is required for diagnosis (except for SCLC)
- CK(AE1/AE3): Dot-like staining pattern in SCLC







Asamura H. et al. *J Clin Oncol.* 2006 Jan 1;24(1):70-6.

	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell lung carcinoma
Average age	Sixth decade	Sixth decade	Seventh decade	Seventh decade
Sex predominance	Female	Female	Male	Male
Smoking association	No	Variable*	Yes	Yes
Diagnostic criteria				
Mitoses per 2 mm^2	0–1	2–10	> 10 (median of 70)	> 10 (median of 80)
Necrosis	No	Focal, if any	Yes	Yes
Neuroendocrine morphology	Yes	Yes	Yes	Yes
Ki-67 proliferation index (%) {2020}	Up to 5%	Up to 20%	40–80%	50–100%
TTF1 expression {1377}	Mostly negative	Mostly negative	Positive (50%)	Positive (85%)
p63 expression {301,2019}	Negative	Negative	Variably positive	Variably positive
p40 expression {301}	Negative	Negative	Negative	Negative
Combined with a non-small cell lung carcinoma component	No	No	Sometimes	Sometimes

* The majority of carcinoid patients are never-smokers or light smokers, although atypical carcinoid is more associated with current or former smokers than typical carcinoid patients.

OUTLINE

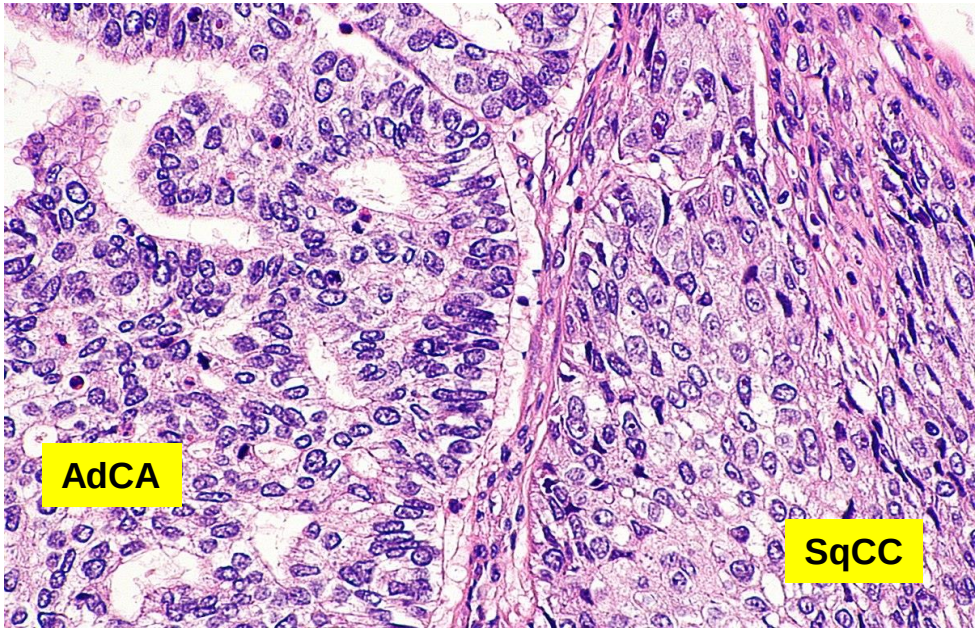
1. Squamous cell carcinoma
2. Neuroendocrine tumors
3. Adenosquamous carcinoma
4. Sarcomatoid carcinoma
5. Lymphoepithelioma-like carcinoma and NUT carcinoma

Adenosquamous Carcinoma

- Carcinoma showing components of both squamous cell carcinoma and adenocarcinoma
- Each component constitute >= 10% of the tumor
- Diagnosis may be suggested in small biopsies, but definite diagnosis requires resection specimens
- Account for 0.4 – 4% of all lung cancers

Histopathology of AdenoSq Carcinoma

AdCA & SqCC components may be separate or intermingled

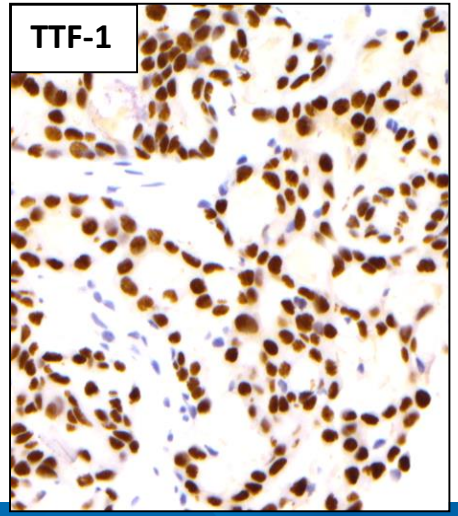


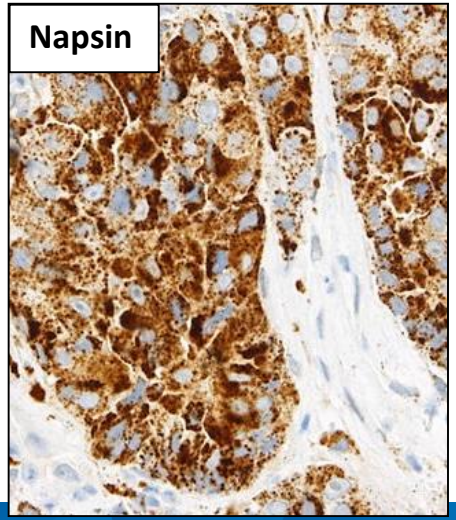
https://en.wikipedia.org/wiki/Adenosquamous_carcinoma

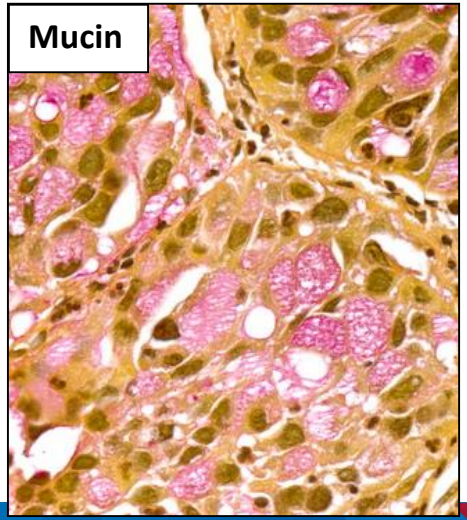
Ancillary Studies for AdenoSq Carcinoma

- **Adenocarcinoma markers:**

  TTF-1 (best): ~80% sensitivity, highly specific;
  Napsin, Surfactant apoprotein A, Mucin stain



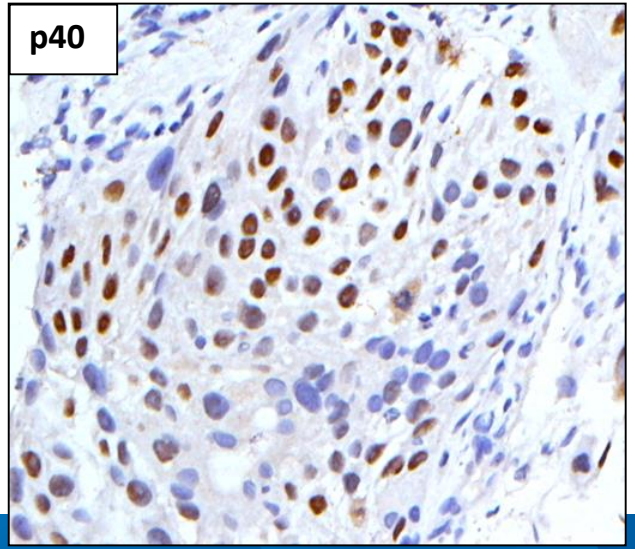


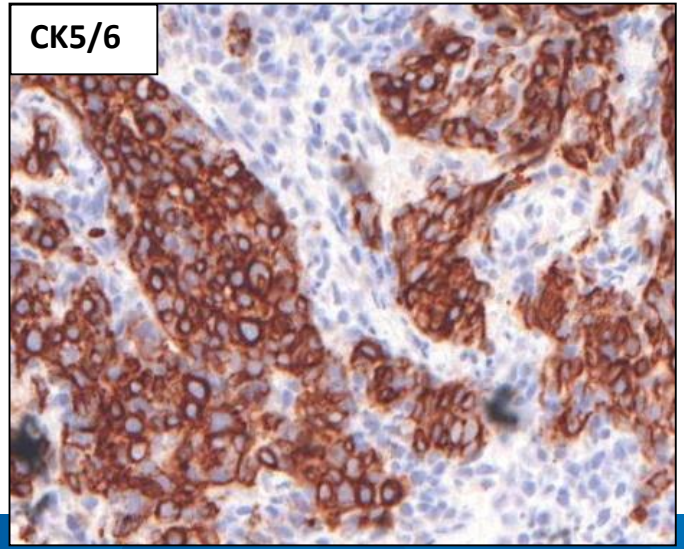


Ancillary Studies for AdenoSq Carcinoma

- **Squamous cell carcinoma markers:**

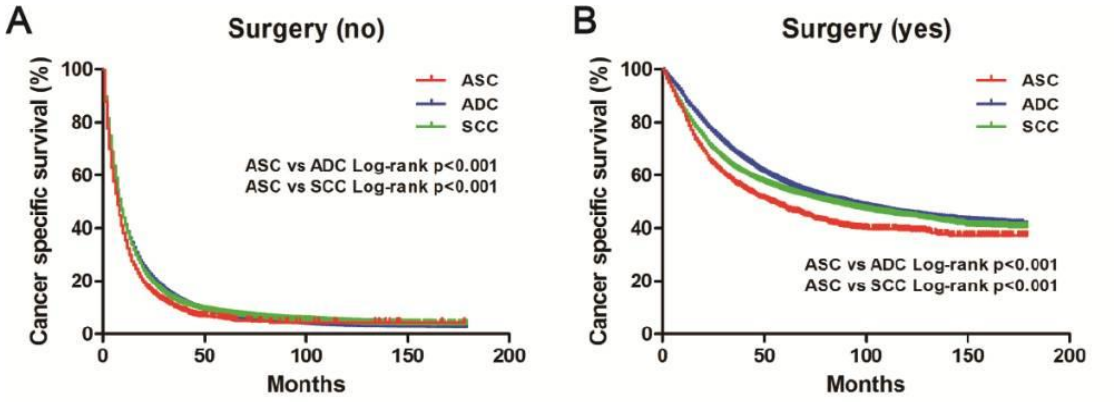
  p40 (best): >95% sensitivity, but can be focally positive in adenocarcinoma; p63, CK5/6, CK34βE12





Prognosis of AdenoSq Carcinoma

- **Worse than pure AdenoCA and SqCC**



	1-year	3-year	5-year
ASC	32.4%	10.1%	5.8%
ADC	38.9%	13.5%	7.1%
SCC	38.4%	12.8%	7.7%

	1-year	3-year	5-year
ASC	80.8%	56.8%	47.9%
ADC	88.0%	68.6%	57.3%
SCC	83.0%	62.8%	54.5%

Wang J et al. Oncotarget. 2018; 9(8): 8133–8146.

OUTLINE

1. Squamous cell carcinoma
2. Neuroendocrine tumors
3. Adenosquamous carcinoma
4. Sarcomatoid carcinoma
5. Lymphoepithelioma-like carcinoma and NUT carcinoma

Sarcomatoid Carcinoma

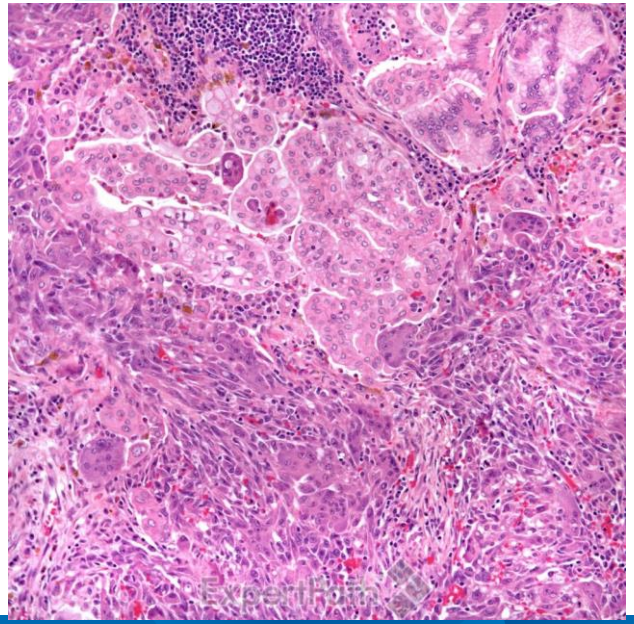
- Account for 2-3% of all resected lung cancers

- A general term includes the followings:
  - Pleomorphic carcinoma
  - Spindle cell carcinoma
  - Giant cell carcinoma
  - Carcinosarcoma
  - Pulmonary blastoma

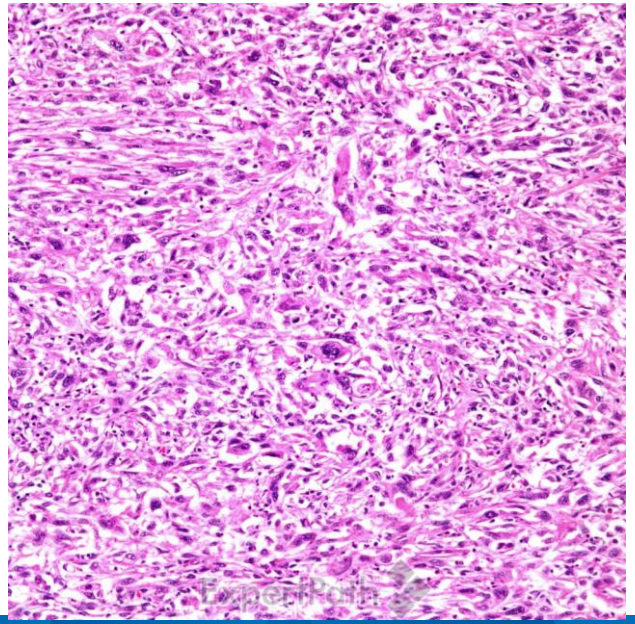
} Very rare

Pleomorphic Carcinoma

Adenocarcinoma component

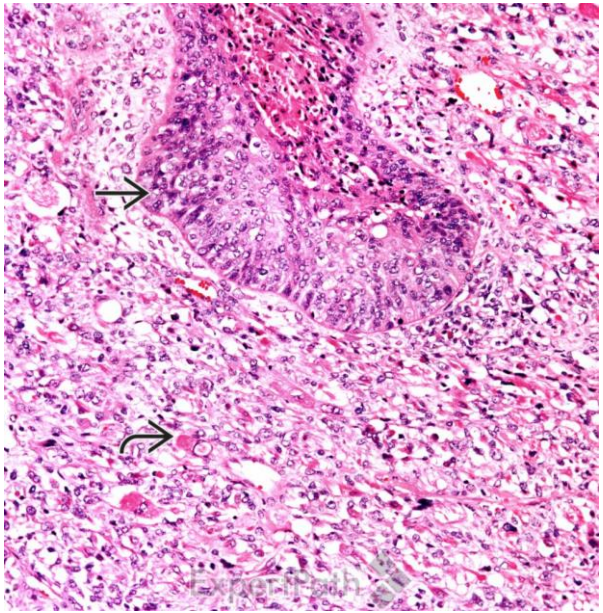


Spindle cell component

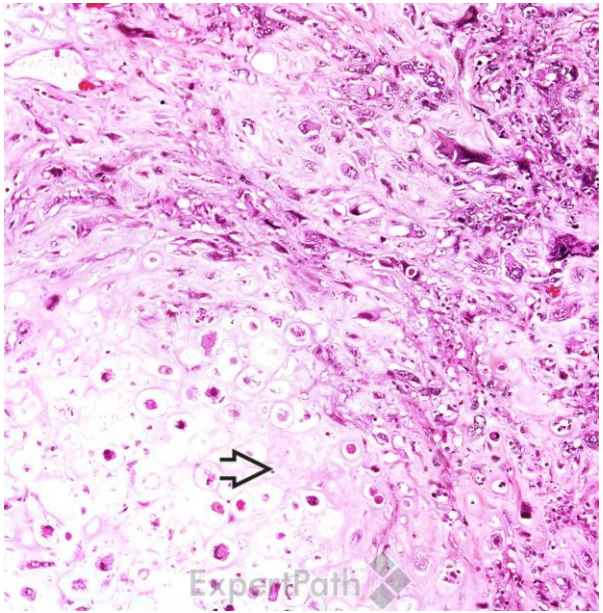


Carcinosarcoma

SqCC + rhabdomyosarcoma



Chondrosarcoma component



Molecular Profile of Sarcomatoid Carcinoma

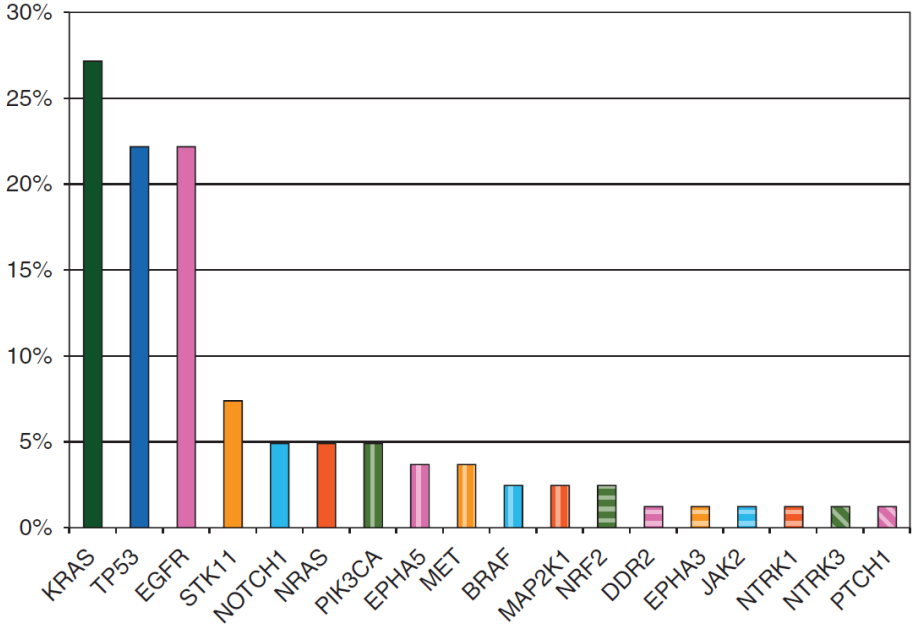
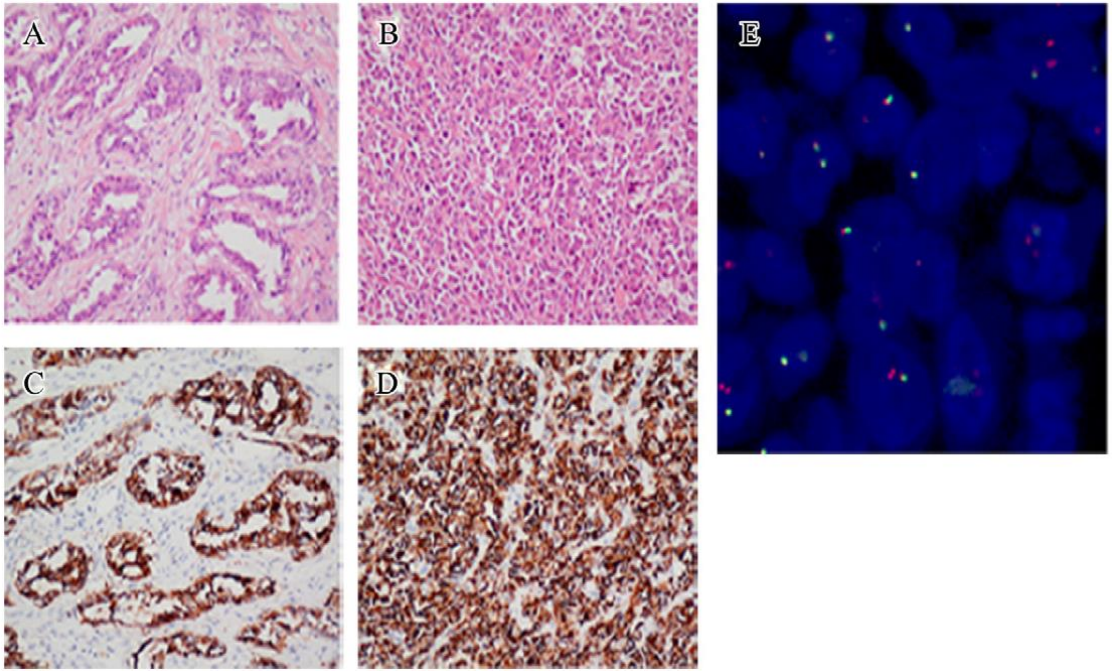


Figure 1. Mutated genes in pulmonary sarcomatoid carcinoma.

Fallet V. et al. Ann Oncol. 2015 Aug;26(8):1748-53.

Molecular Profile of Sarcomatoid Carcinoma

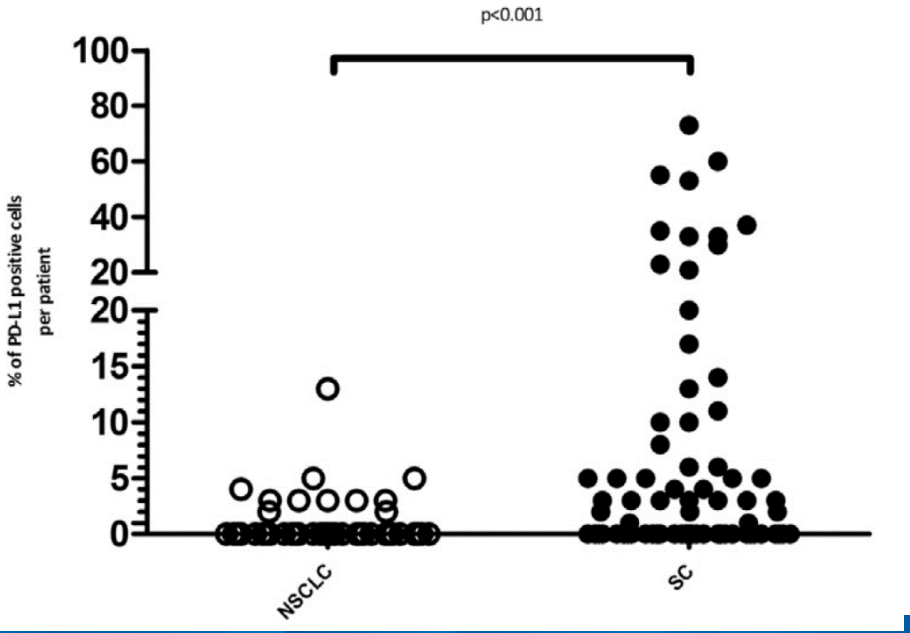
ALK rearrangement: 3.5% (5/141)



Chen X. et al. Transl Oncol. 2017 Apr;10(2):115-120.

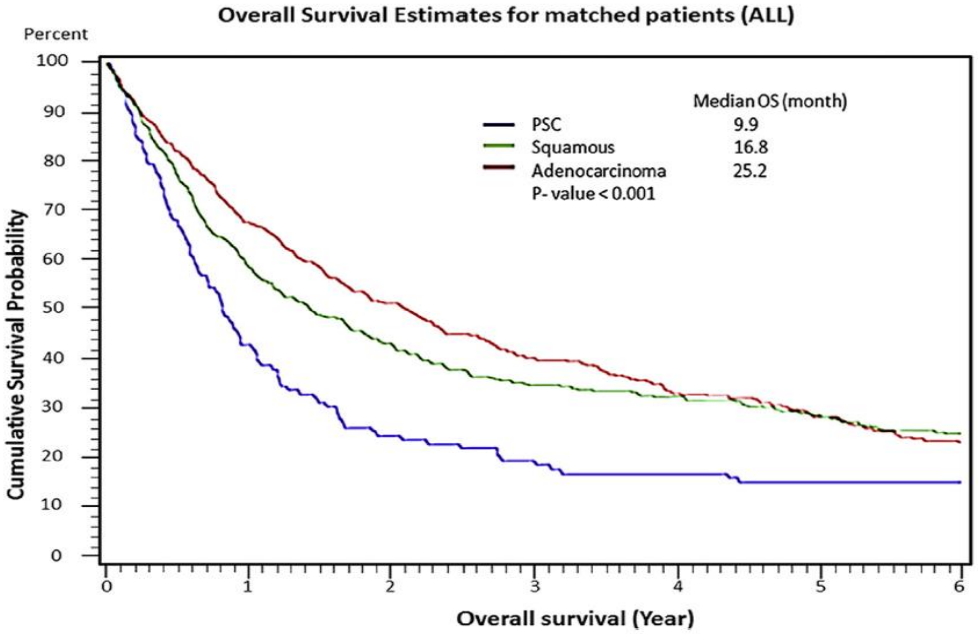
Molecular Profile of Sarcomatoid Carcinoma

- **Frequently show high levels of PD-L1 expression**



Vieira T. et al. Lung Cancer. 2016 Aug;98:51-58.

Prognosis of Sarcomatoid Carcinoma



Maneenil K. et al. Clin Lung Cancer. 2017 Dec 21. pii: S1525-7304(17)30347-9. [Epub ahead of print]

OUTLINE

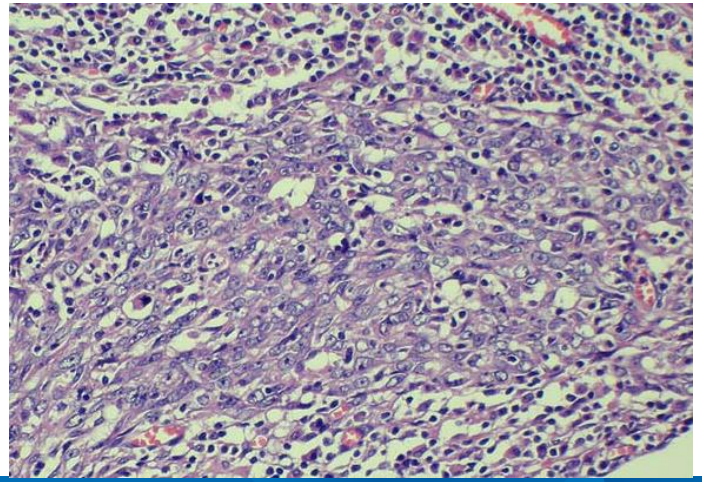
1. Squamous cell carcinoma
2. Neuroendocrine tumors
3. Adenosquamous carcinoma
4. Sarcomatoid carcinoma
5. Lymphoepithelioma-like carcinoma and NUT carcinoma

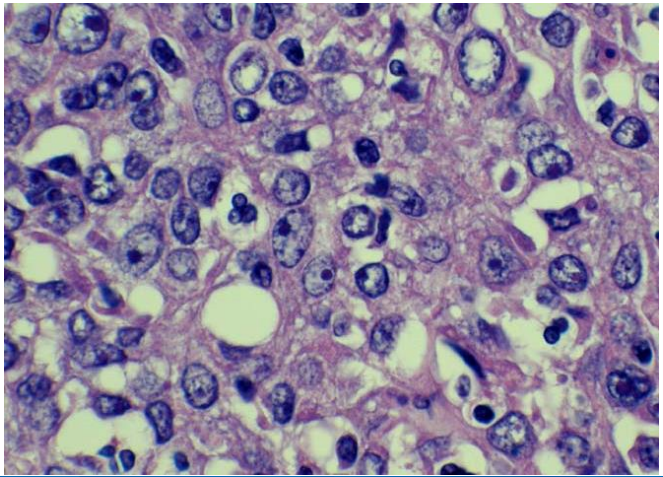
Lymphoepithelioma-like Carcinoma in the Lungs

- Account for ~1% of all lung cancers
- More common in South-East Asia
- Patient characteristics
  - Non-smoking
  - Younger patients
  - Mostly women

Histopathology of Lymphoepithelioma-like Carcinoma

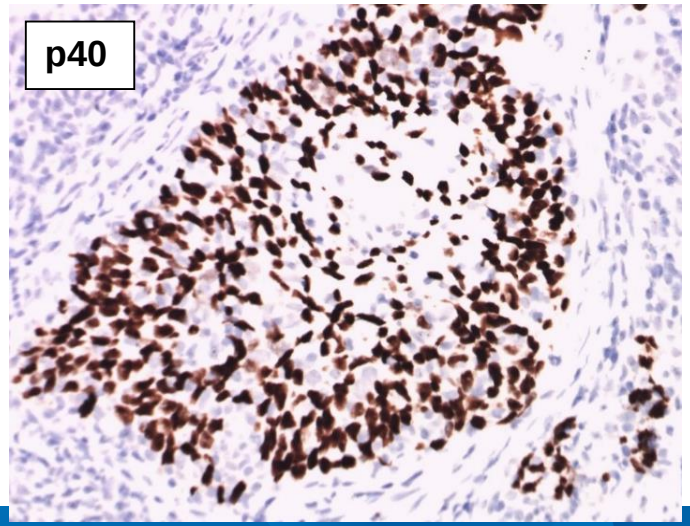
- Syncytial growth pattern
- Large vesicular nuclei with prominent nucleoli
- Marked lymphocytic infiltrate

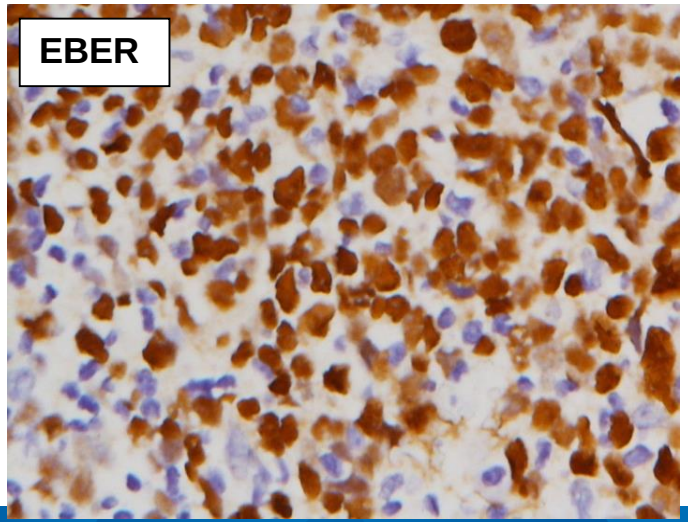




Histopathology of Lymphoepithelioma-like Carcinoma

- Typically express squamous cell lineage markers: CK5/6, p40, p63
- EBER in-situ hybridization (+)



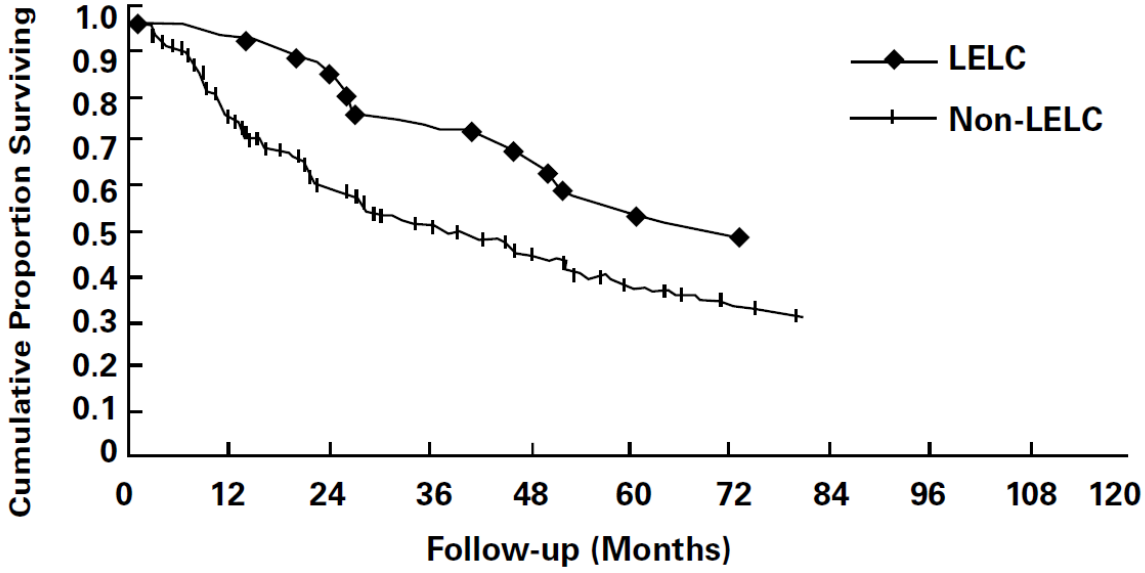


Molecular Characteristics of Lymphoepithelioma-like Carcinoma

- Typically lack driver mutations (EGFR, KRAS, ALK, ROS1, BRAF)
- High frequency of PD-L1 expression (65-75%)

Prognosis of Lymphoepithelioma-like Carcinoma

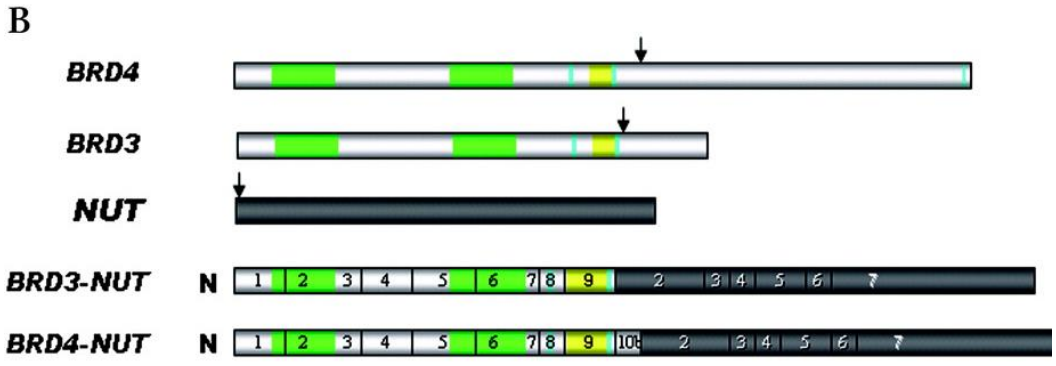
Better than other NSCLC

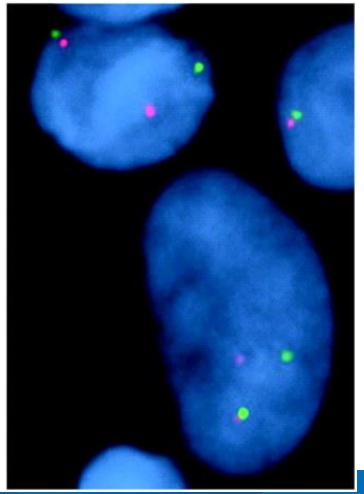


Han AJ. et al. Am J Clin Pathol. 2001 Jun;115(6):841-50.

NUT (midline) carcinoma

- An aggressive poorly differentiated carcinoma
- NUT gene rearrangement (+)
  - Most common fusion: BRD4-NUT fusion (70%)



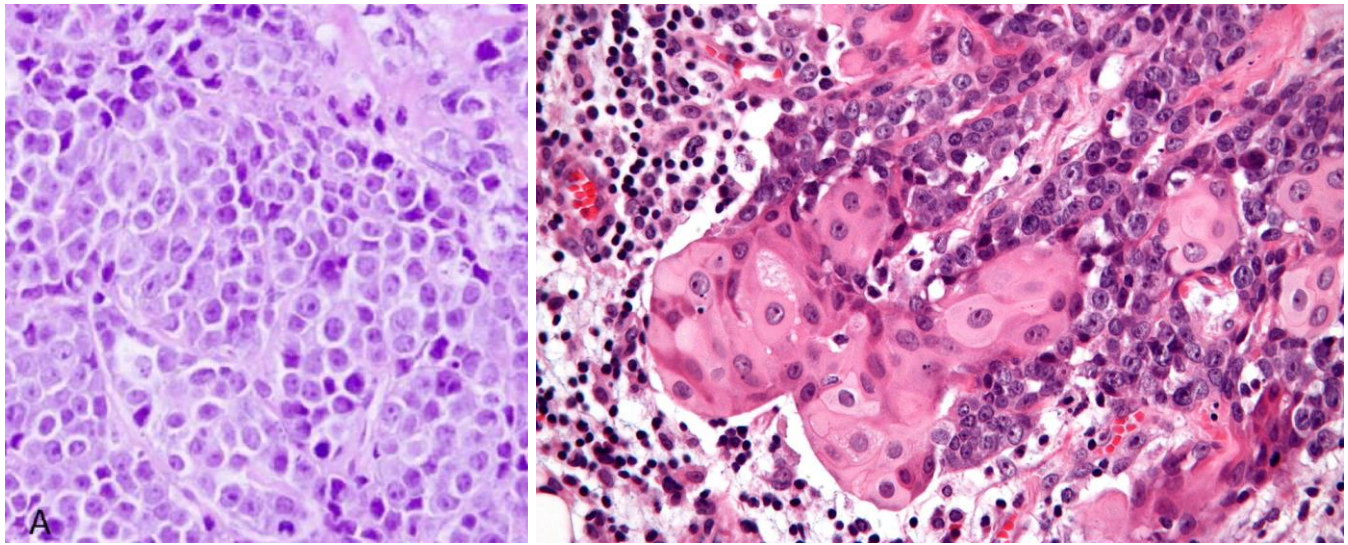


NUT (midline) Carcinoma

- Rare, about 100+ cases reported
- Affect individuals at any age
  - Range: 0-78 years
  - Median: 16
- Location: Head and Neck: most common (~45%)
  - Mediastinum
  - Lung
  - Bladder, Kidney, iliac bone, …

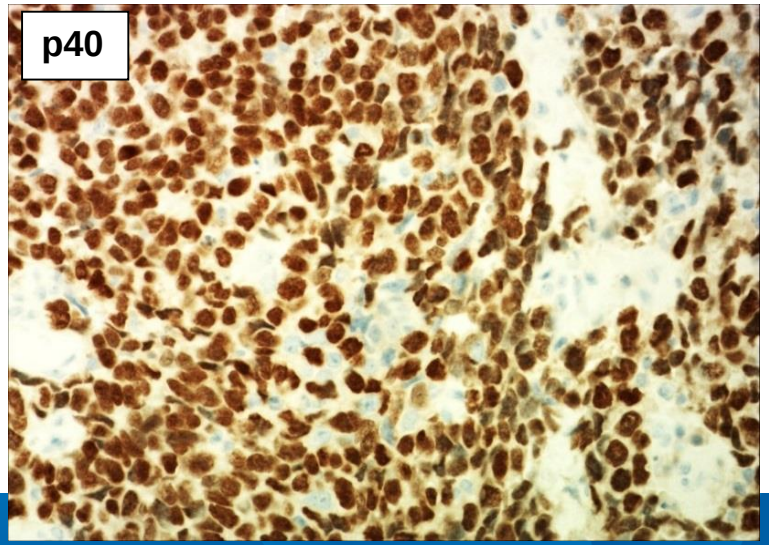
Histopathology of NUT Carcinoma

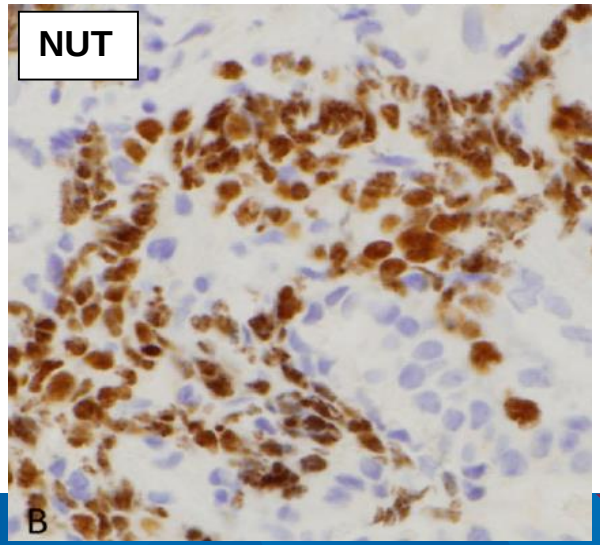
- Small to intermediate-sized undifferentiated cells
- Abrupt foci of keratinization



Histopathology of NUT Carcinoma

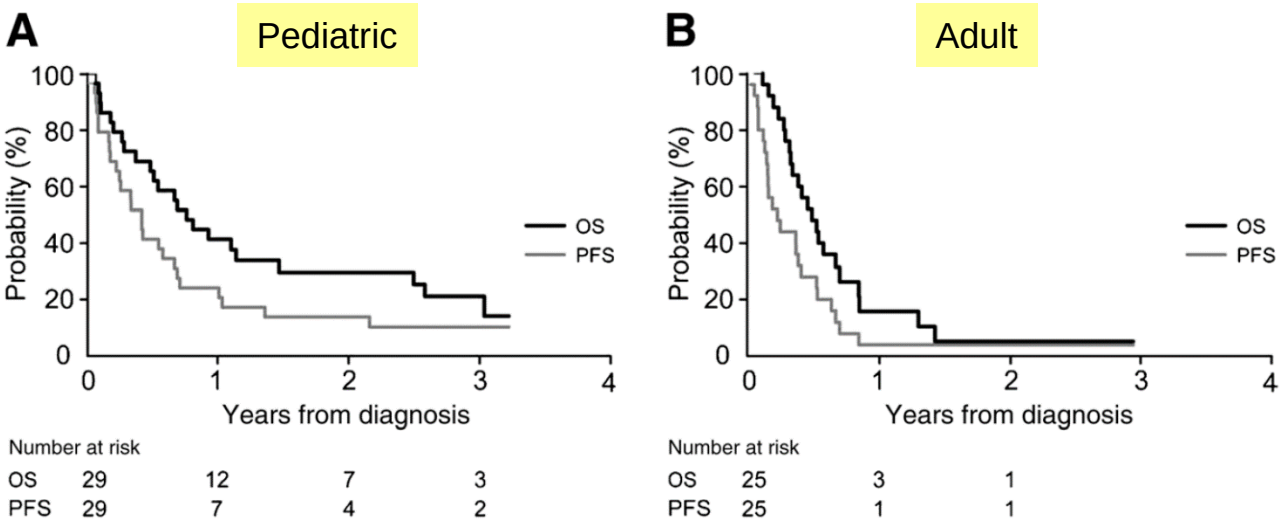
- Most cases are p63 / p40 (+)
- Occasionally TTF-1, chromogranin A, synaptophysin (+)
- Consistently nuclear reactivity to NUT antibody





Prognosis of NUT Carcinoma

- **Extremely aggressive**
- **Median survival: 7 months**



Bauer DE. et al. Clin Cancer Res. 2012 Oct 15;18(20):5773-

TAKE HOME MESSAGE

- **Squamous cell carcinoma** is classified into keratinizing, non-keratinizing and basaloid types. The p40 (or p63) is helpful in diagnosing squamous cell carcinoma, if keratinization of the tumor cells is not appreciable.
- **Neuroendocrine tumor** comprises of four categories: small cell carcinoma, large cell carcinoma, typical carcinoid and atypical carcinoid, with variable degrees of malignant potential.
- **Adenosquamous carcinoma** is rare, with presence of both adenocarcinoma and squamous cell carcinoma components and each component comprising more than 10% is required.
- **Sarcomatoid carcinoma** is further subcategorized into pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma. Sarcomatoid carcinoma needs to be thoroughly sampled before the final diagnoses are made.
- **NUT carcinoma** is a poorly differentiated carcinoma with *NUT* gene rearrangement, which affects people of any age and both sexes.