Yale University School of Medicine

Neuroendocrine Neoplasms of the Lung: Diagnostic Challenges in Cytology Specimens

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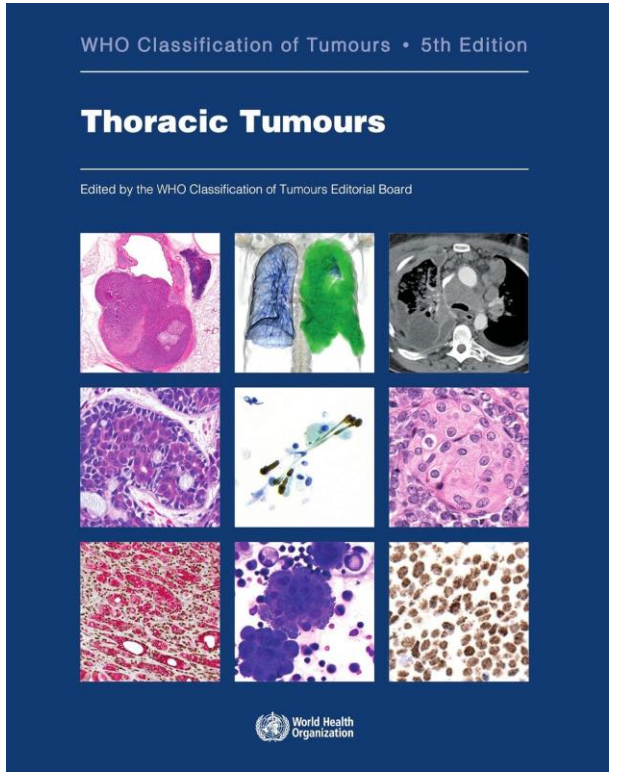
Where Knowledge is Created and Shared

Yale Pathology

Classification of Neuroendocrine Neoplasms

- Pulmonary Neuroendocrine Neoplasms, 20%
  - Neuroendocrine Tumors (NETs), 2%
    - Typical Carcinoid (TC)
    - Atypical Carcinoid (AC)
  - Neuroendocrine Carcinomas (NECs), 18%
    - Small Cell Lung Carcinoma (SCLC), 15%
    - Large Cell Neuroendocrine Carcinoma (LCNEC), 3%



NETs vs NECs

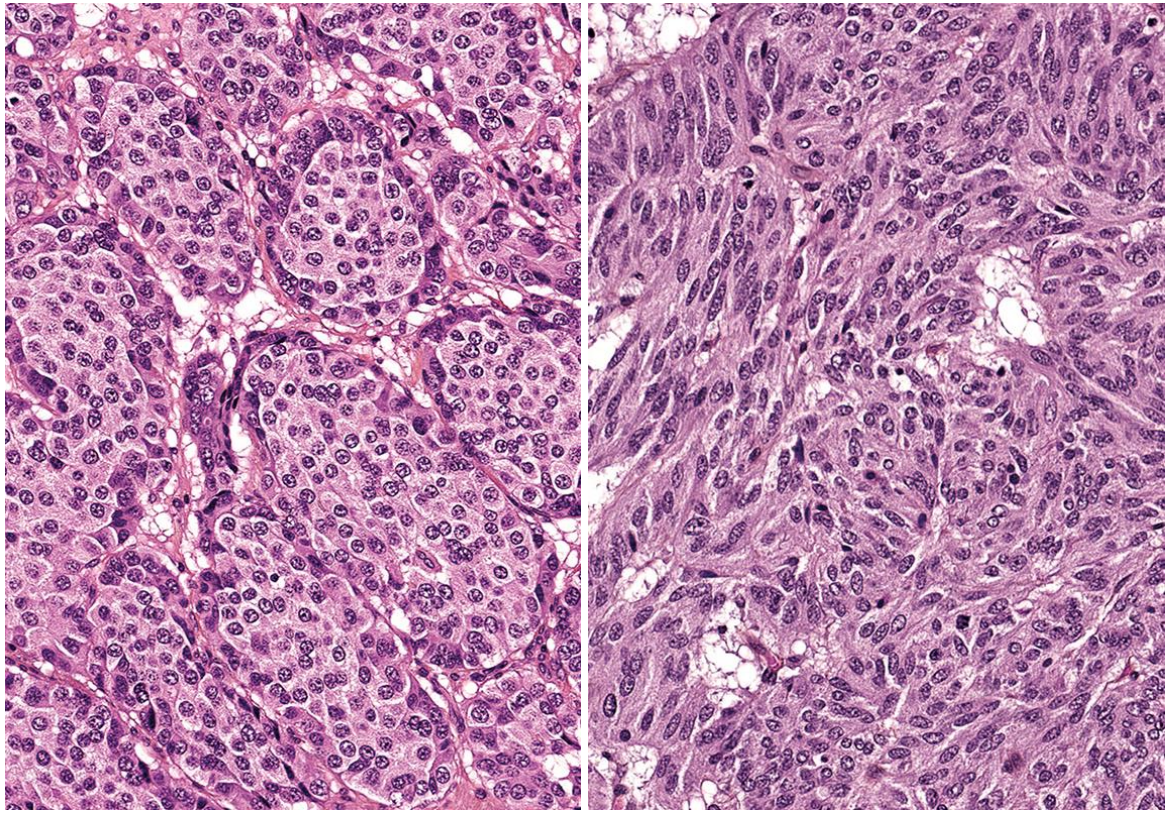
	Neuroendocrine Tumor	Neuroendocrine Carcinoma
Age	Younger	Older
Gender predilection	Male = female	Male > female
Association with smoking	No	Yes
Precursor lesion	Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	No
Tumor stage at diagnosis	Earlier	Late
Molecular alterations	Less frequent	More frequent, *RB, TP53*
Treatment options	Surgery, systemic therapies less likely	Systemic therapies, surgery less likely
Prognosis	Good	Poor

Carcinoid Tumor

- Rare tumor, accounting for ≤ 2% of all lung malignancies
- Neuroendocrine malignancy with a well-differentiated organoid architecture
- Associated with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)
- Genetic causes include *MEN1* gene mutations in the setting of hereditary multiple endocrine neoplasia type 1

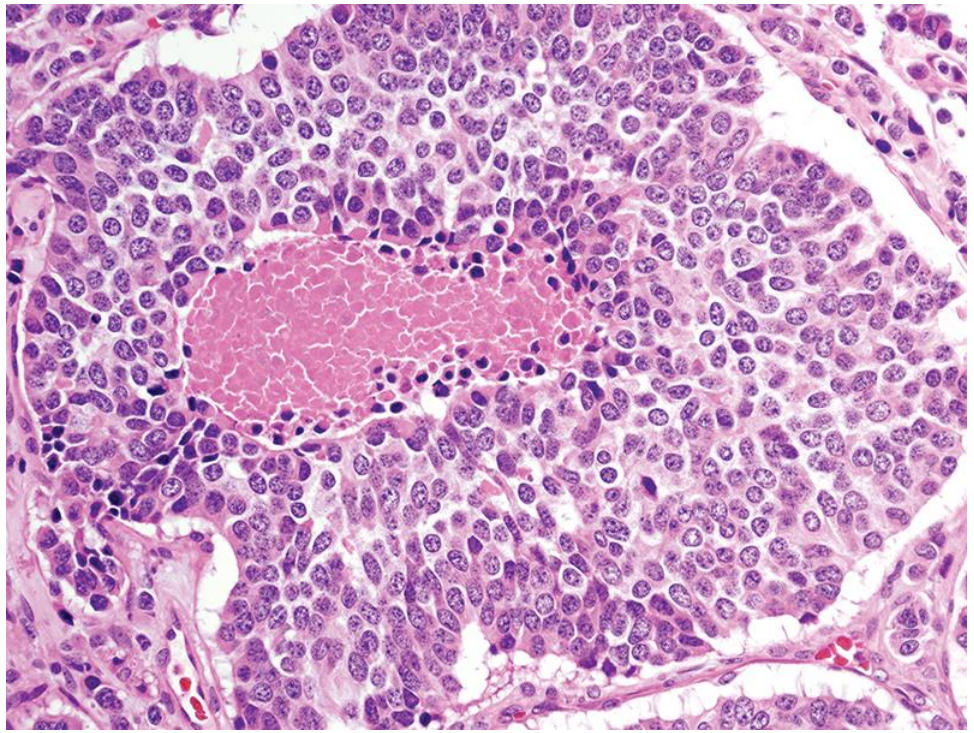
Carcinoid Tumor

- Architecture: organoid nesting, trabeculae, rosettes, and palisading arrangements
- Cell morphology: moderate to abundant cytoplasm and round, oval, or spindle nuclei with finely granular chromatin
- Expression of neuroendocrine markers



Typical Carcinoid vs Atypical Carcinoid

- Typical carcinoid (low grade tumor):
  - No necrosis
  - <2 mitoses/2 mm^2 or/and Ki-67 index: <5%
- Atypical carcinoid (intermediate grade tumor):
  - Punctate necrosis
  - 2-10 mitoses/2 mm^2 or/and Ki-67 index: 5-30%



Grading Carcinoid Tumors

Carcinoid tumors of the lung

Terminology	Grade	Mitotic Rate	Ki-67 Index
Typical carcinoid	Low	<2 mitoses/2 mm^2	<5%
Atypical carcinoid	Intermediate	2-10 mitoses/2 mm^2	5-30%

Well-differentiated neuroendocrine tumors of the pancreas

Terminology	Grade	Mitotic Rate	Ki-67 Index
NET, G1	Low	<2 mitoses/2 mm^2	<3%
NET, G2	Intermediate	2-20 mitoses/2 mm^2	3-20%
NET, G3	High	>20 mitoses/2 mm^2	>20%

Grading Carcinoid Tumors

Two- vs Three-tier Grading

- Lung carcinoid tumors
  - Typical carcinoid - low grade
  - Atypical carcinoid - intermediate grade
- NETs at other sites
  - NET, G1 - low grade
  - NET, G2 - intermediate grade
  - NET, G3 - high grade

Grading Carcinoid Tumors

Mitotic Figure Counting

- Lung carcinoid tumors
  - Typical carcinoid:
    <2 mitoses/2 mm^2
  - Atypical carcinoid:
    2-10 mitoses/2 mm^2

- NETs at other sites
  - NET, G1: <2 mitoses/2 mm^2
  - NET, G2: 2-20 mitoses/2 mm^2
  - NET, G3: >20 mitoses/2 mm^2

Grading Carcinoid Tumors

Ki-67 Proliferation Index

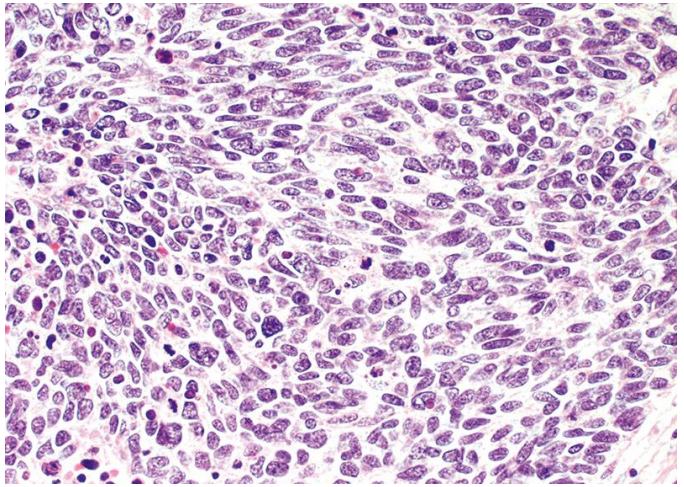
- Lung carcinoid tumors
  - Typical carcinoid: <5%
  - Atypical carcinoid: 5-30%
- NETs at other sites
  - NET, G1: <3%
  - NET, G2: 3-20%
  - NET, G3: >20%

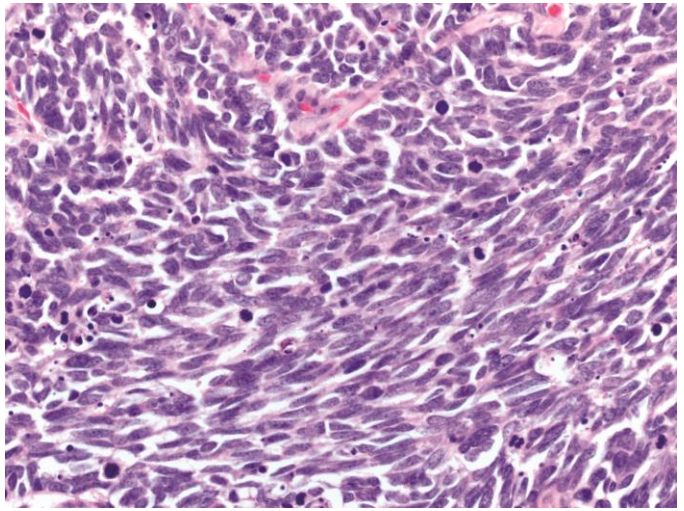
Small Cell Lung Carcinoma

- Approximately 15% of all lung carcinomas
- Strong association with smoking
- Small cells with scant cytoplasm, finely granular chromatin, and absent or inconspicuous nucleoli
- High mitotic count and frequent necrosis
- Sometimes component of non-small cell carcinoma

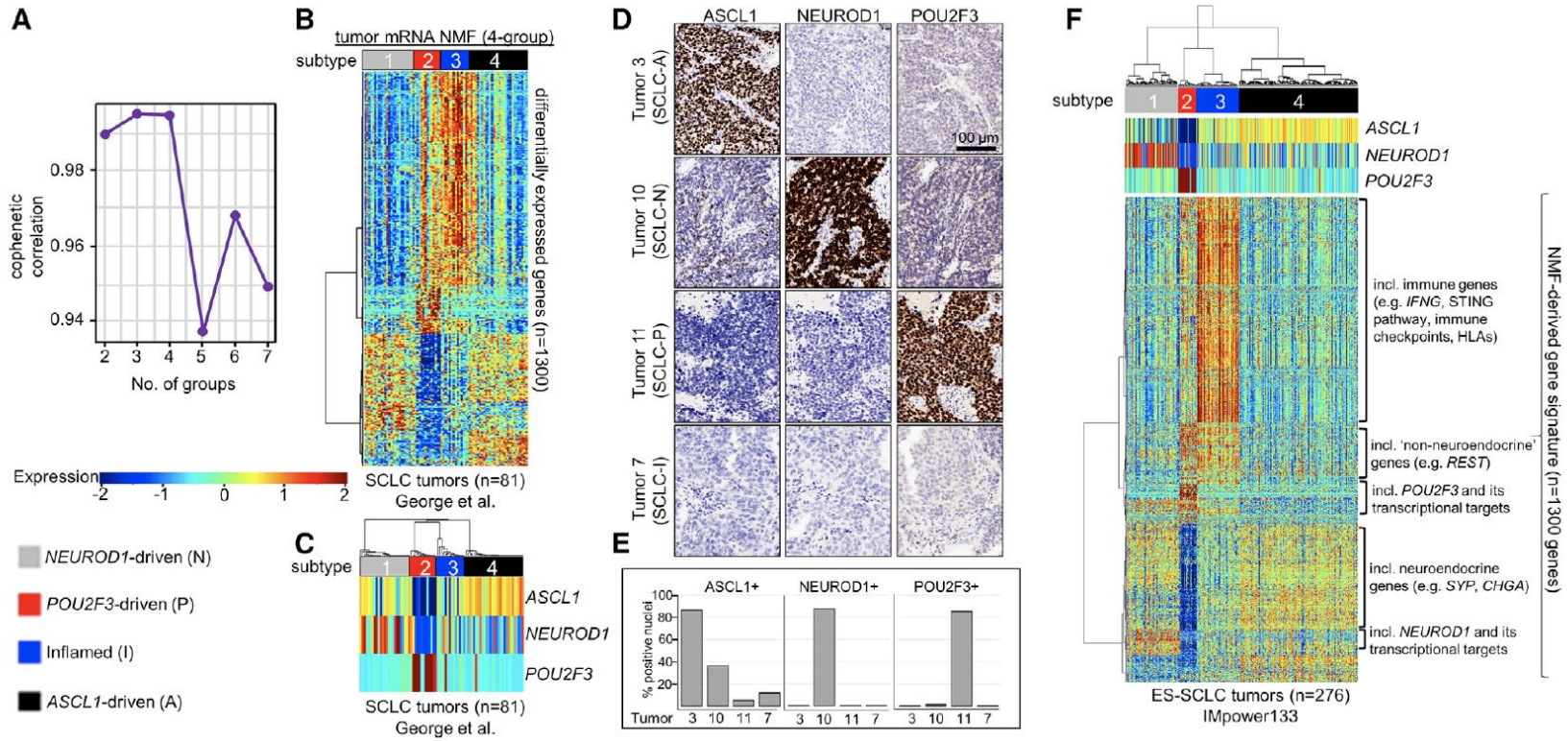
Small Cell Lung Carcinoma

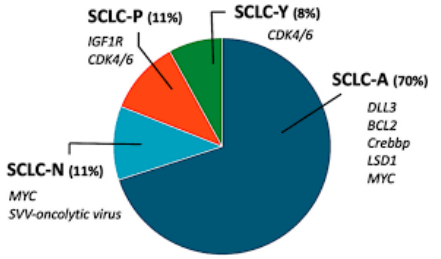
- Densely packed, sheet-like growth
- Small cells (usually <3 lymphocytes)
- Scant cytoplasm, high N:C ratio
- Oval to spindle nuclei with finely granular chromatin and inconspicuous nucleoli
- Mitosis: >10 mitoses/2 mm^2, median 80
- Geographic necrosis
- Likely expression of neuroendocrine markers





SCLC Subclassification





ASCL1 dominant:
- Type A

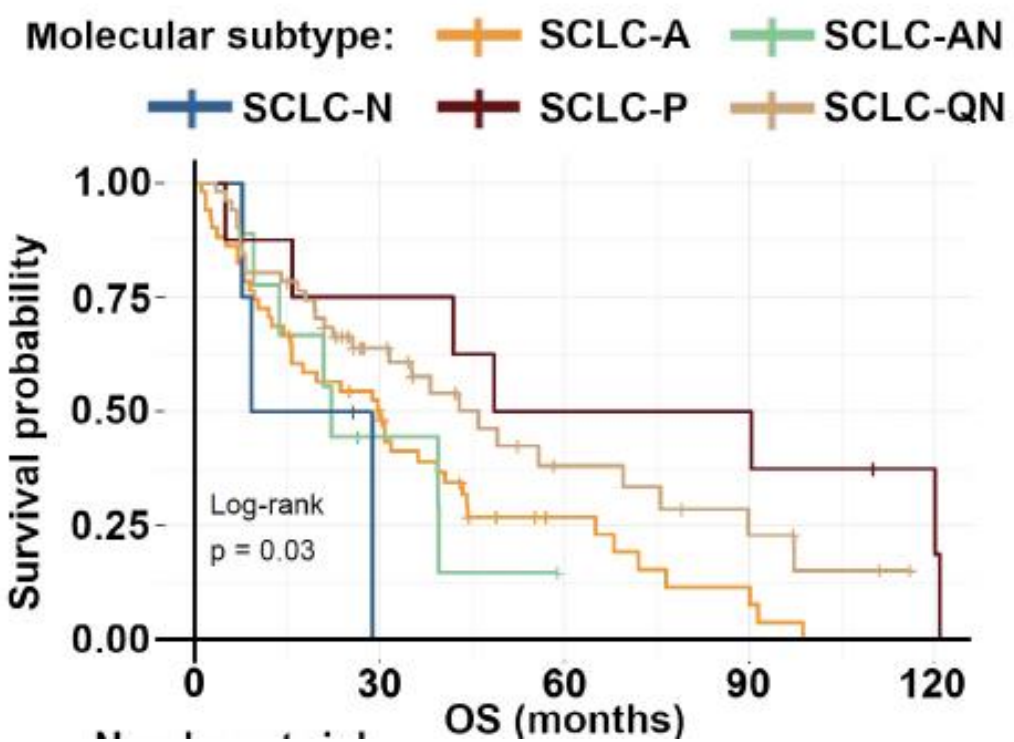
NEUROD1 dominant:
- Type N

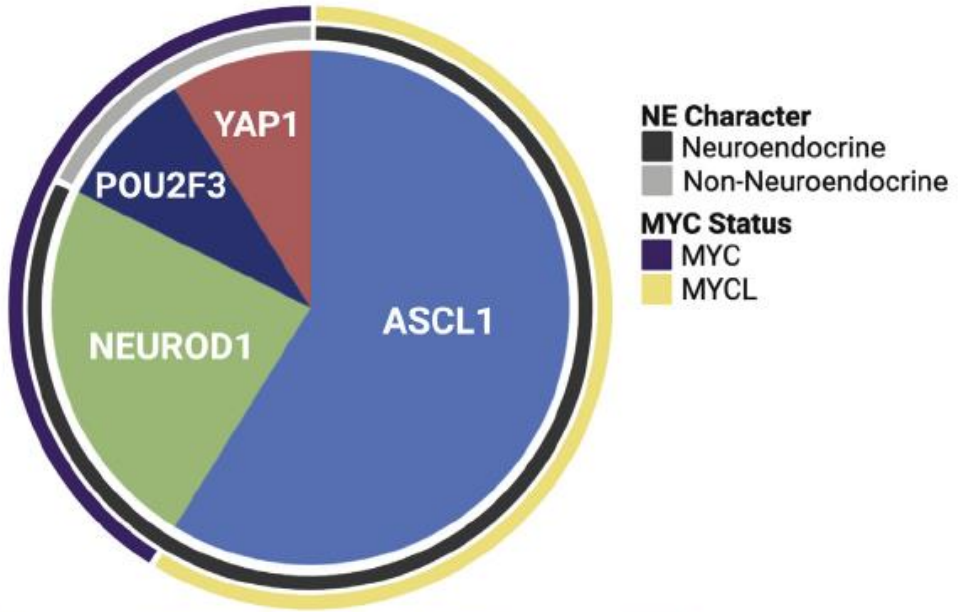
POU2F3 expression:
- Type P

NULL:
- Type Y/I

- *Gay CM, et al. Cancer Cell 2021; 39:346–360.*
- *Baine MK, et al. J Thorac Oncol. 2020; 15(12):1823-1835.*

SCLC Subclassification





	ASCL1	NEUROD1	POU2F3	YAP1
Targeted Therapies	BCL2 CREBBP DLL3 LSD1	Arginine Deprivation AURKA/B CHK1 IMPDH LSD1	Arginine Deprivation AURKA/B CHK1 IGF-R1 IMPDH	Arginine Deprivation AURKA/B CHK1 IMPDH IO

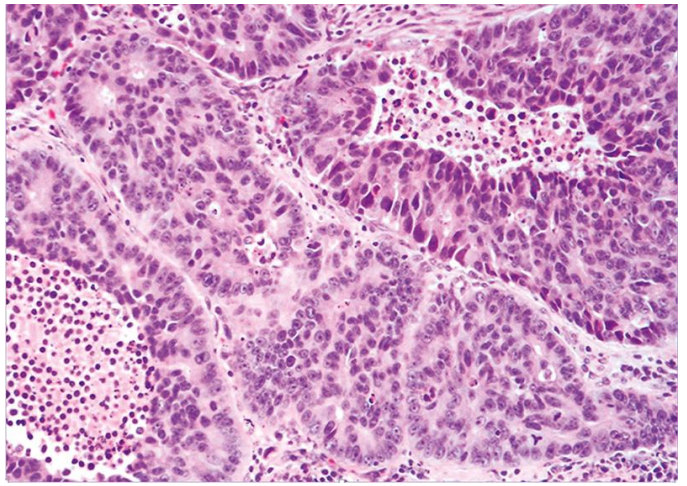
- *Megyesfalvi Z, et al. J Pathol. 2022; 257(5):674-686.*
- *Poirier JT, et al. J Thorac Oncol. 2020; 15(4):520-540.*

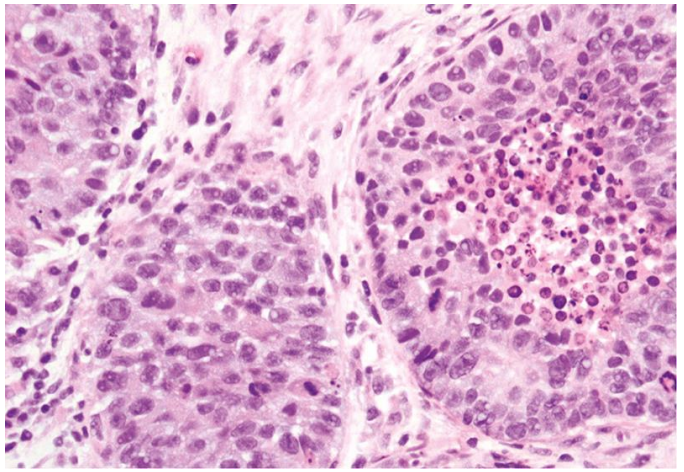
Large Cell Neuroendocrine Carcinoma

- Approximately 3% of all lung carcinomas
- Highly related to smoking
- Commonly seen in the upper lobes with peripheral location
- Asymptomatic or having post-obstructive symptoms in centrally located tumors
- NSCLC with histological features of neuroendocrine morphology and expression of neuroendocrine markers
- Tendency to recur and shorter survival than other NSCLCs

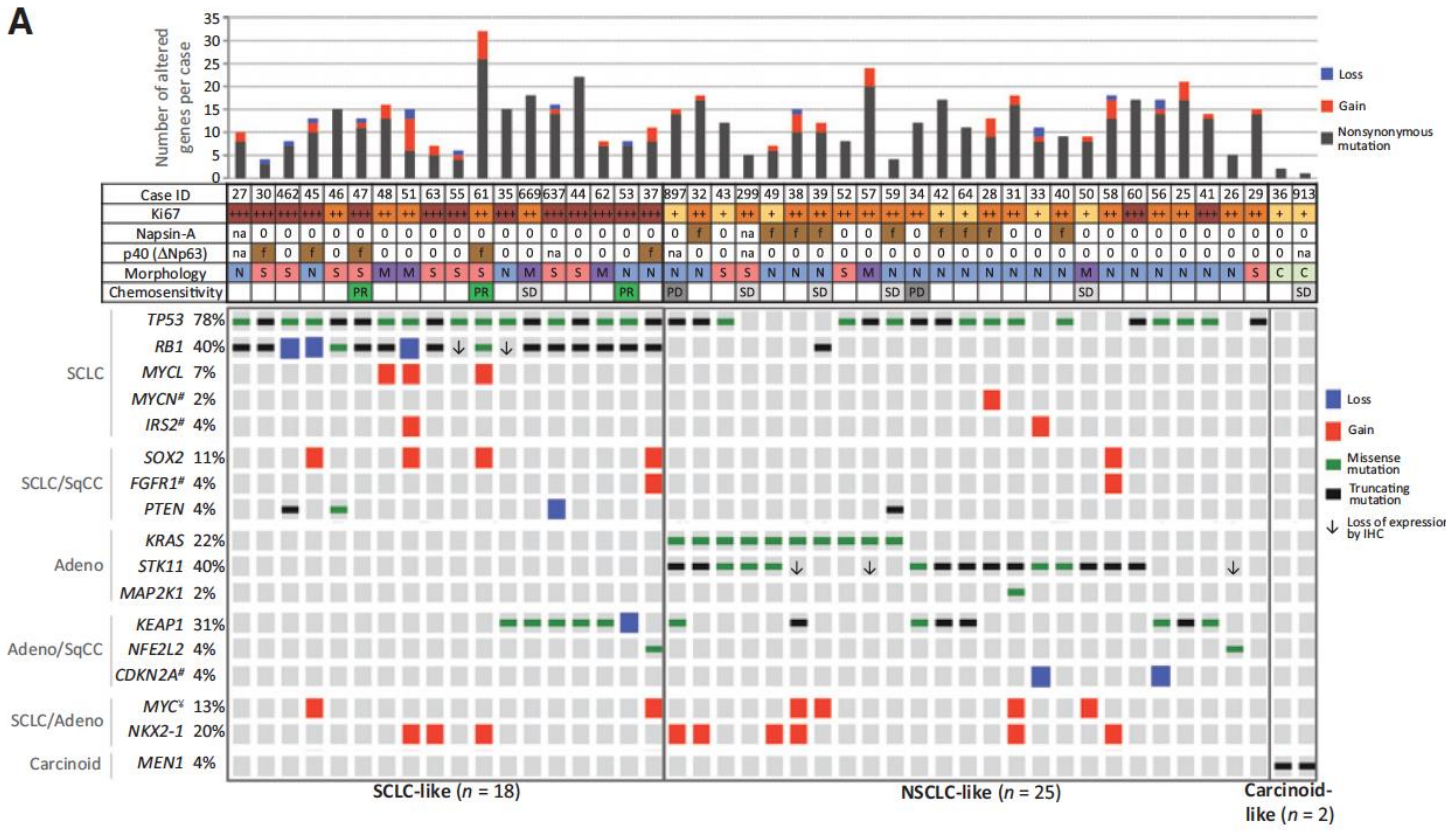
Large Cell Neuroendocrine Carcinoma

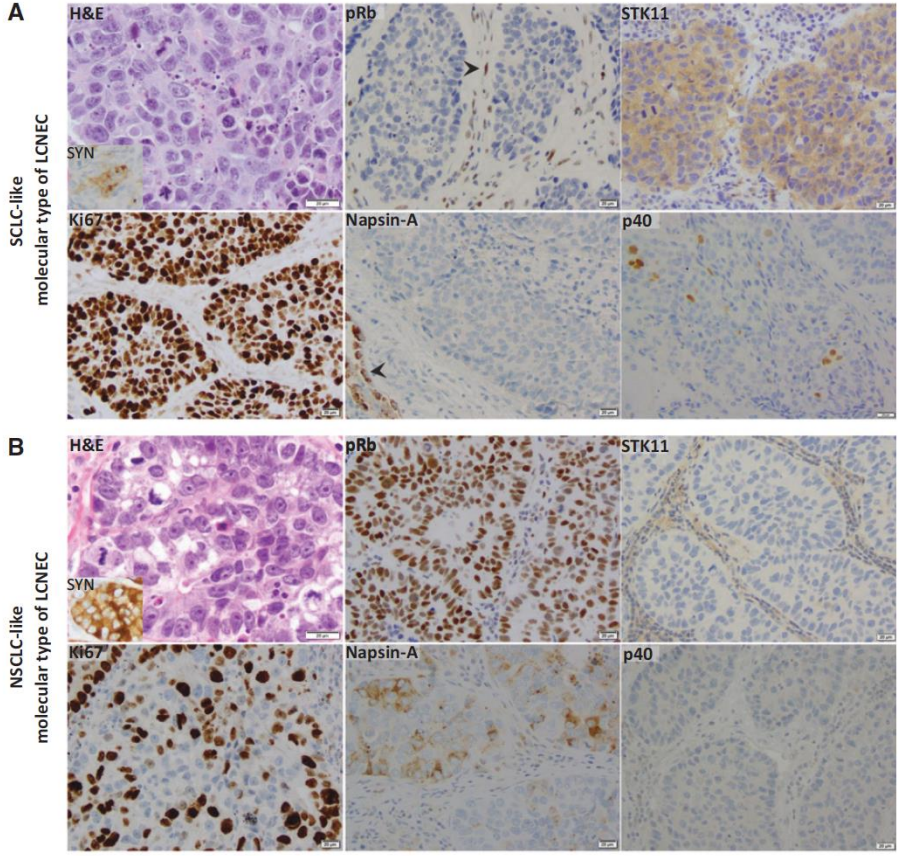
- Architecture: organoid nesting, trabeculae, peripheral palisading, rosettes
- Larger cell size (> 3 lymphocytes)
- Moderate to abundant cytoplasm
- Round to oval nuclei with stippled or vesicular chromatin and prominent nucleoli
- Mitosis: >10 mitoses/2 mm^2, median 70
- Extensive necrosis
- Expression of neuroendocrine markers





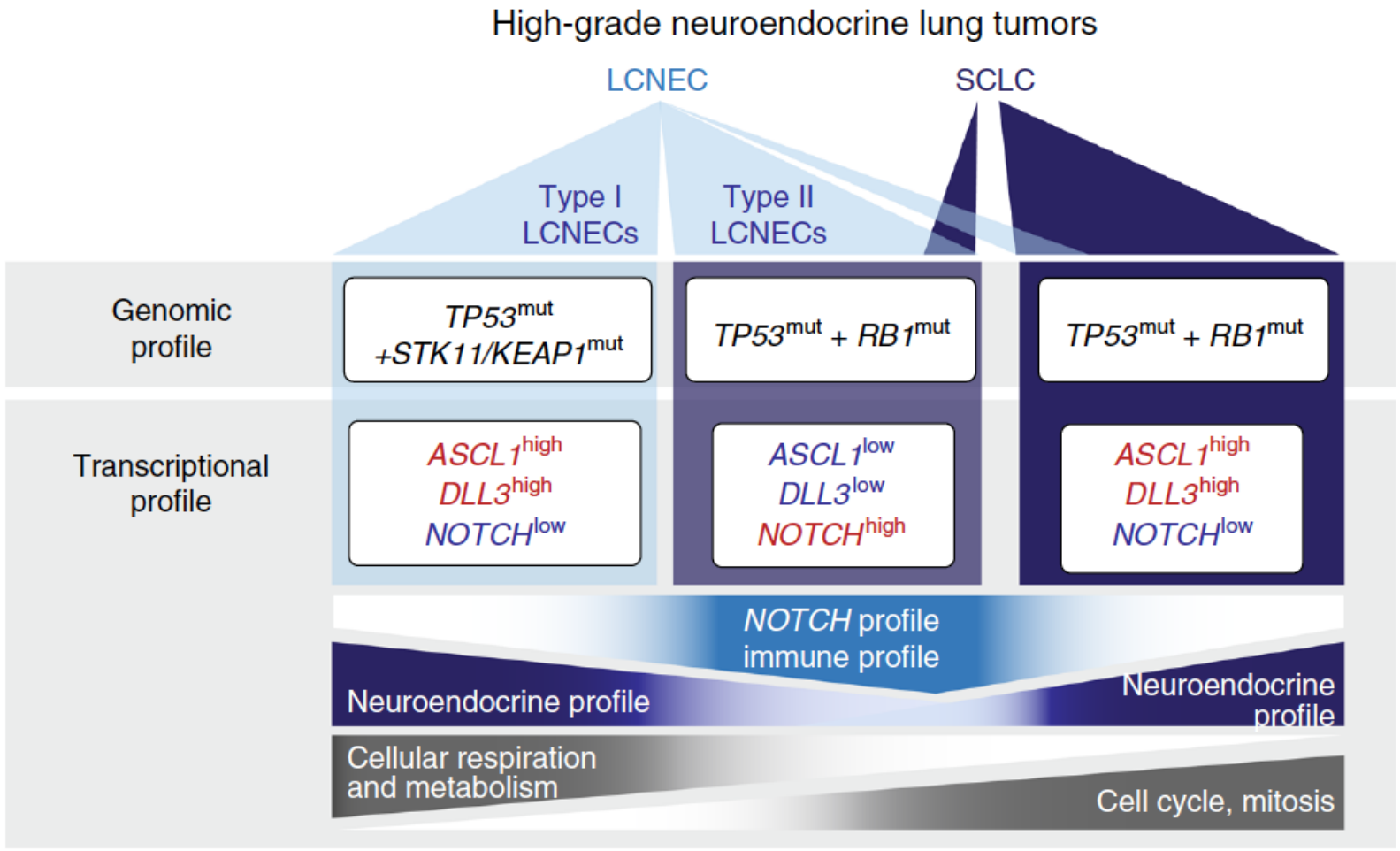
LCNEC Subclassification





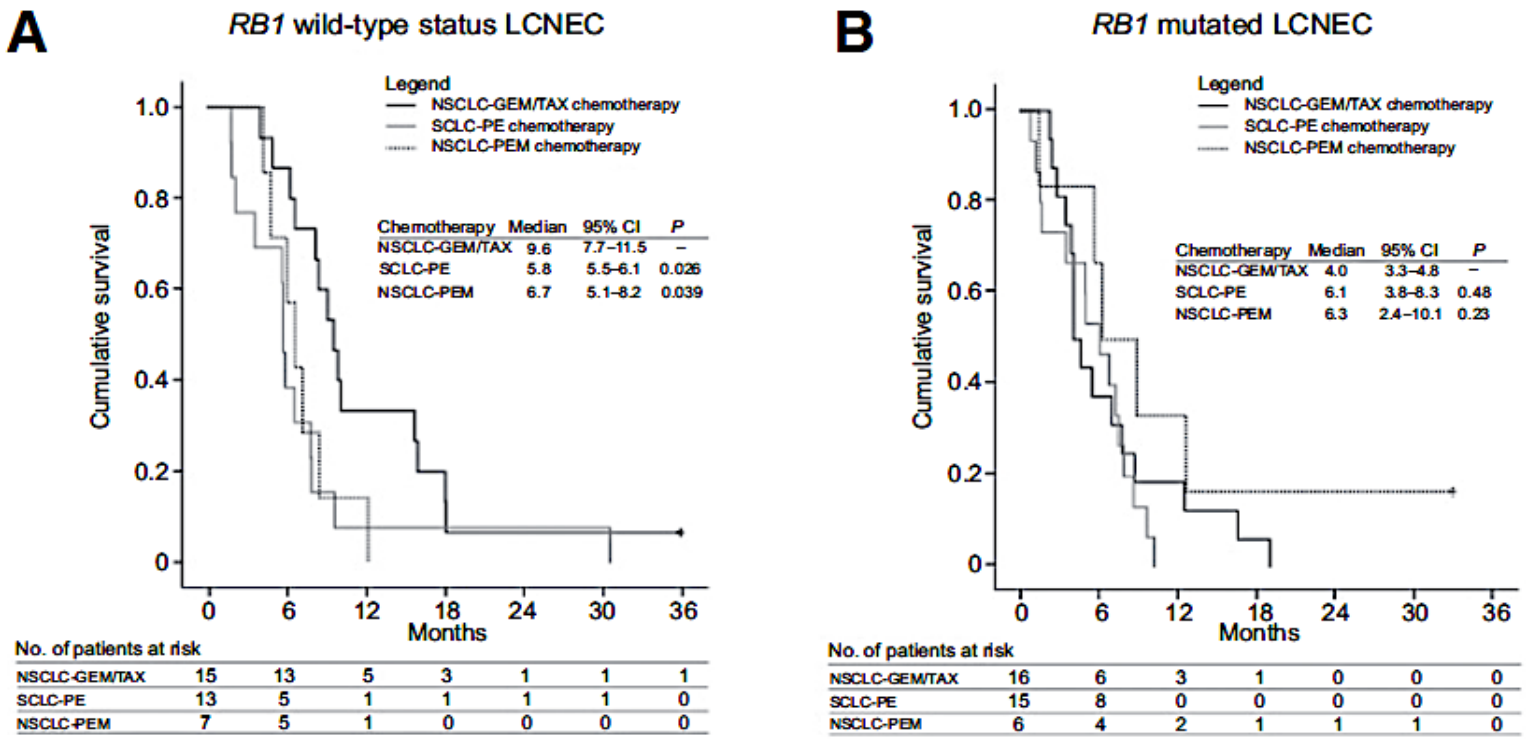
- *Rekhtman N, et al. Clin Cancer Res 2016; 22(14):3618–3629.*

LCNEC Subclassification



- *George J, et al. Nature Commun 2018; 9(1):1048.*

Molecular Subtypes Predict Responses to Chemotherapy Options

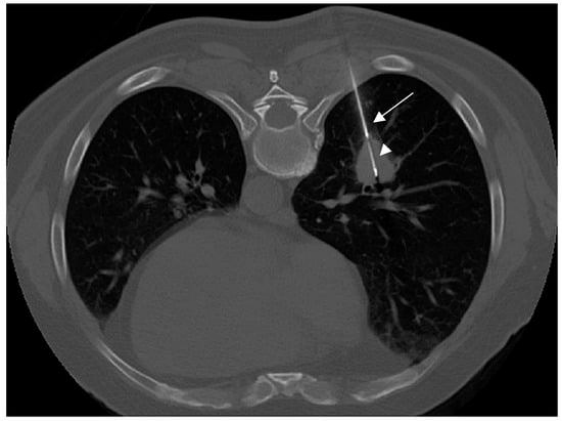


Patients with LCNEC tumors that carry a wild-type *RB1* gene or express the RB1 protein do better with NSCLC-GEM/TAX treatment than with SCLC-PE chemotherapy. However, no difference was observed for *RB1* mutated or with lost protein expression.

- *Derks JL, et al. Clin Cancer Res 2018; 24(1):33–42.*

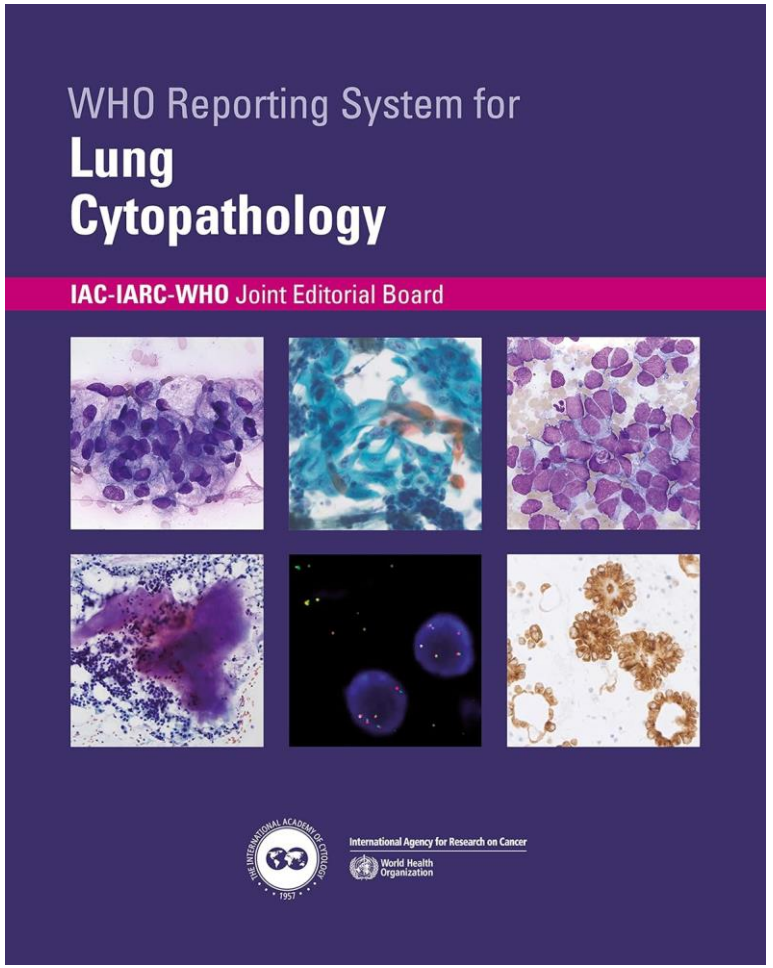
Cytology Samples/Sampling Methods

- Bronchial brushing
- Bronchial washing
- Bronchioalveolar lavage
- Fine-needle aspiration (FNA) biopsy
  - Transbronchial: bronchoscopy-guided
  - Transthoracic: CT-guided
- Biopsy touch preparation
- Serous fluid sample



WHO Reporting System

I. Insufficient/inadequate/non-diagnostic
II. Benign/negative for malignancy
    - Nonneoplastic
    - Neoplastic
III. Atypical
IV. Suspicious for malignancy
V. Malignant

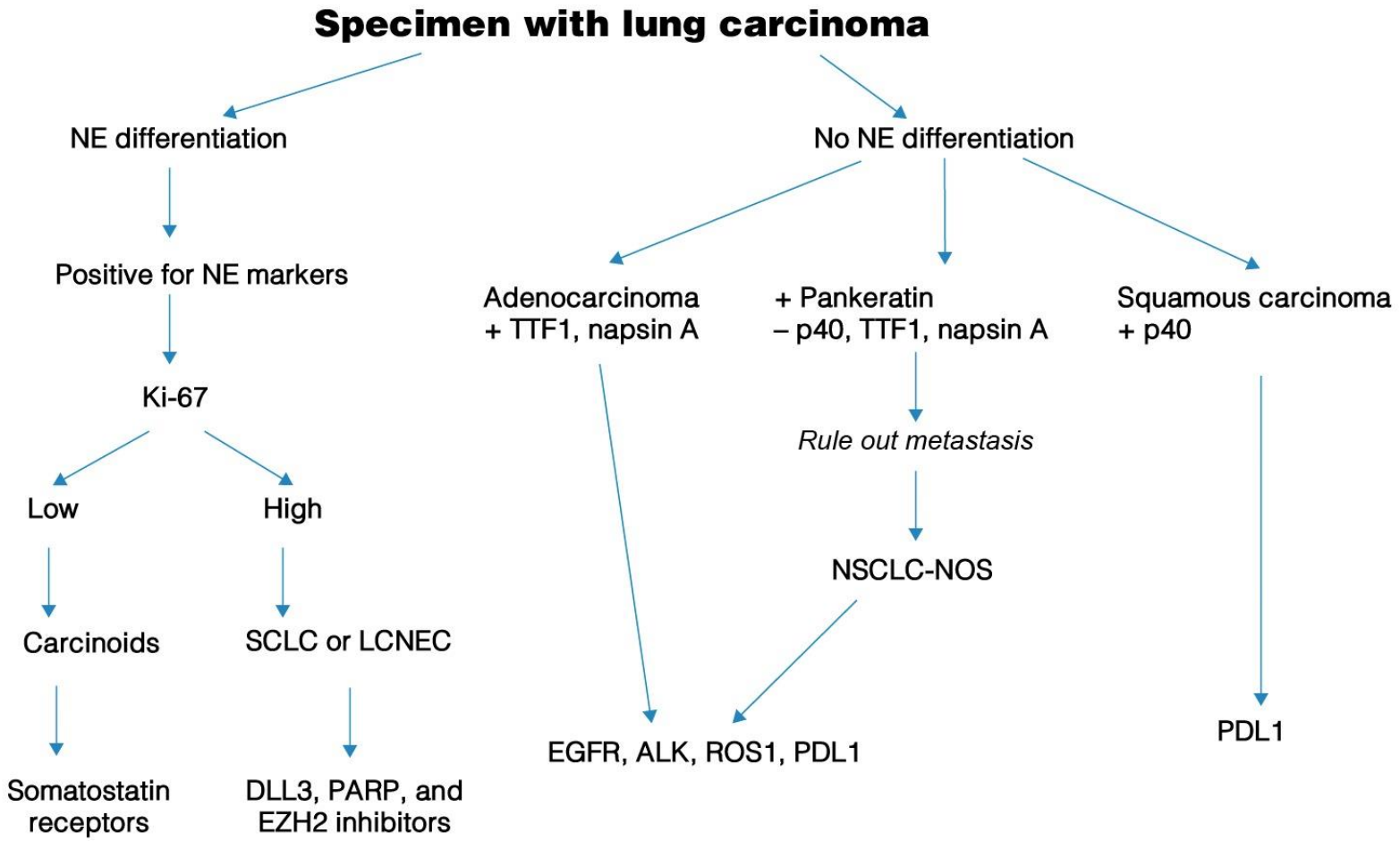


WHO Reporting System

Diagnostic Category	Risk of Malignancy	Clinical Management Options
Insufficient/inadequate/ non-diagnostic	43-53%	*Ideally, discuss at a multidisciplinary team meeting.* Repeat FNAB +/- core needle biopsy
Benign/negative for malignancy Nonneoplastic or neoplastic	19-64%	*Clinically confirmed to be benign?* Routine follow-up in 3-6 months
		No clinical confirmation of a benign diagnosis? Repeat FNAB +/- core needle biopsy
Atypical	46-55%	*Clinical correlation supports a benign diagnosis?* Routine follow-up in 3-6 months
		If there is no correlation with clinical findings? Repeat FNAB with ROSE +/- core needle biopsy
Suspicious for malignancy	75-88%	*Clinical correlation supports a malignant diagnosis?* Consider definitive treatment
		No clinical correlation that lesion is malignant? Repeat FNAB with ROSE +/- core needle biopsy
Malignancy	87-100%	*Clinical correlation supports a malignant diagnosis?* Provide definitive treatment
		No clinical correlation that lesion is malignant? Repeat FNAB with ROSE +/- core needle biopsy

- *Schmitt FC, et al. Acta Cytologica 2023; 67:80-91.*

Immunocytochemistry



Neuroendocrine markers:

- Chromogranin
- Synaptophysin
- CD56
- INSM1
- POU2F3

Non-neuroendocrine markers:

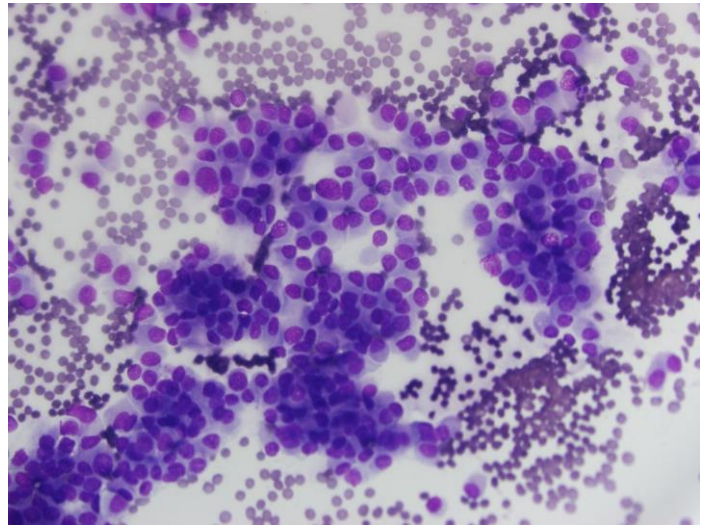
- TTF1
- Napsin A
- P40
- Cytokeratin
- Ki-67

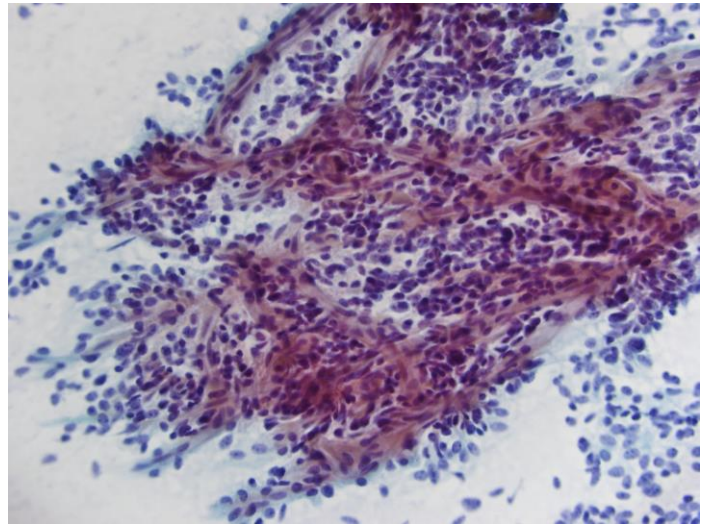
Diagnostic Challenges in Cytology Samples

	Resection	Cytology
Specimen volume	Ample	Limited
Artifacts	Absent	Often present
Architecture	Preserved	Absent
Background information	Preserved	Lost
Sampling issue	None	Relevant
Ancillary testing	Unlimited	Limited

Cytomorphology of Carcinoid Tumor

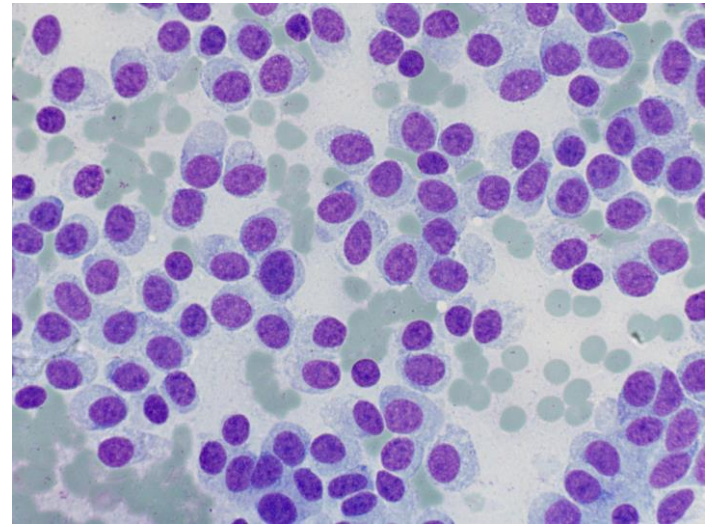
- Small dyscohesive sheets, trabeculae, cords, papillary or acinar-like architecture and pseudo-rosettes
- Intact single cells
- Larger tissue fragments consisting of plexiform, branching, thin fibrovascular strands
- Stripped branching and anastomosing fibrovascular strands

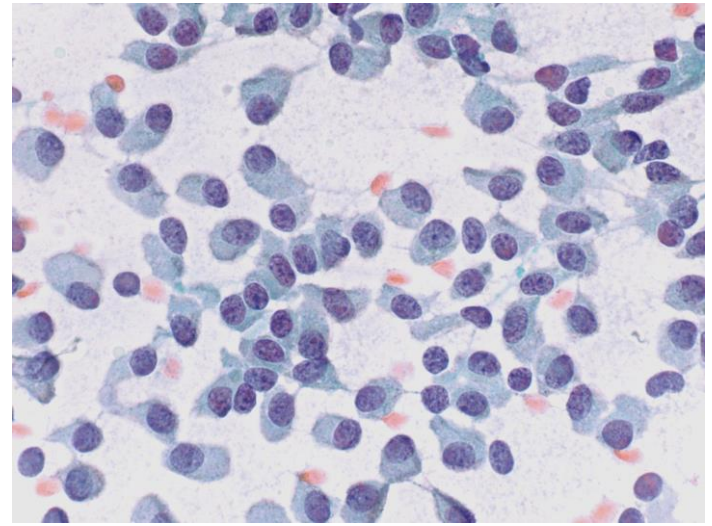




Cytomorphology of Carcinoid Tumor

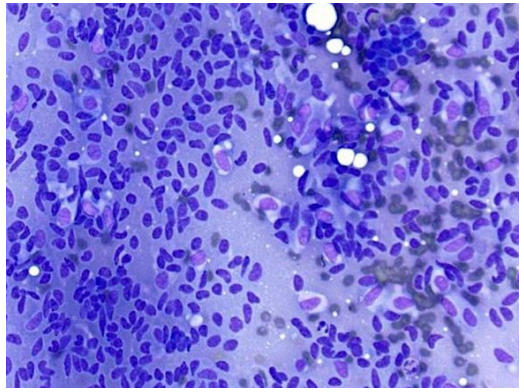
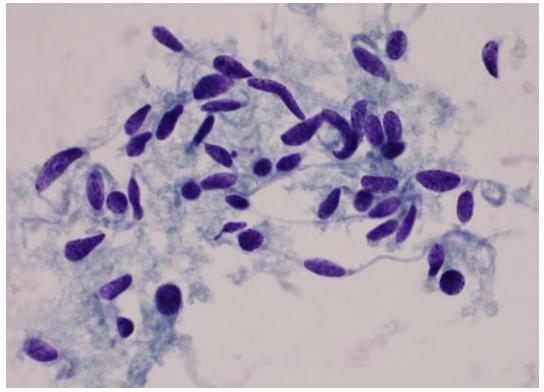
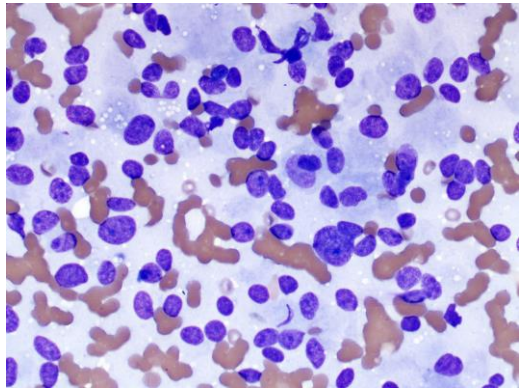
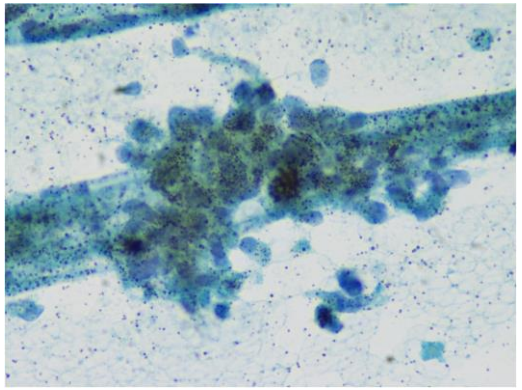
- Moderate amount of fine granular cytoplasm
- Uniform, round to oval nuclei
- Eccentrically located nuclei - plasmacytoid appearance
- Finely granular chromatin
- Small or inconspicuous nucleoli
- Binucleation, pseudo-inclusions
- Naked nuclei





Cytomorphology of Carcinoid Tumor

- Spindle cell variant
  - Elongated spindled nuclei
- Oncocytic variant
  - Abundant granular cytoplasm and prominent nucleoli
- Pigmented variant
  - Small melanin pigment granules in the cytoplasm

Grading Carcinoid Tumor

Resection

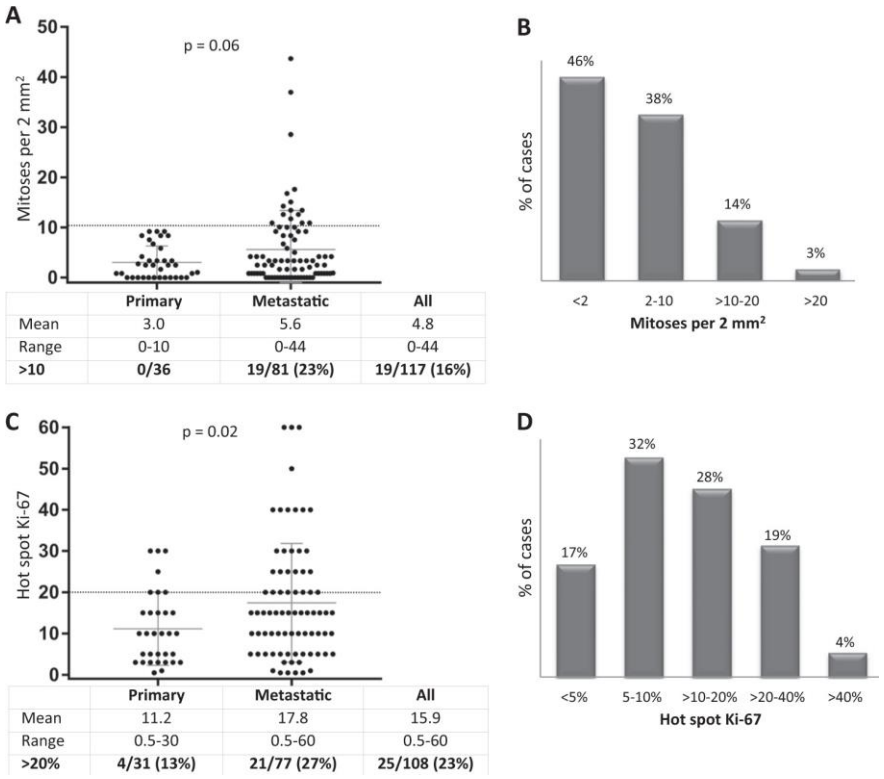
- Typical carcinoid tumor:
  - No necrosis
  - <2 mitoses/2 mm^2 or/and Ki-67 index: <5%
- Atypical carcinoid tumor:
  - Punctate necrosis
  - 2-10 mitoses/2 mm^2 or/and Ki-67 index: 5-30%

Cytology

- Mitotic counts may be difficult to assess accurately.
- Presence of mitotic figures, single cell necrosis or Ki-67 > 5% favors AC.
- Distinction between TC and AC is not possible in most cases.
- Reported as “Carcinoids NOS”.

Carcinoid Tumor in Metastatic Sites

- No grading, carcinoids NOS



	Primary	Metastatic	All
Mean	3.0	5.6	4.8
Range	0-10	0-44	0-44
>10	**0/36**	**19/81 (23%)**	**19/117 (16%)**

	Primary	Metastatic	All
Mean	11.2	17.8	15.9
Range	0.5-30	0.5-60	0.5-60
>20%	**4/31 (13%)**	**21/77 (27%)**	**25/108 (23%)**

- Lung vs. other primaries
  - History
  - Clinical/imaging findings
  - Immunohistochemistry

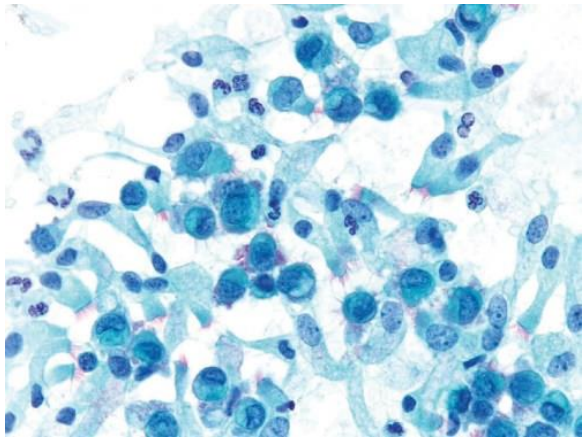
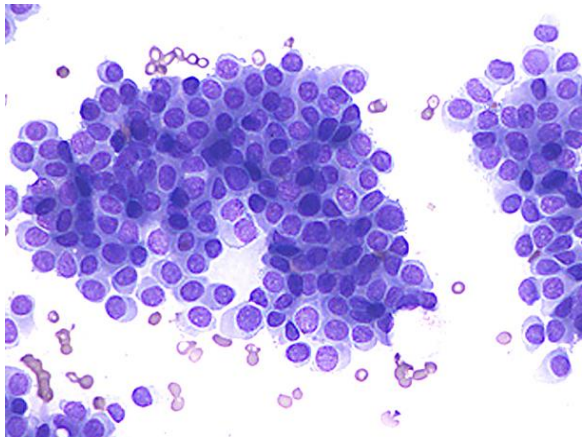
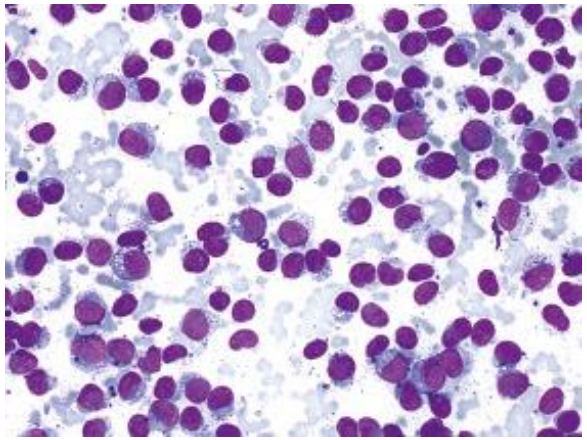
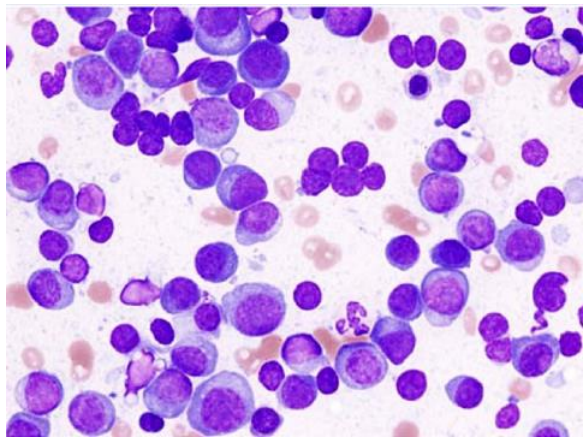
	TTF1 (n [%])		OTP (n [%])	
	Positive	**Negative**	**Positive**	**Negative**
Histologic subtype				
Typical carcinoid	51 (41.5)	72 (58.5)	105 (85.4)	18 (14.6)
Atypical carcinoid	8 (38.1)	13 (61.9)	10 (47.6)	11 (52.4)
Cell type				
Polygonal	23 (22.1)	81 (77.9)	75 (72.1)	29 (27.9)
Mixed	11 (100)	0 (0)	11 (100)	0 (0)
Spindle	25 (86.2)	4 (13.8)	29 (100)	0 (0)
Location				
Central	19 (23.2)	63 (76.8)	63 (76.8)	19 (23.2)
Peripheral	49 (79.0)	13 (21.0)	52 (83.9)	10 (16.1)

➢ *Rekhtman N, et al. Mod Pathol. 2019; 32(8):1106-1122.*

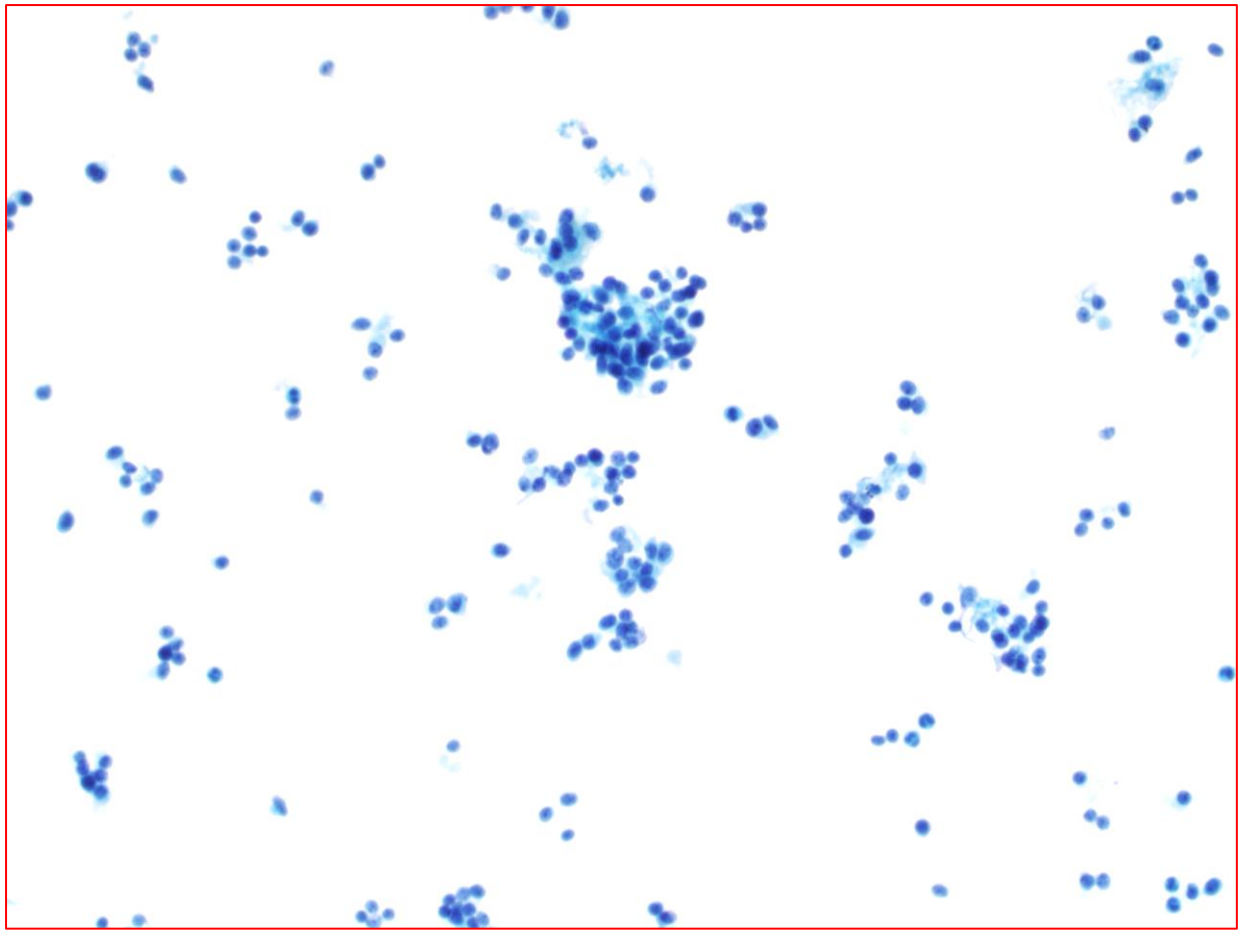
➢ *Nonaka D, et al. Am J Surg Pathol. 2016; 40(6):738-44.*

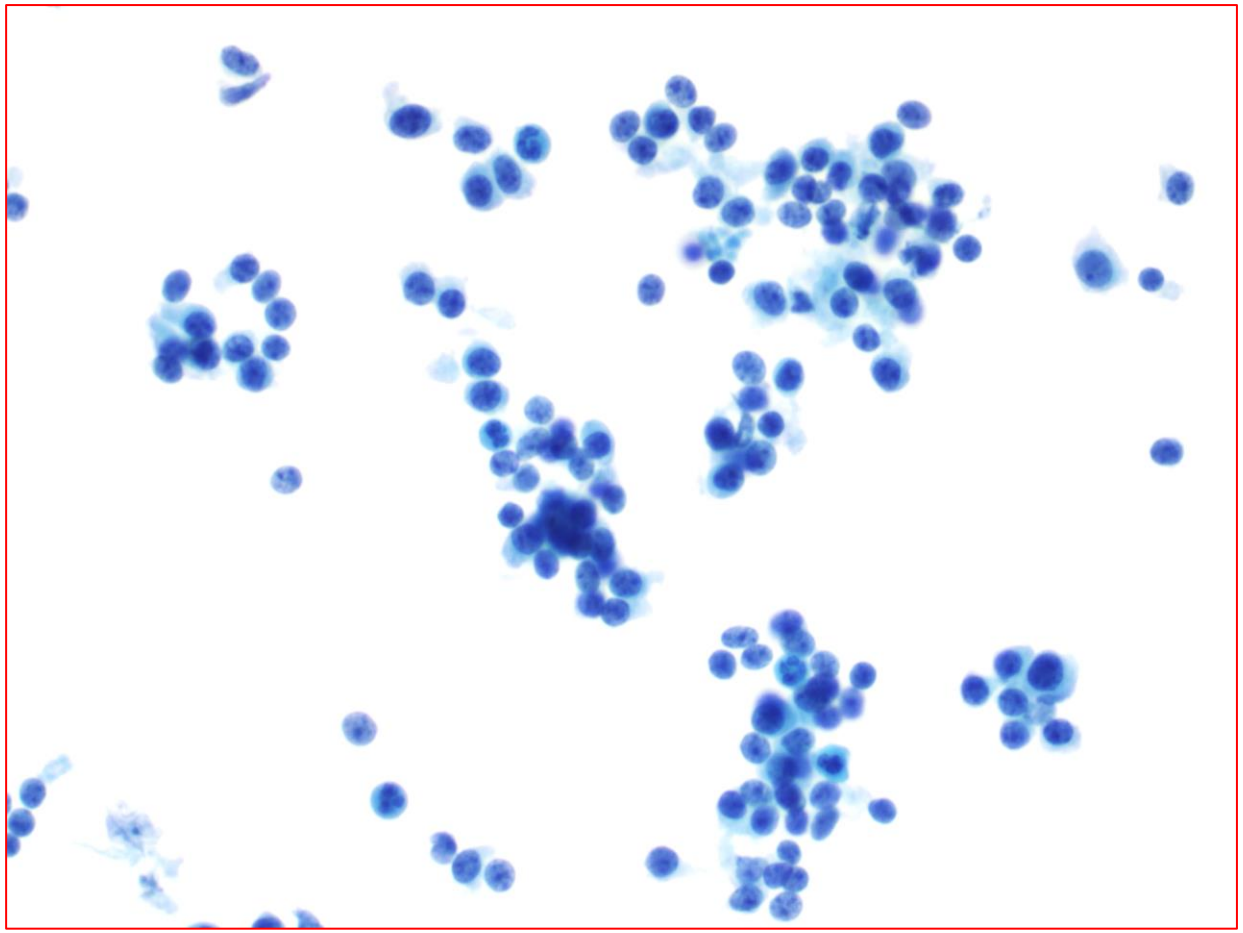
Carcinoid Tumor: Differential Diagnosis

- Bronchial cells, especially in bronchial brushes
- Breast lobular carcinoma
- Melanoma
- Plasmacytoma

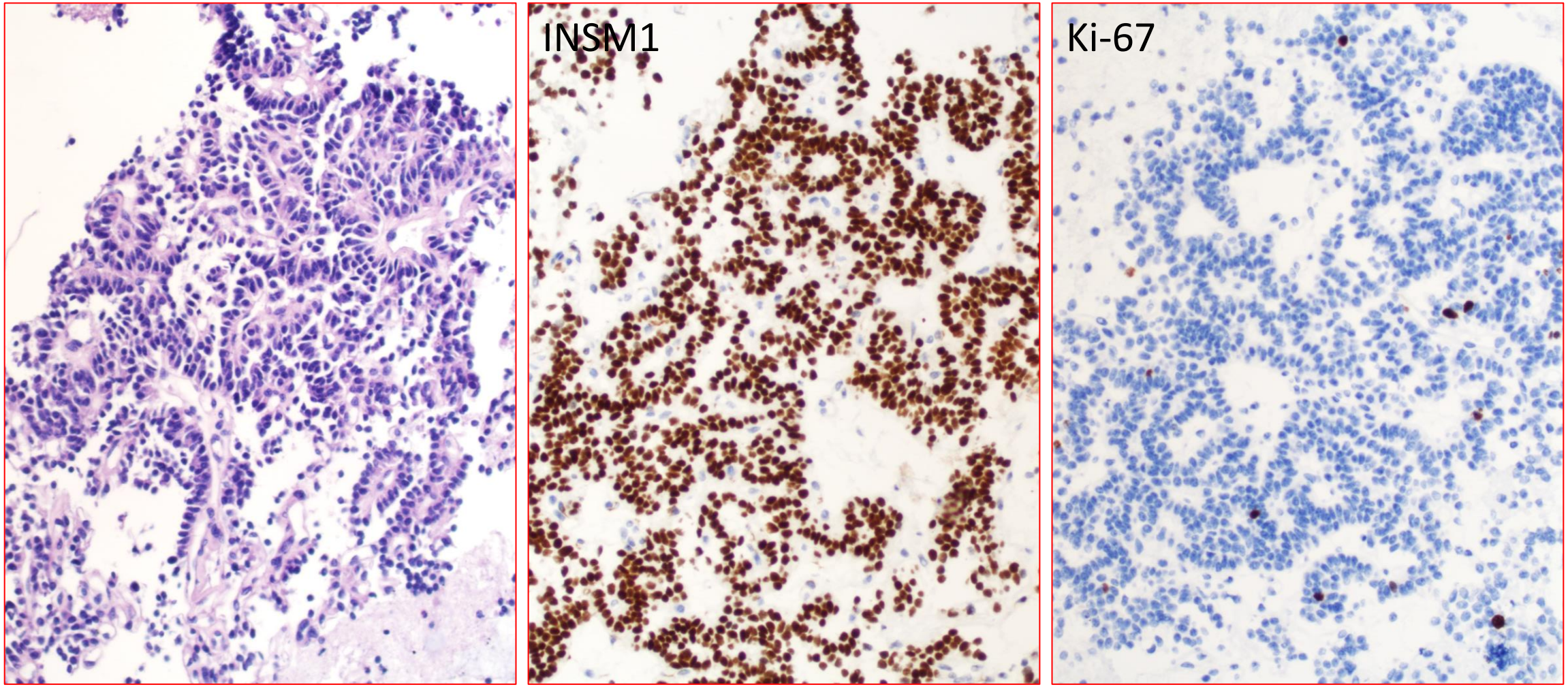





Carcinoid Tumor

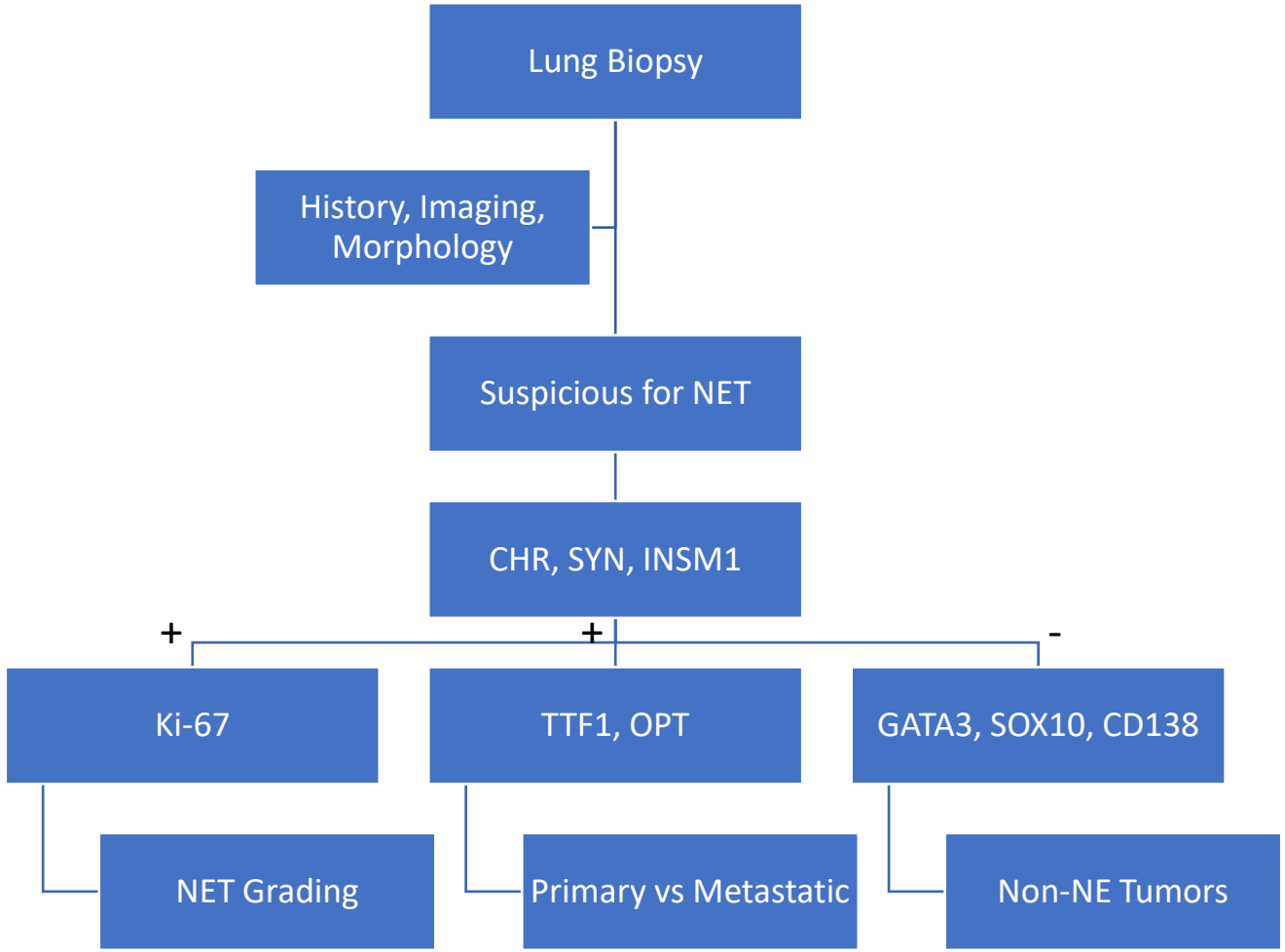




Carcinoid Tumor

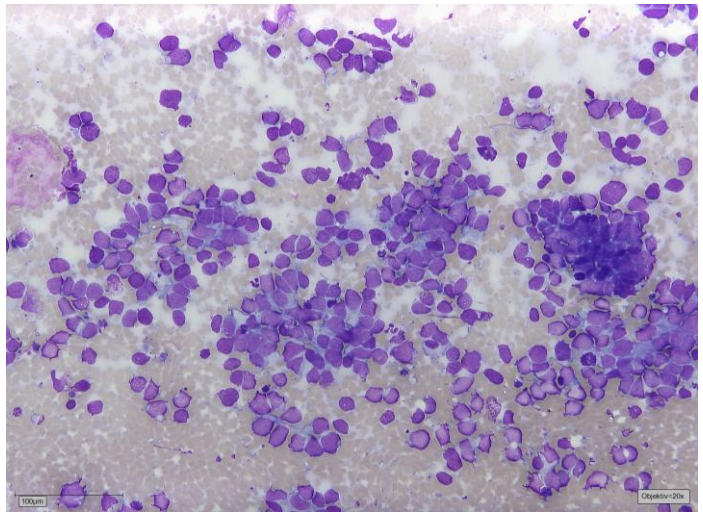


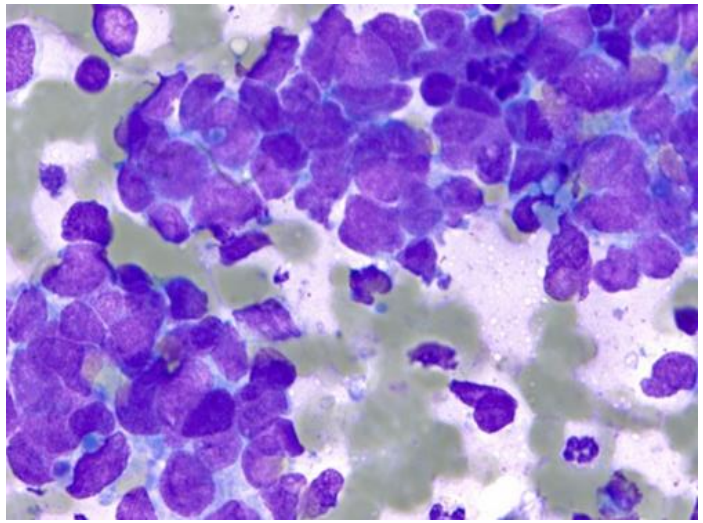
Diagnostic Workup for Carcinoid Tumor



Cytomorphology of Small Cell Carcinoma

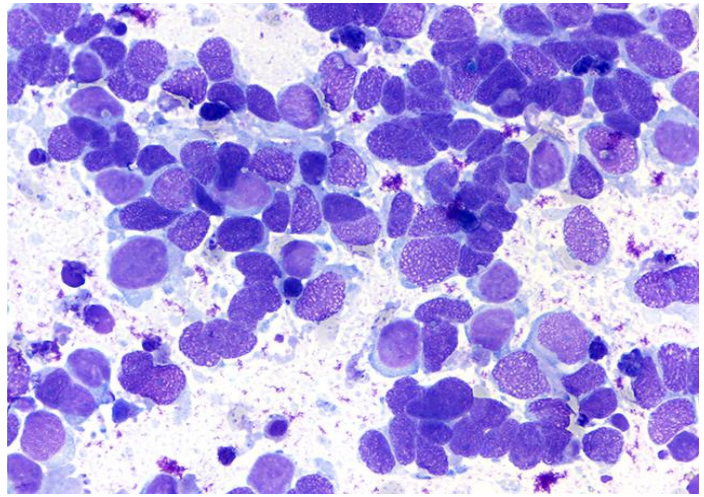
- Loosely cohesive cohesive cell groups
- Single intact cells
- Crowded irregular tissue fragments
- Chromatin/nuclear smearing crush artefact
- Paranuclear blue bodies, not entirely specific
- Necrotic background and apoptotic bodies

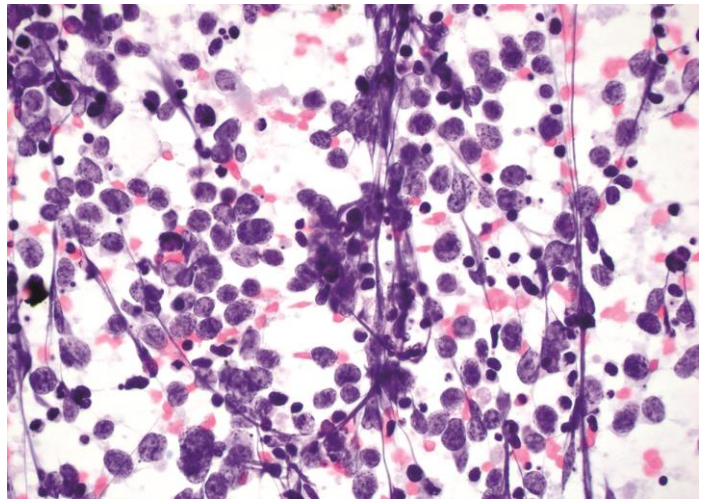




Cytomorphology of Small Cell Carcinoma

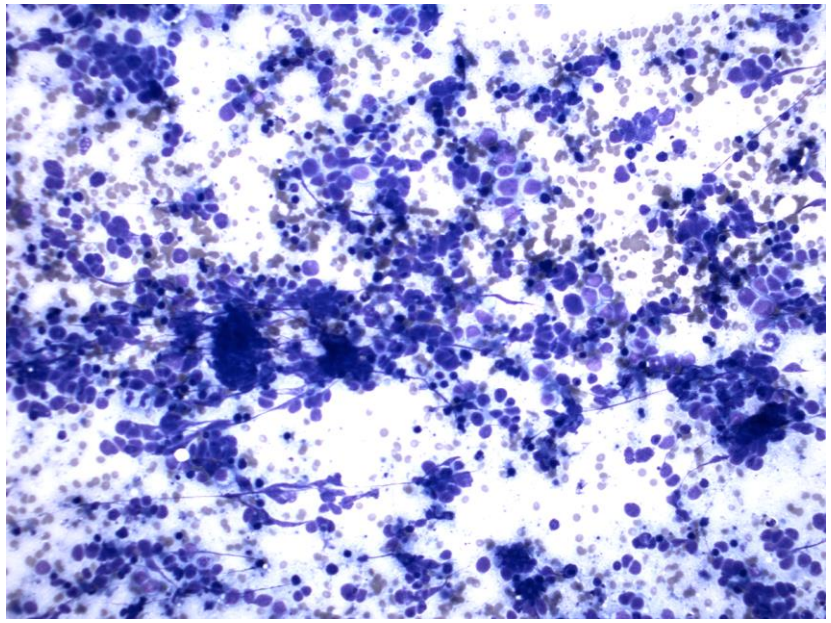
- Cell size < 3 times of a small lymphocyte
- Scant cytoplasm
- Angulated nuclei and nuclear moulding
- Finely granular chromatin
- Plentiful mitoses but difficult to appreciate or count
- More subtle cytomorphologic features In liquid-based preparations

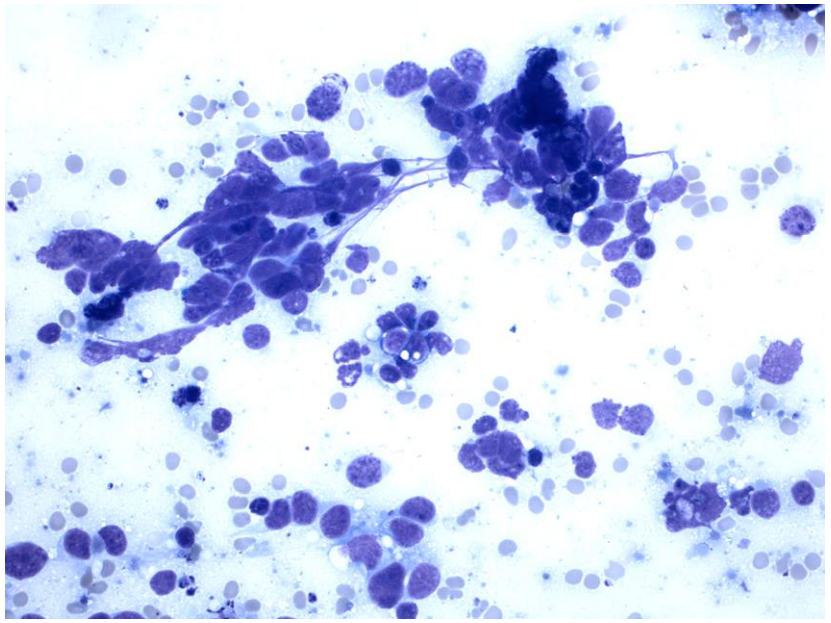




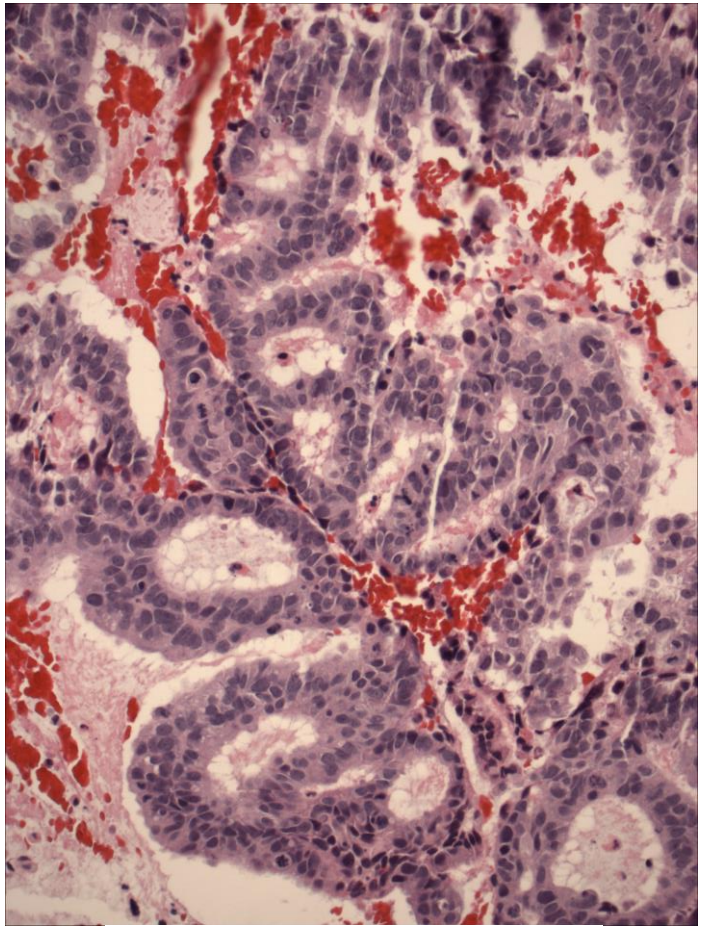
Diagnostic Challenges

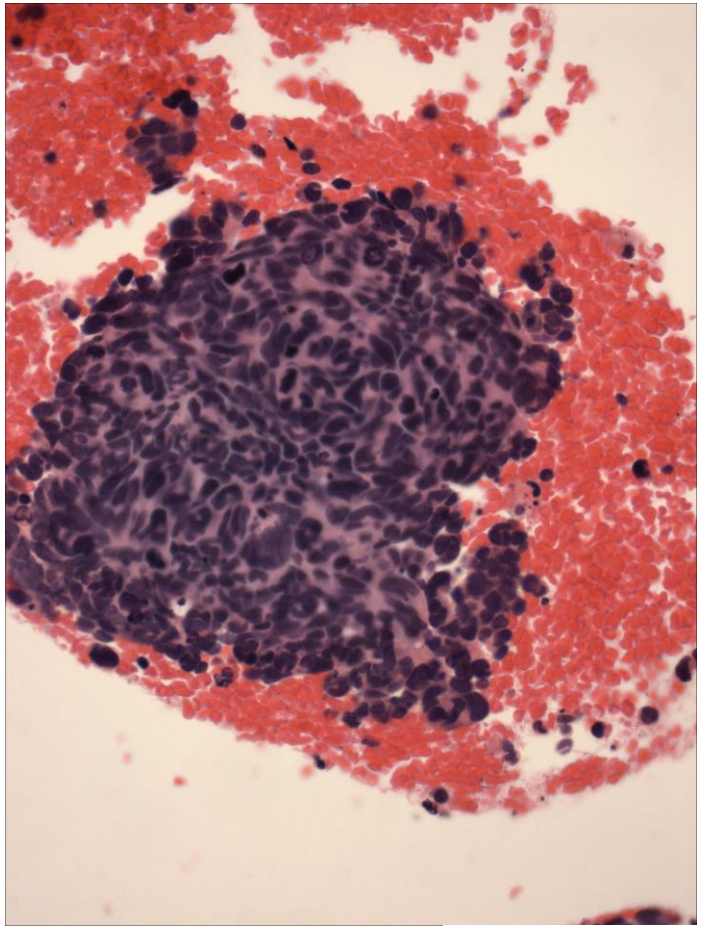
- Diagnosis may be hampered due to:
  - Limited material
  - Extensive necrosis
  - Preparation artifacts: crush/nuclear streaming

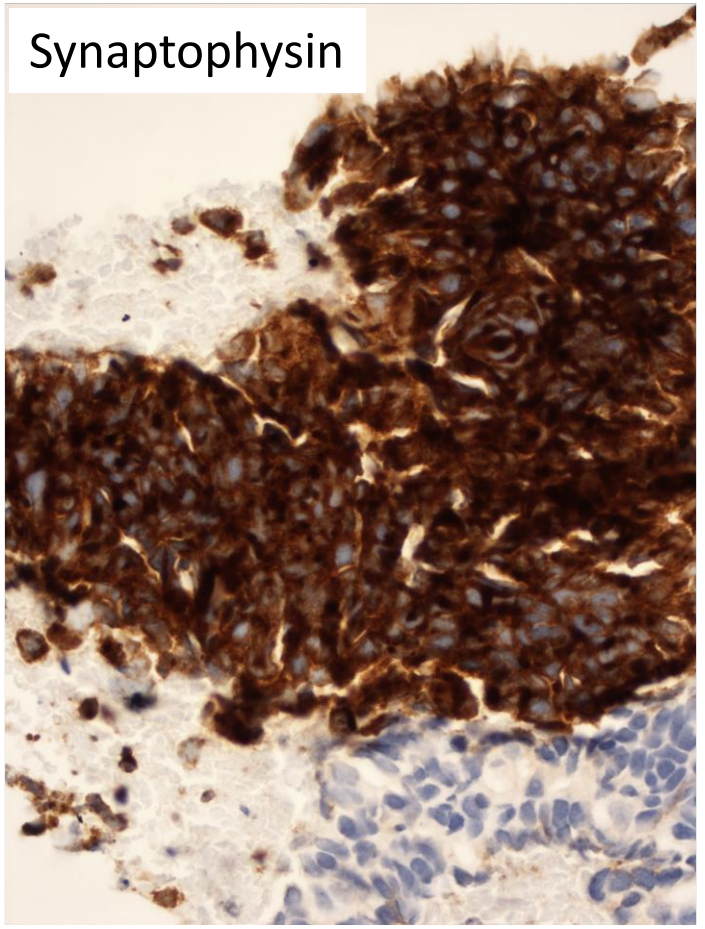




Small Cell Carcinoma Transformation





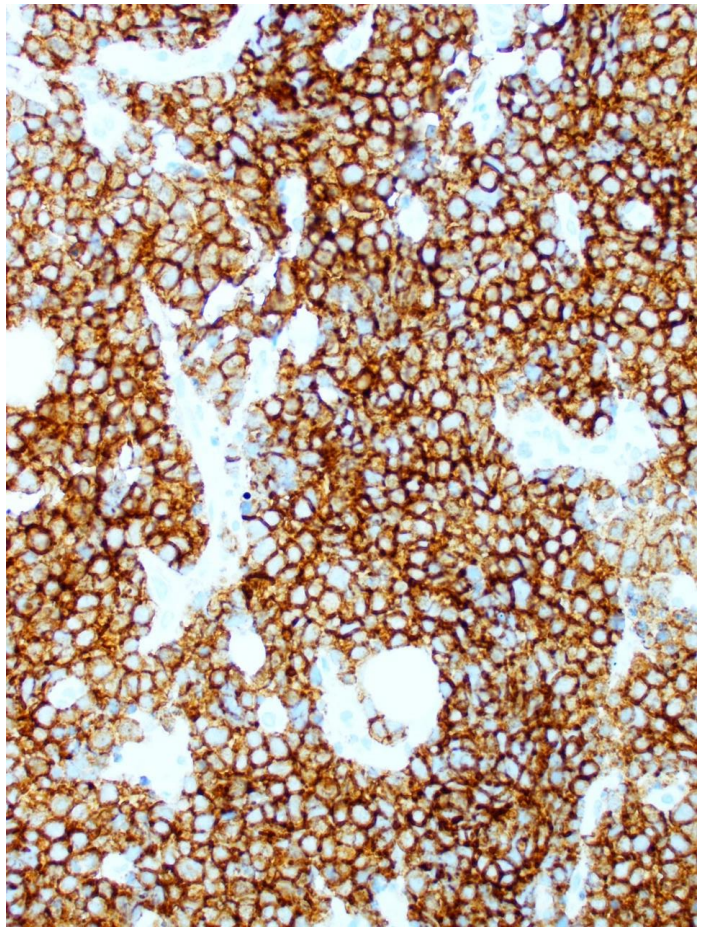


Prior specimen

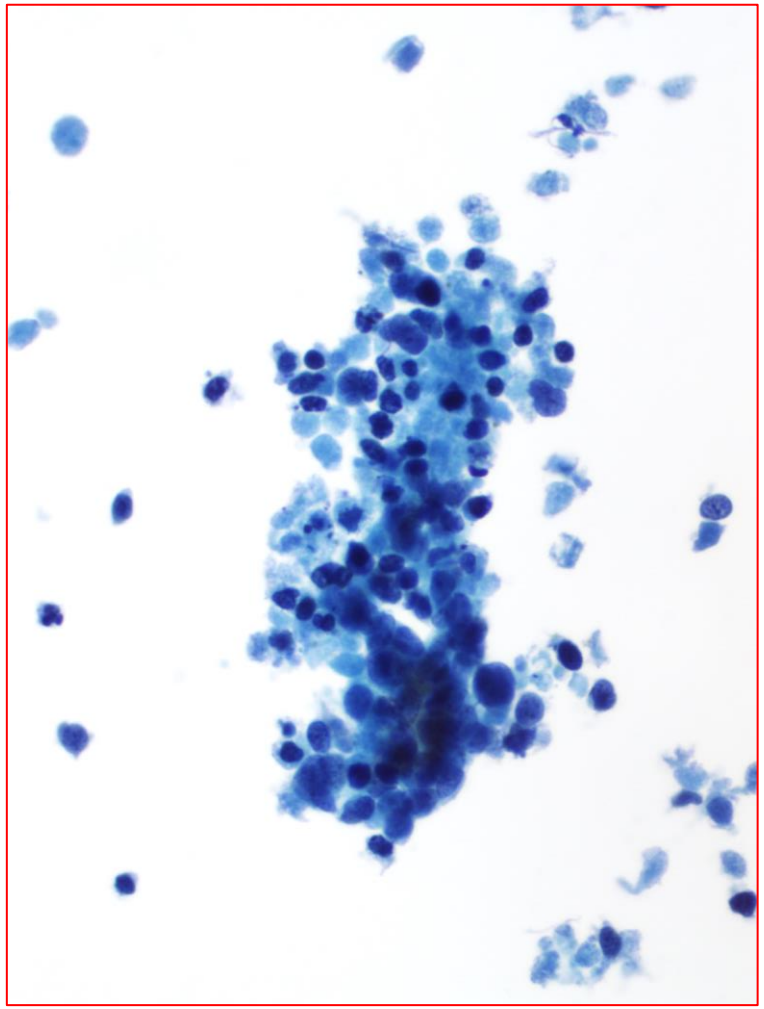
Current specimen

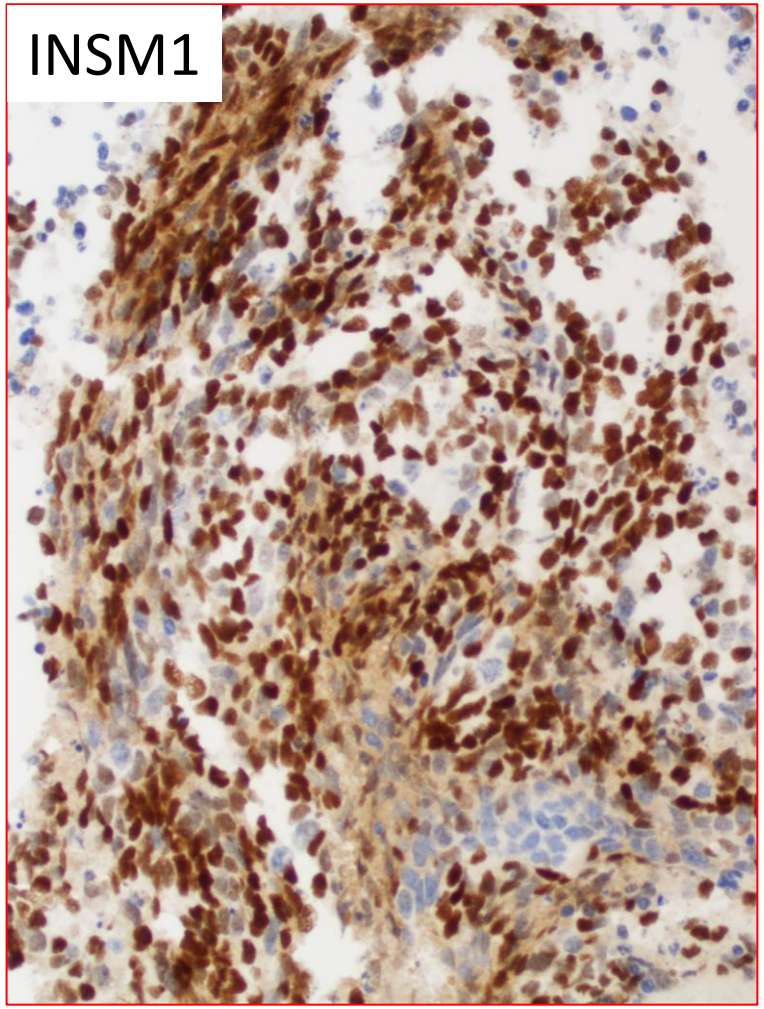
SCLC: Ancillary Tests

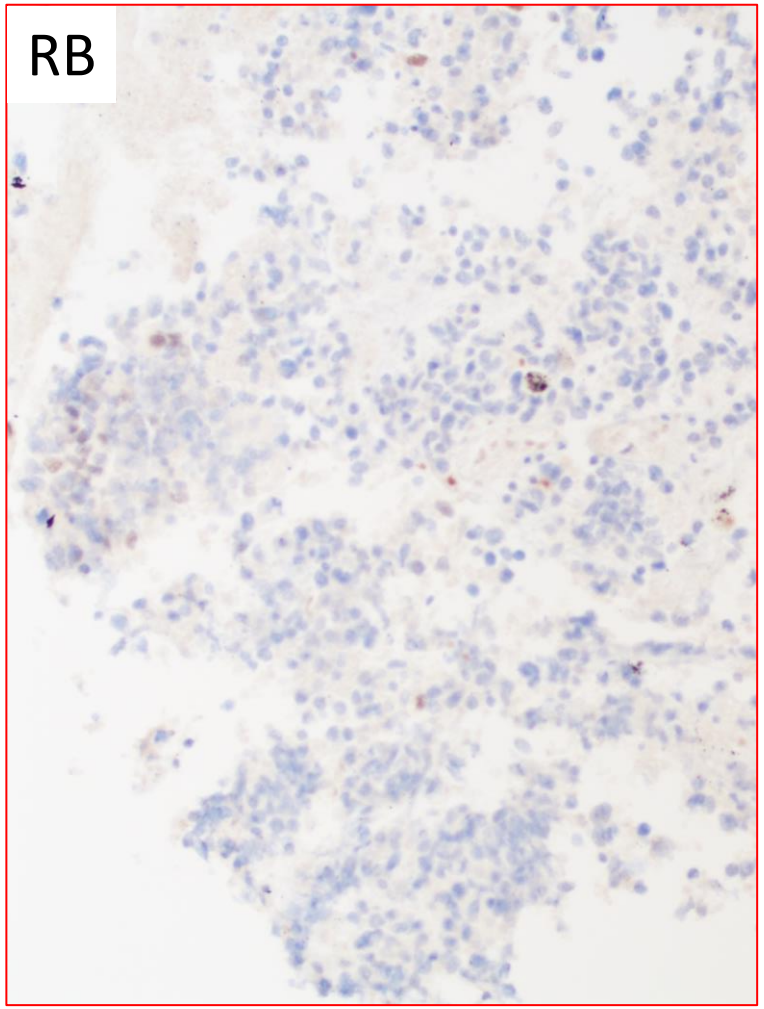
- Not required but often needed for diagnosis
  - Neuroendocrine markers: chromogranin, synaptophysin, INSM1, CD56
  - POU2F3: 10%
  - RB, p53
  - TTF1, Napsin A, p40, Ki-67
- Biomarker testing
  - PD-L1 not performed
- Molecular testing not performed



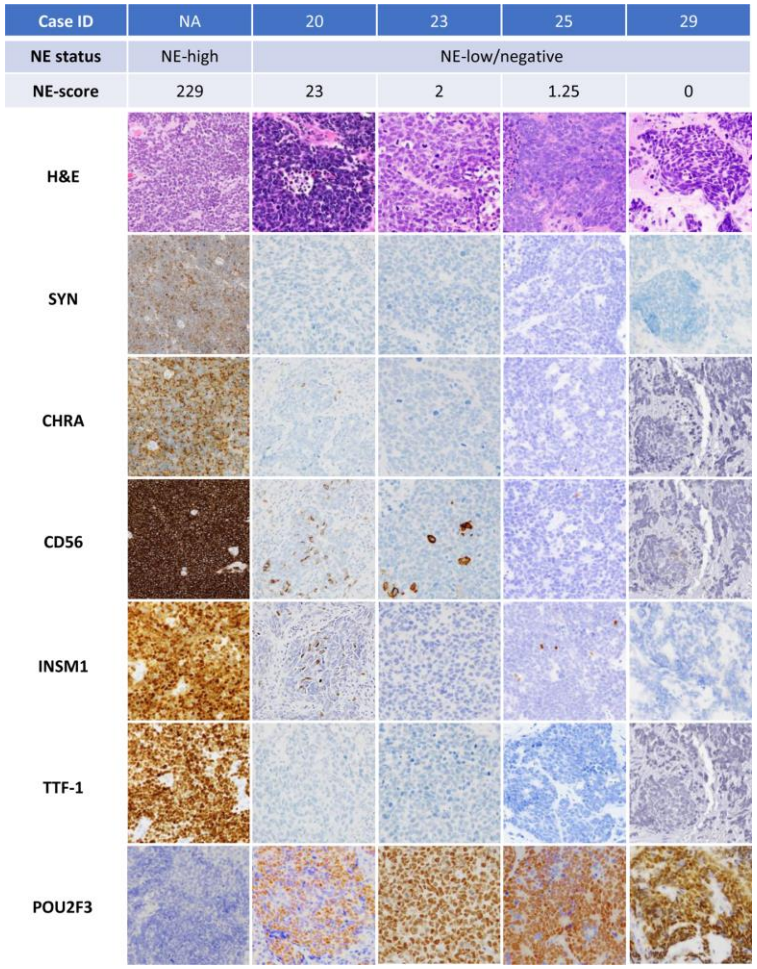
Small Cell Lung Carcinoma







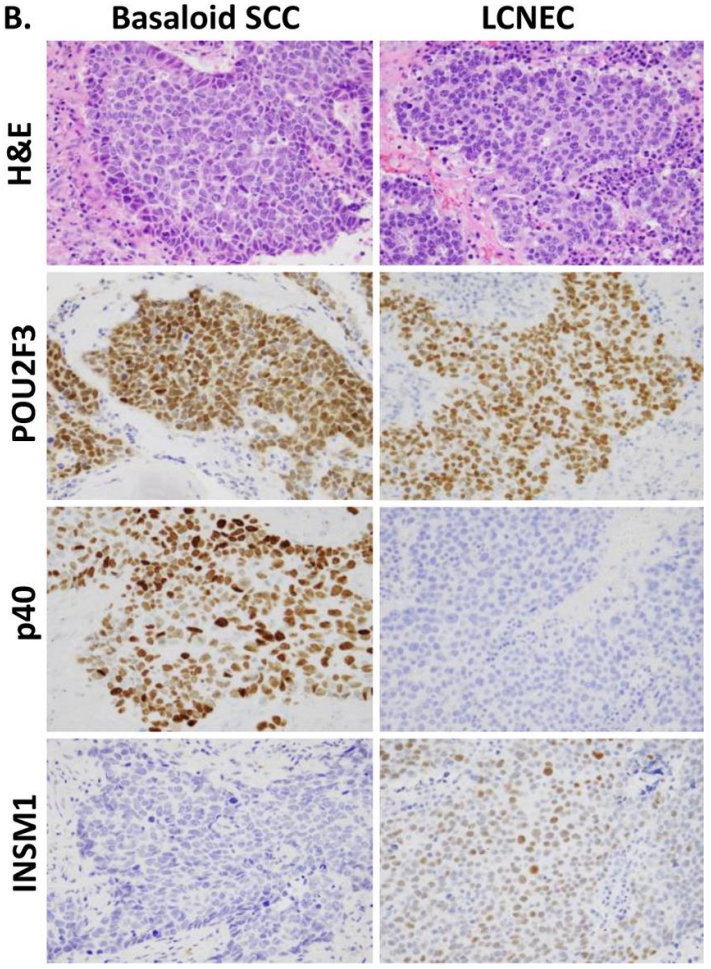
POU2F3: New Neuroendocrine Tumor Marker



A.

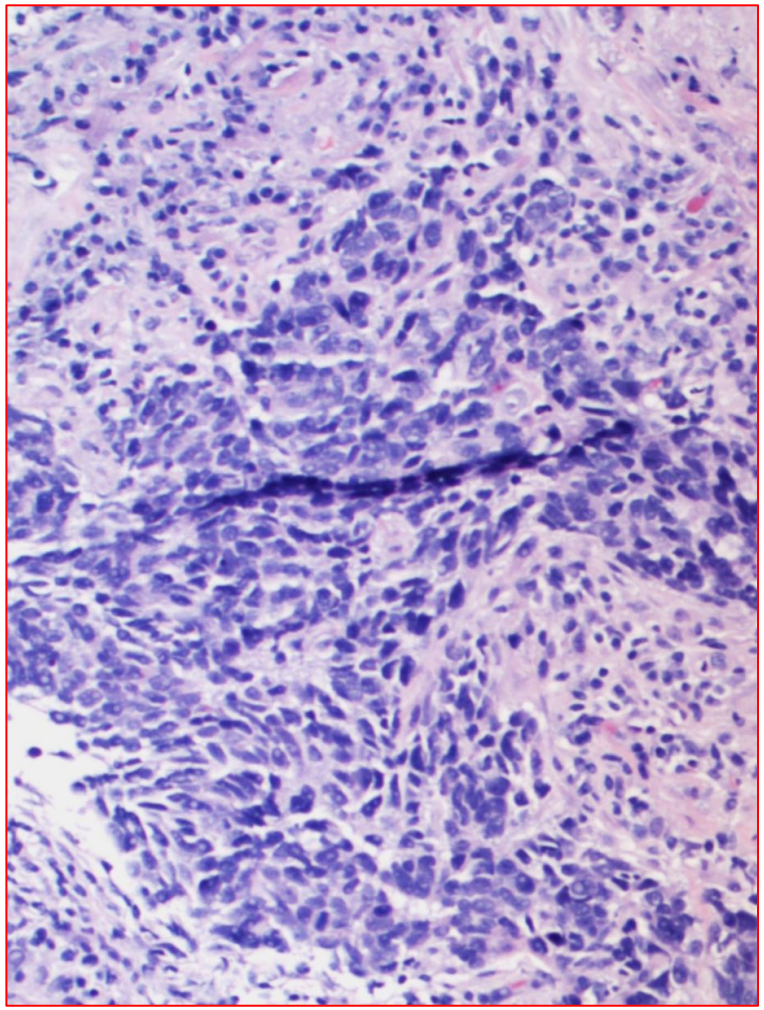
	Total tested	POU2F3+ N (%)
Lung tumors:		
Adenocarcinoma	100	0
SCC, NOS	63	0
SCC, basaloid	32	7 (22%)*
LCNEC	52	6 (12%)**
Carcinoids Typical Atypical	136 31	0 0
SMARCA4-UT	19	0
Other tumors that can mimic SCLC#:		
Merkel cell carcinoma	49	0
Melanoma	25	0
Lymphoma	29	0
Round cell sarcoma	20	0

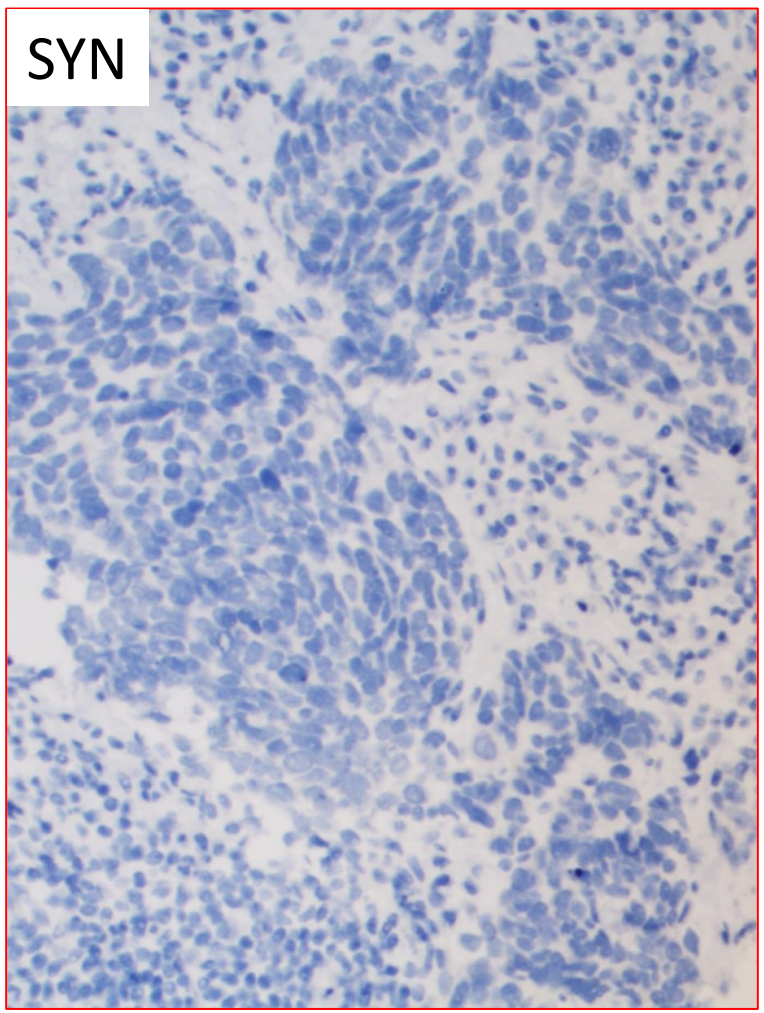
B.

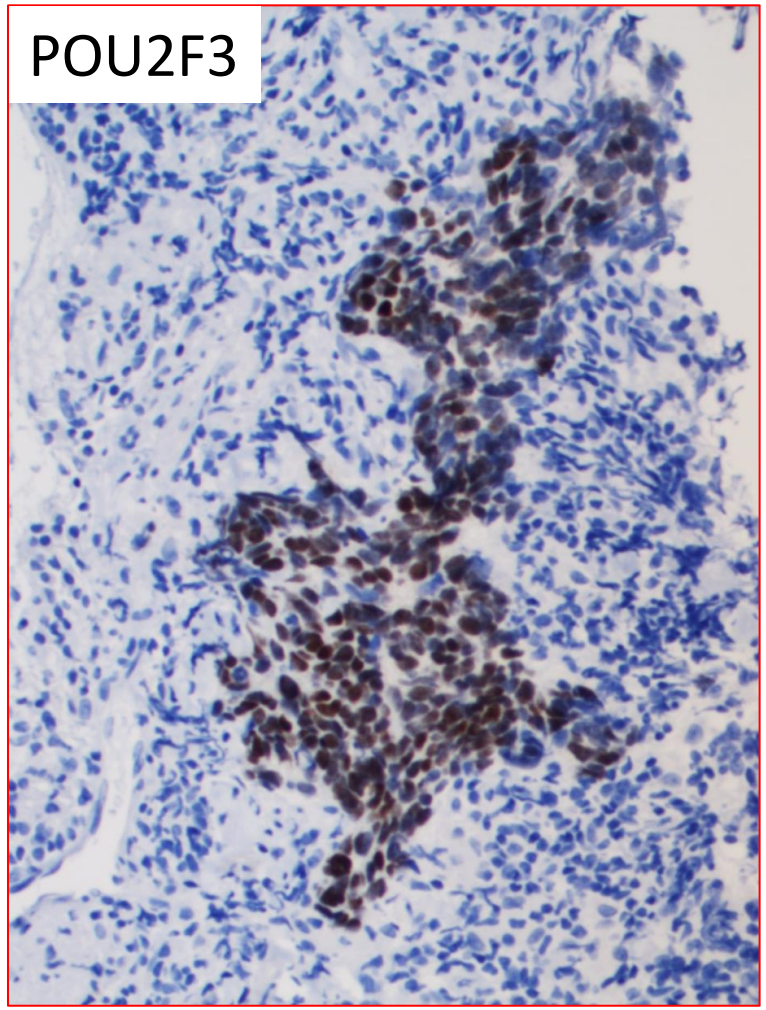


- *Baine MK, et al. J Thorac Oncol. 2022; 17(9):1109-1121.*

Small Cell Lung Carcinoma



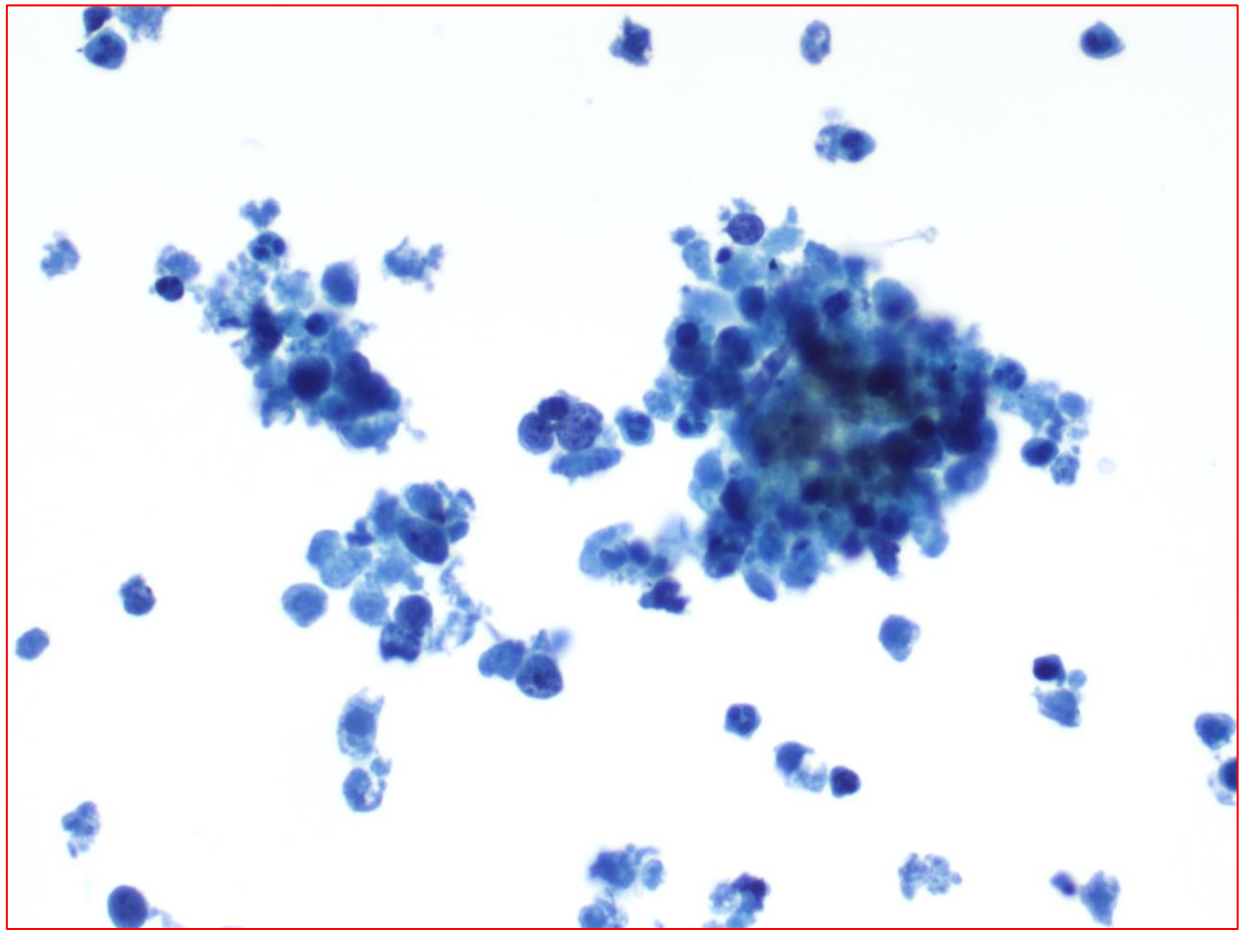


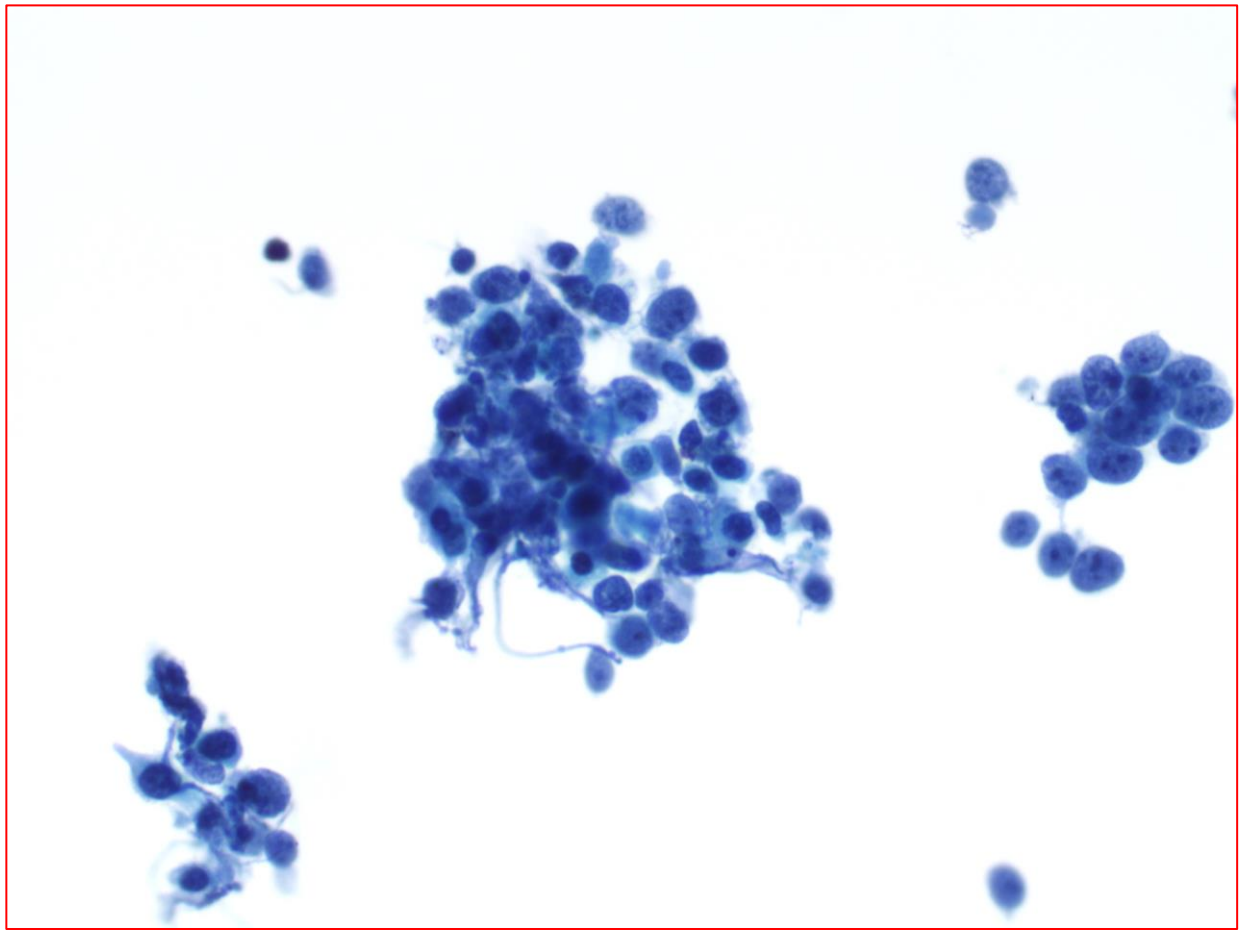


SCLC: Differential Diagnosis

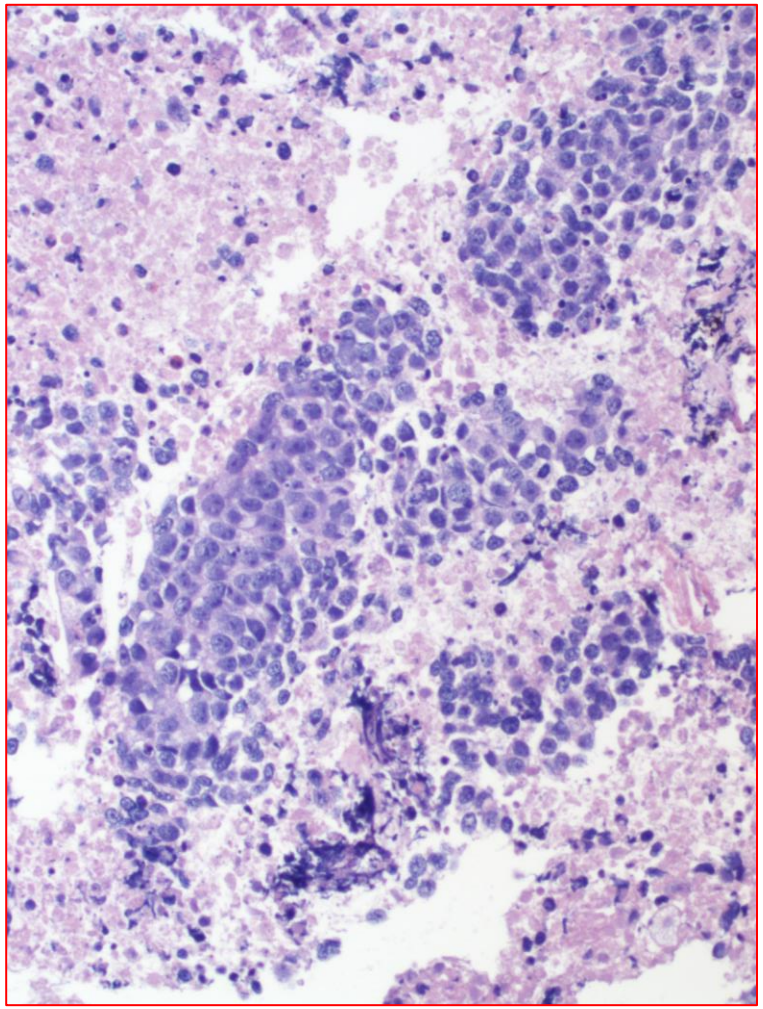
- Basaloid squamous cell carcinoma
- Thoracic SMARCA4-deficient undifferentiated neoplasm
- NUT carcinoma
- Merkel cell carcinoma
- Non-Hodgkin lymphoma
- Large cell neuroendocrine carcinoma
- Carcinoid tumors with increased proliferation rate

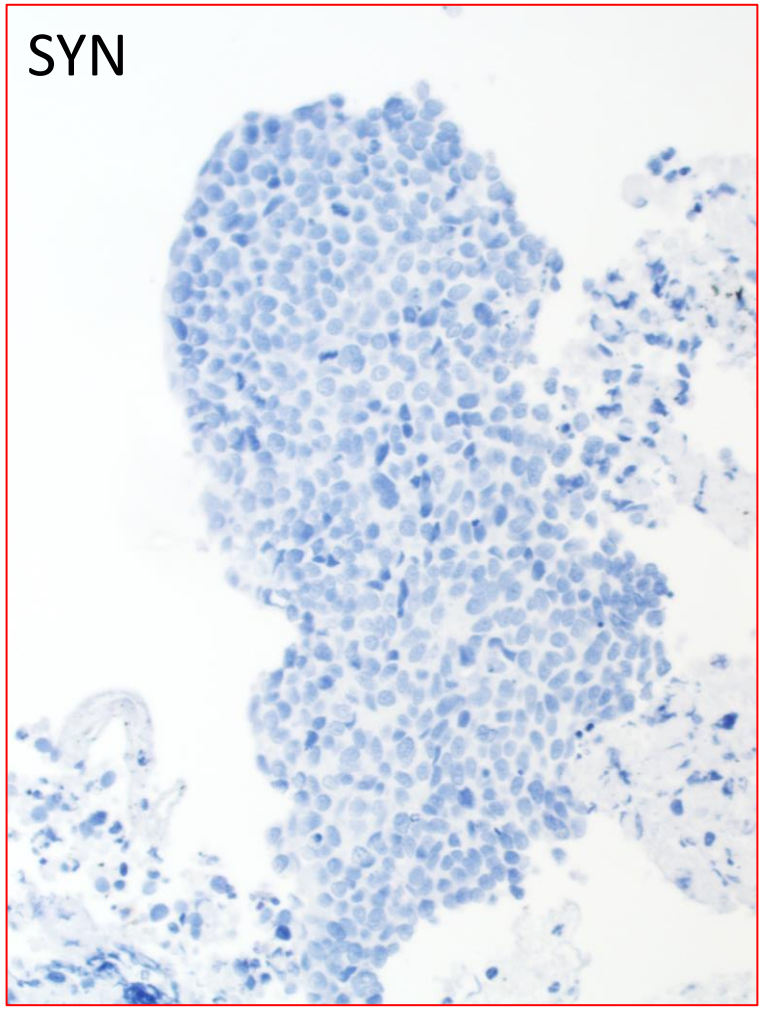
Basaloid Squamous Cell Carcinoma

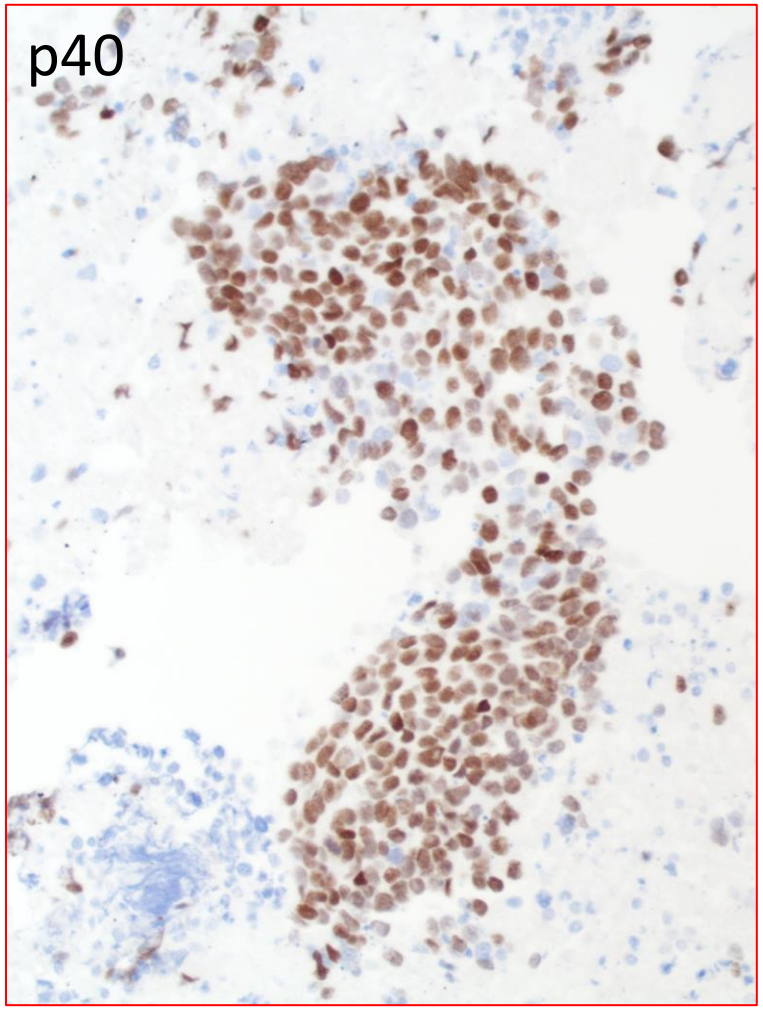




Basaloid Squamous Cell Carcinoma

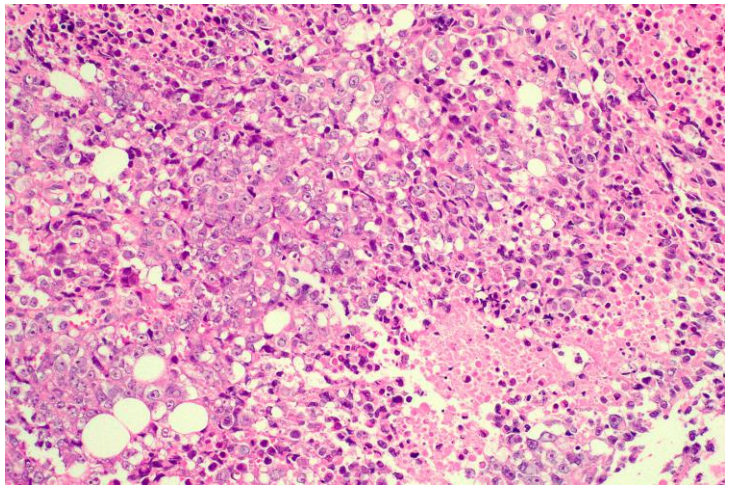


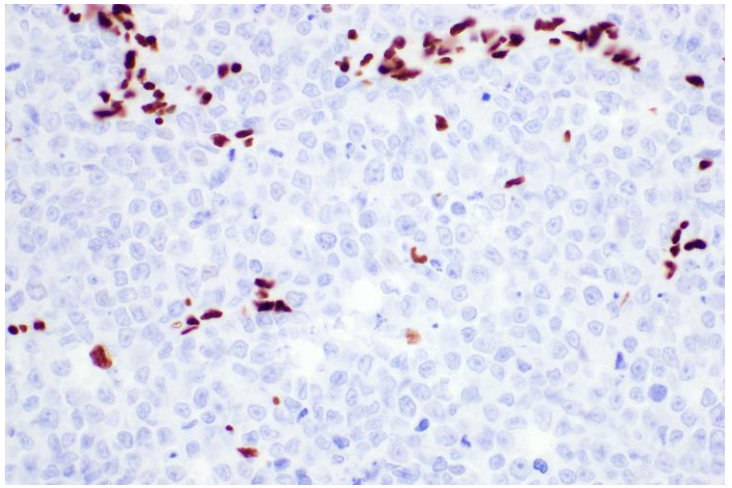




SMARCA4-deficient Undifferentiated Neoplasm

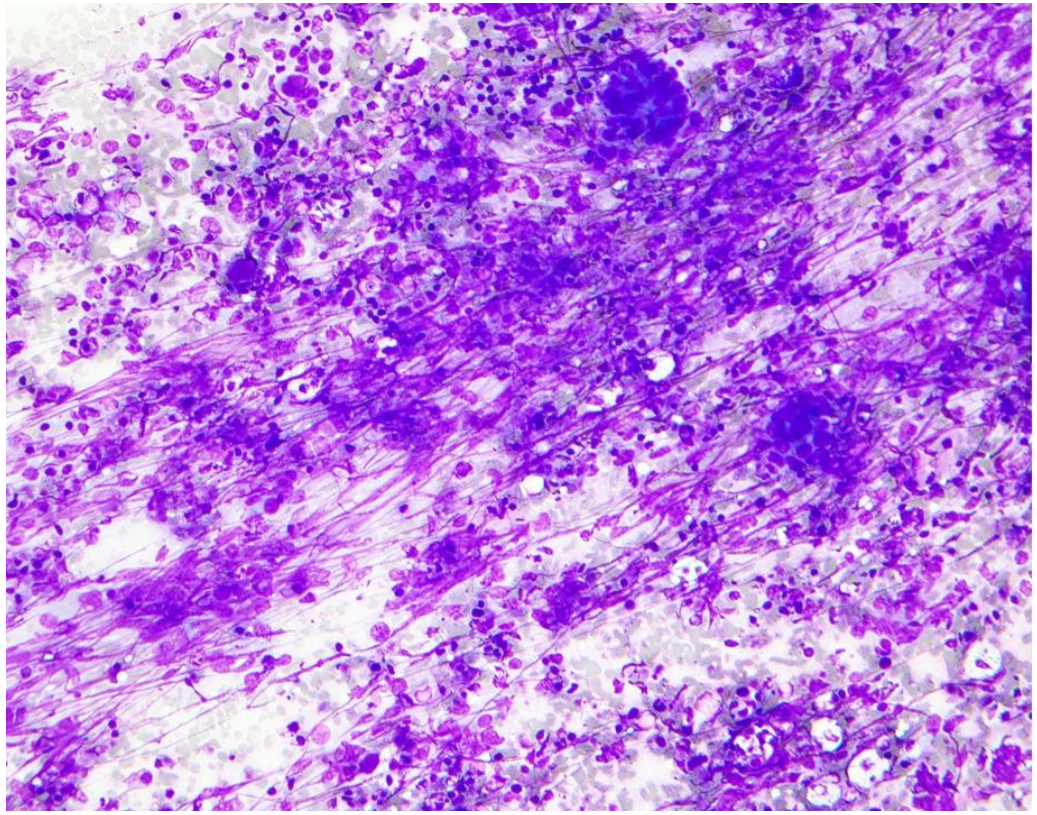
- Smokers, large central masses
- Rhabdoid, may small round cell morphology
- No rosettes, nests or palisading
- Extensive necrosis with crush artifact
- Positive synaptophysin (~70%)
- SMARCA4 loss
- Expression of SALL4, CD34, SOX2
- 5% NSCLC with SMARCA4 loss



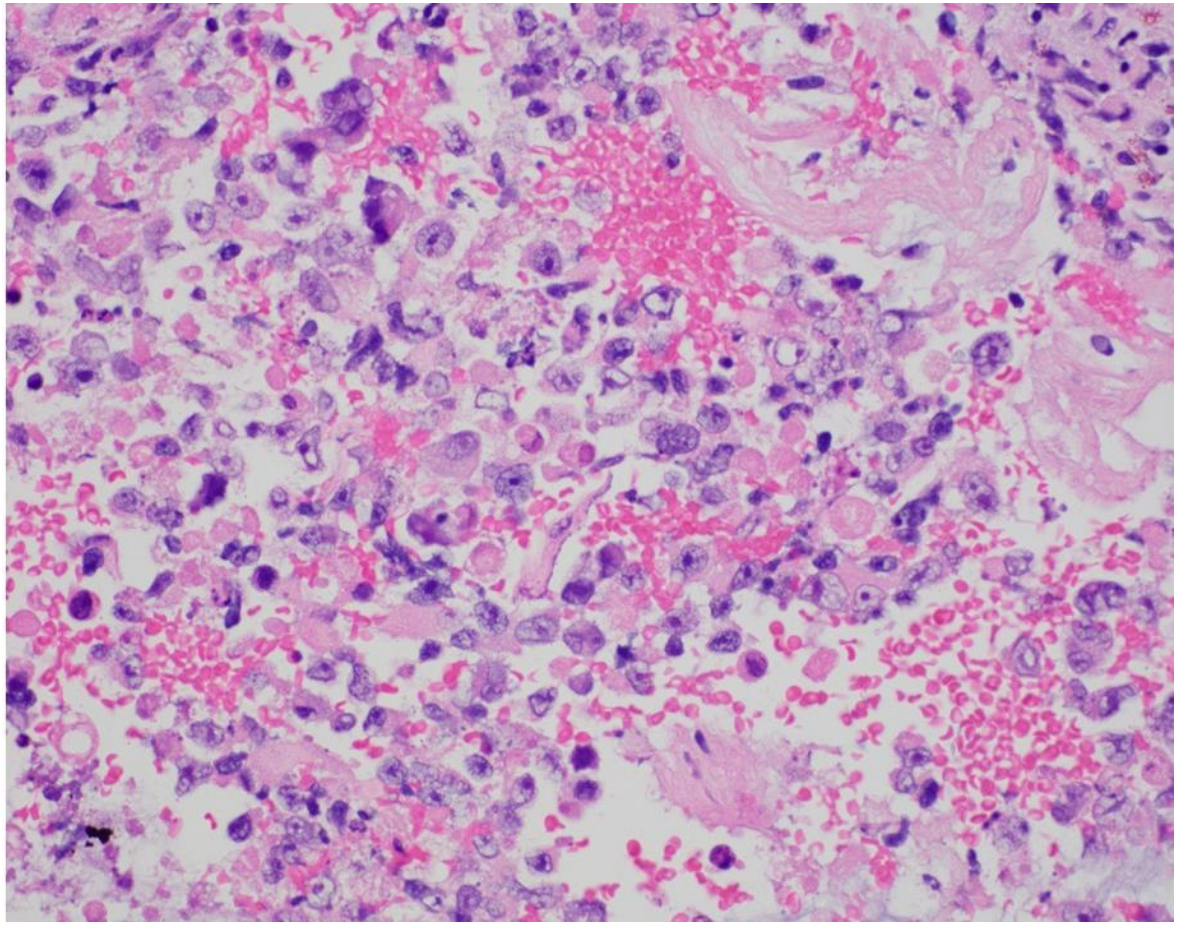


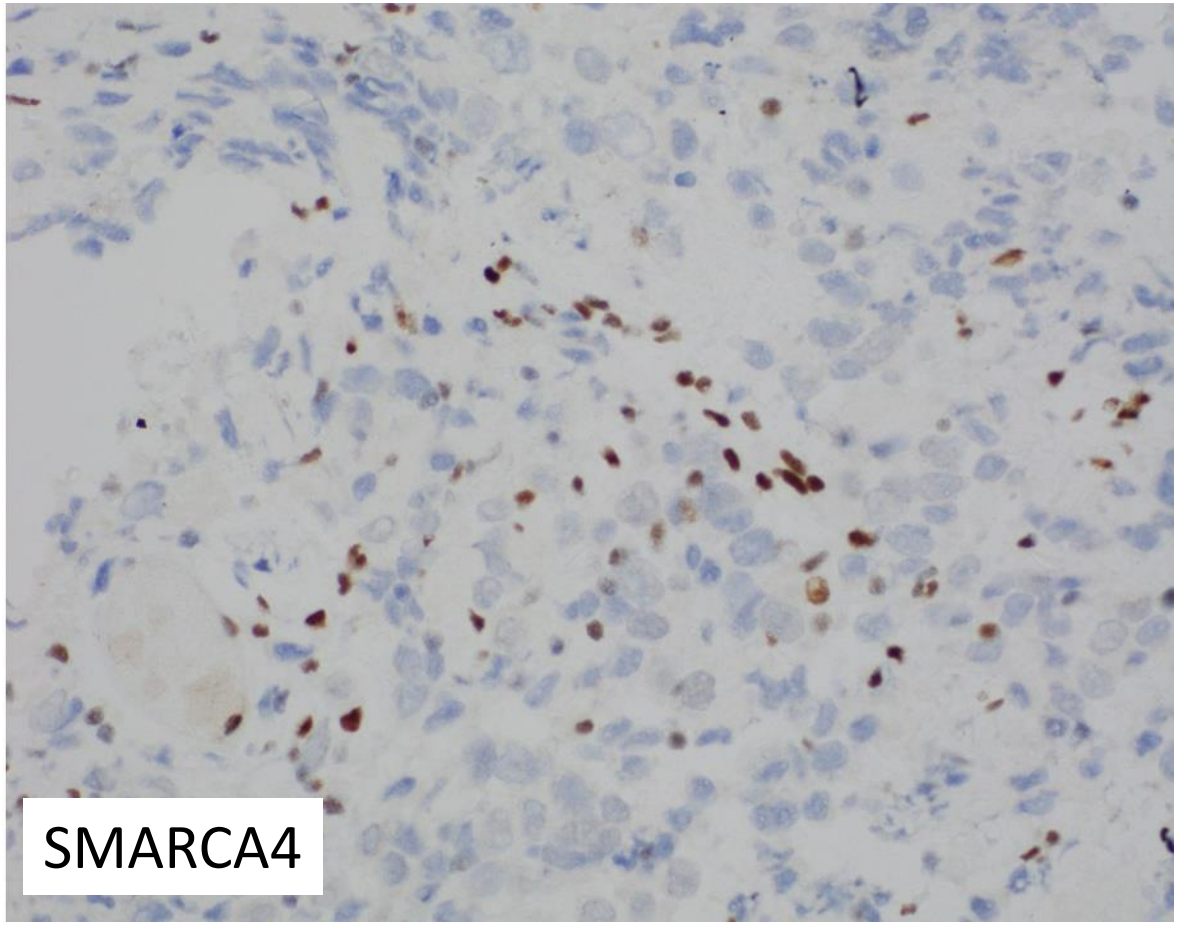
SMARCA4-deficient Undifferentiated Neoplasm

- Dispersed single cells or loosely cohesive sheets
- Intermediate in size
- Characteristic rhabdoid morphology
- Round to oval nuclei with irregular nuclear membranes and prominent nucleoli
- Frequent mitoses and apoptotic bodies
- Nuclear streaking artefact
- Necrotic and inflammatory background



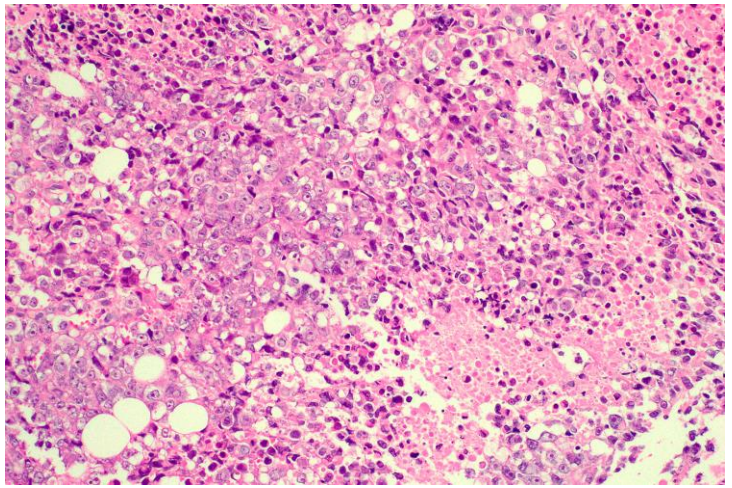
SMARCA4-deficient Undifferentiated Neoplasm

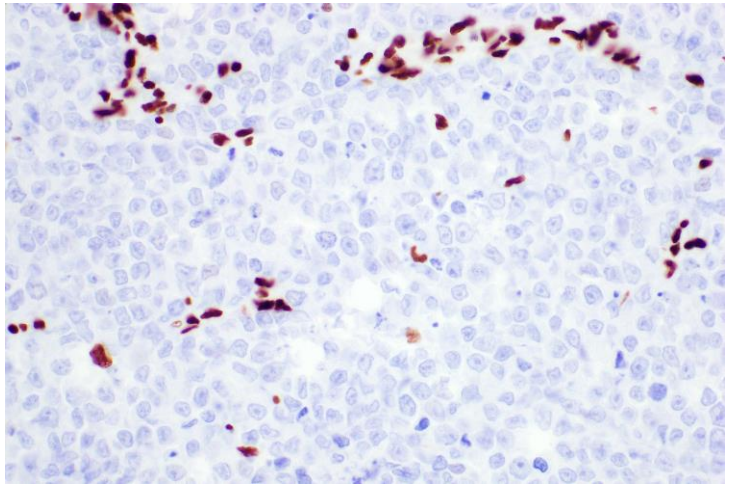




NUT Carcinoma

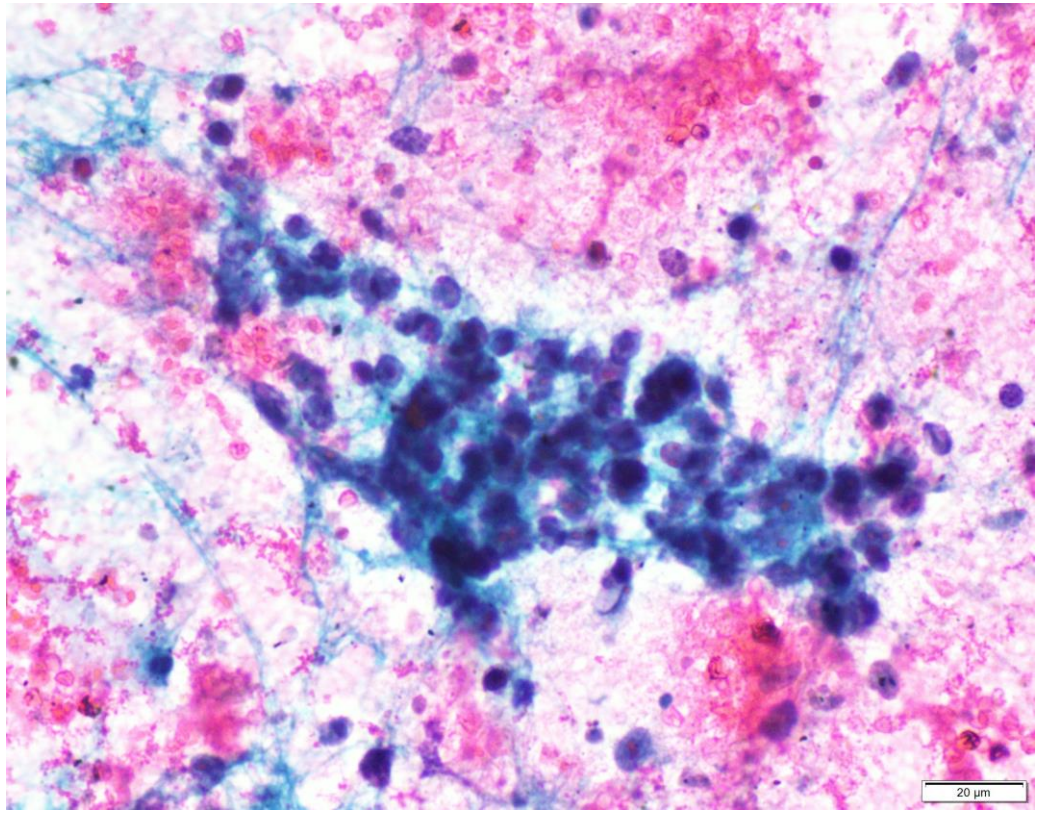
- Wide age distribution, younger
- Sheets of monomorphic intermediate sized undifferentiated cells
- Nuclei with irregular outlines, vesicular chromatin, and prominent nucleoli
- Brisk mitotic activity and necrosis
- Prominent neutrophilic infiltrate
- Characterized by chromosomal translocation t(15;19)(q14;p13.1)
- Positive for NUT (87% of cases)



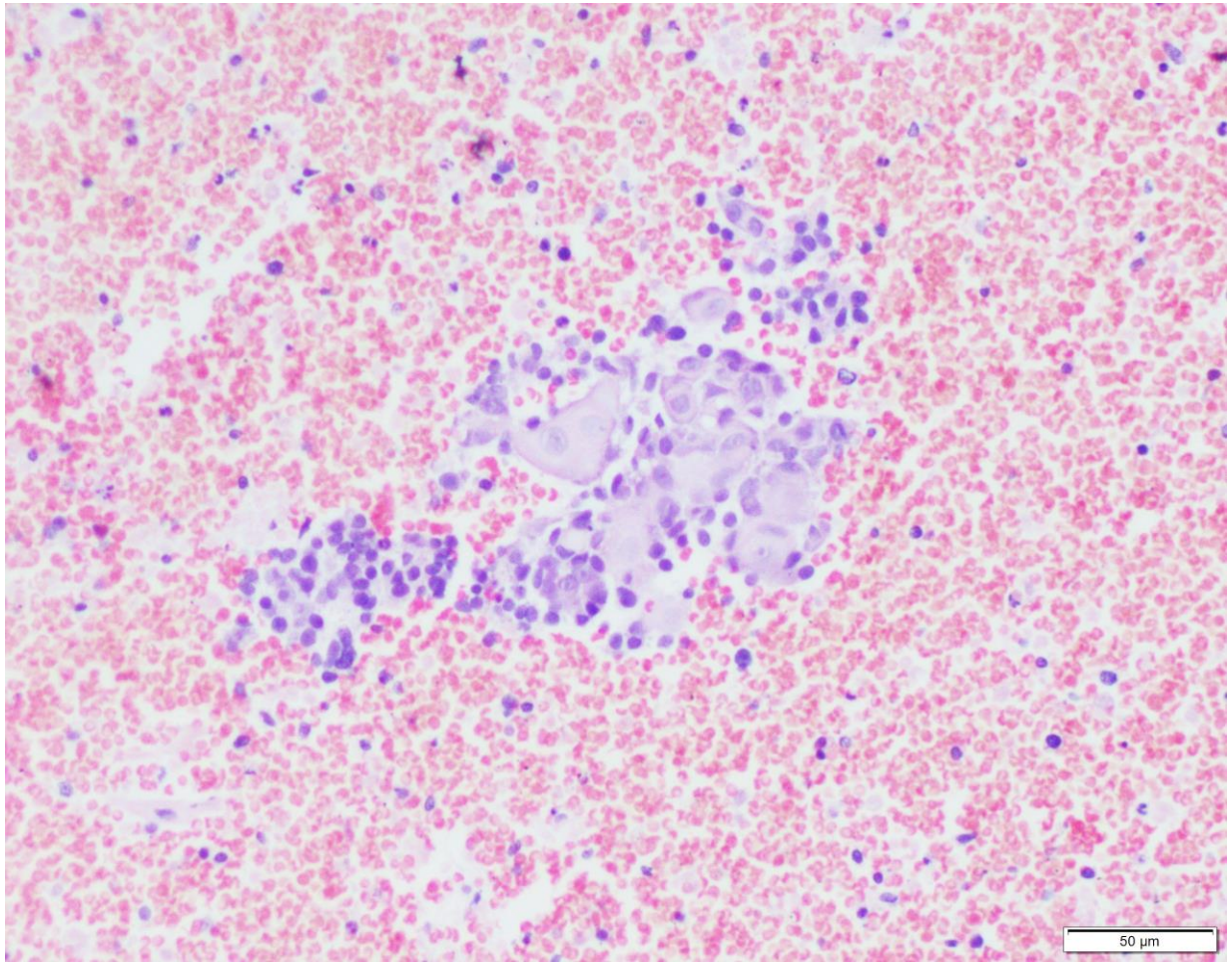


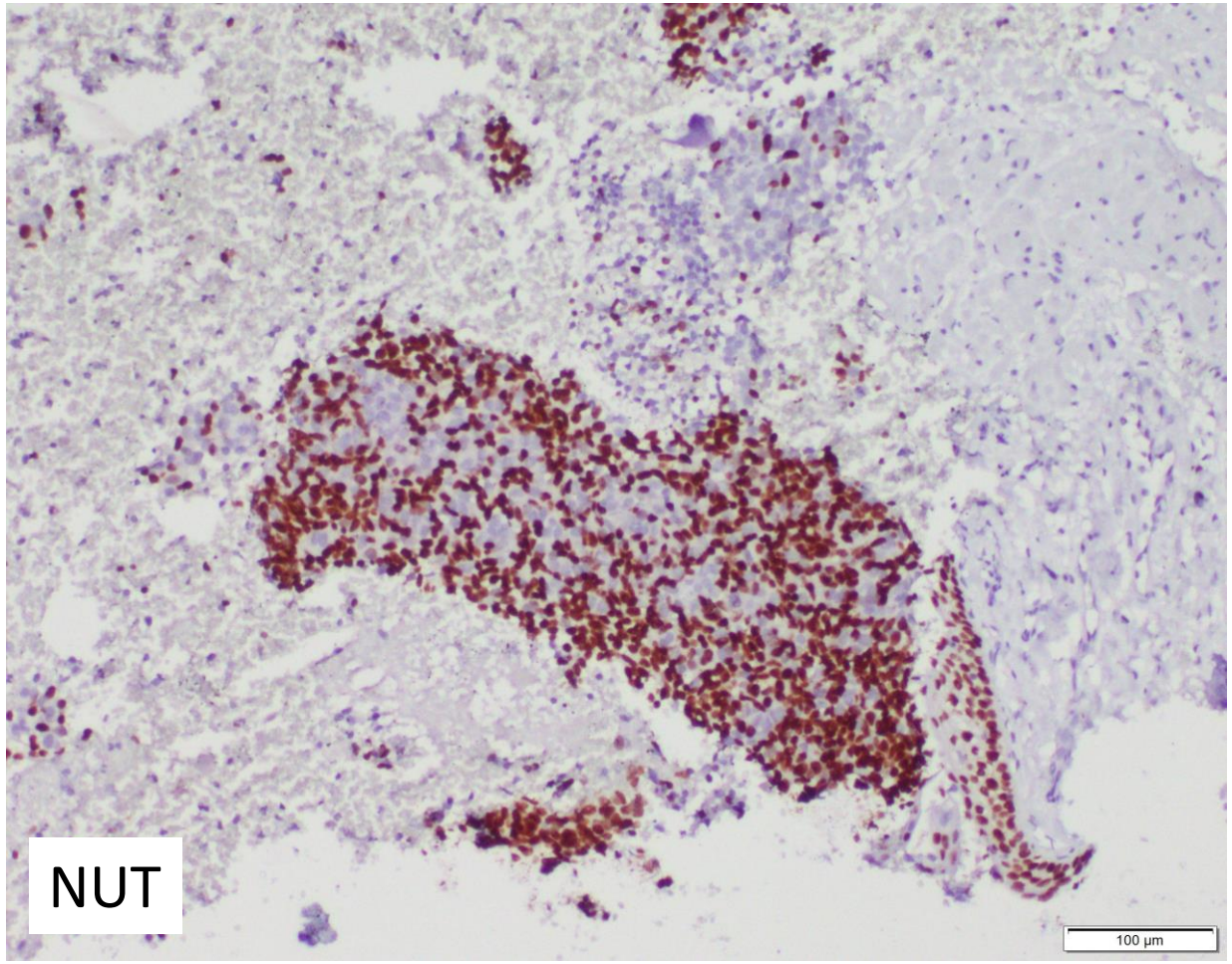
NUT Carcinoma

- Loosely cohesive tissue fragments and single isolated cells
- 2–3 times as large as a lymphocyte
- Cytoplasm is generally scant, high N:C ratios, nuclear moulding
- Round to oval nuclei with finely granular chromatin and prominent nucleoli
- Focal squamoid cells
- Frequent mitoses and neutrophilic infiltrate
- Necrotic background



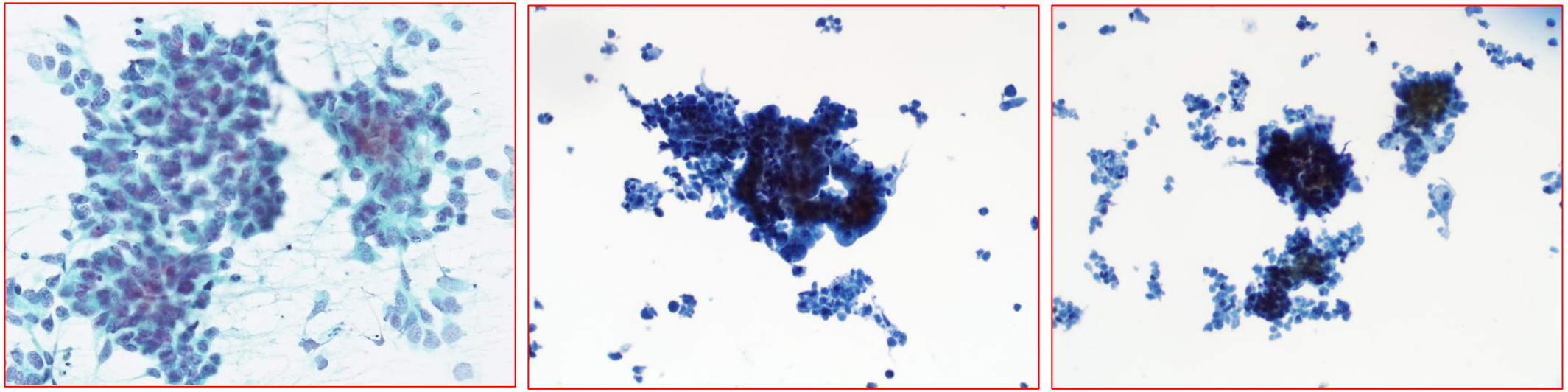
NUT Carcinoma





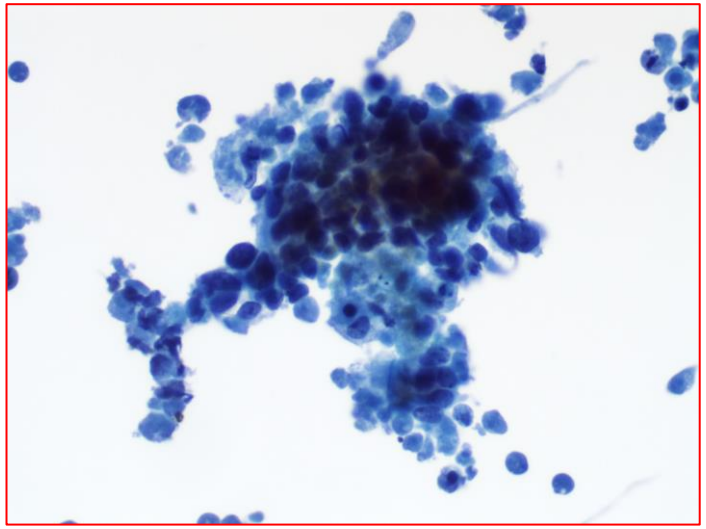
Large Cell Neuroendocrine Carcinoma

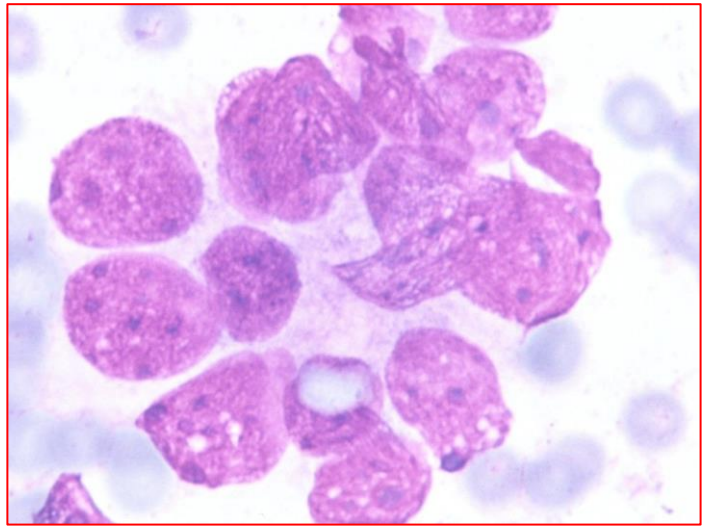
- Small, cohesive or loosely cohesive groups, single cells
- Rare tissue fragments with thin fibrovascular strands
- Chromatin/nuclear smearing crush artefact (less prominent)
- Prominent necrosis

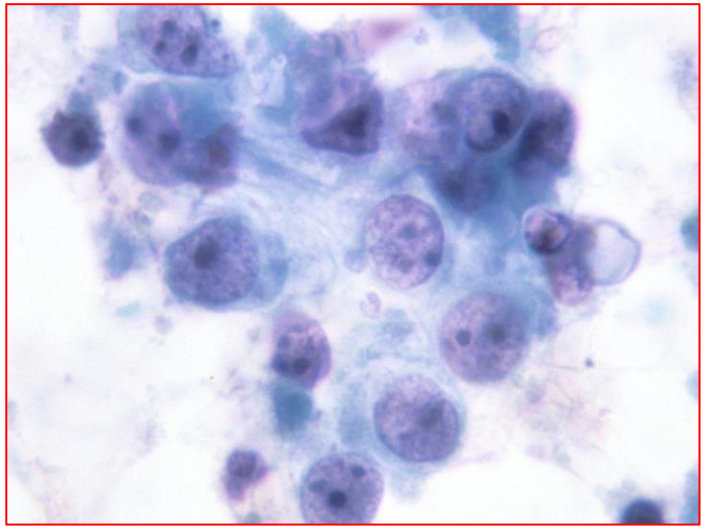


Large Cell Neuroendocrine Carcinoma

- Intermediate to large, > 3 lymphocytes
- Moderate to abundant cytoplasm
- Fine granular, vesicular, or coarse chromatin
- Prominent nucleoli and frequent mitoses







Large Cell Neuroendocrine Carcinoma

- A definitive diagnosis is difficult but can be suggested in cases with cellular cell blocks (morphology and immunohistochemistry)
- Positive for synaptophysin, chromogranin, CD56, and INSM1 (75%)
- TTF1 positive (50%) while Napsin A negative (weak/focal)
- Ki-67 proliferation index > 30% (40-80%)
- Component of non-small cell carcinoma or small cell carcinoma
- A subset of cases harbor non-small cell carcinoma mutations

LCNEC: Differential Diagnosis

- NSCLC with NE differentiation
  - 10-20% of squamous cell carcinoma, adenocarcinoma, and large cell carcinoma demonstrate positive NE markers but lack NE morphology
  - Some large cell carcinoma show NE morphology but negative NE markers (classified as large cell carcinoma with NE morphology)
- Small cell carcinoma
  - Considerable morphologic overlap
  - Difficult to separate, low interobserver diagnostic reproducibility
- Atypical carcinoid
  - “Rarely, a tumor with carcinoid-like morphology has a mitotic rate of >10 mitoses per 2 mm^2, and because it is likely to be aggressive, it is best classified as an LCNEC”

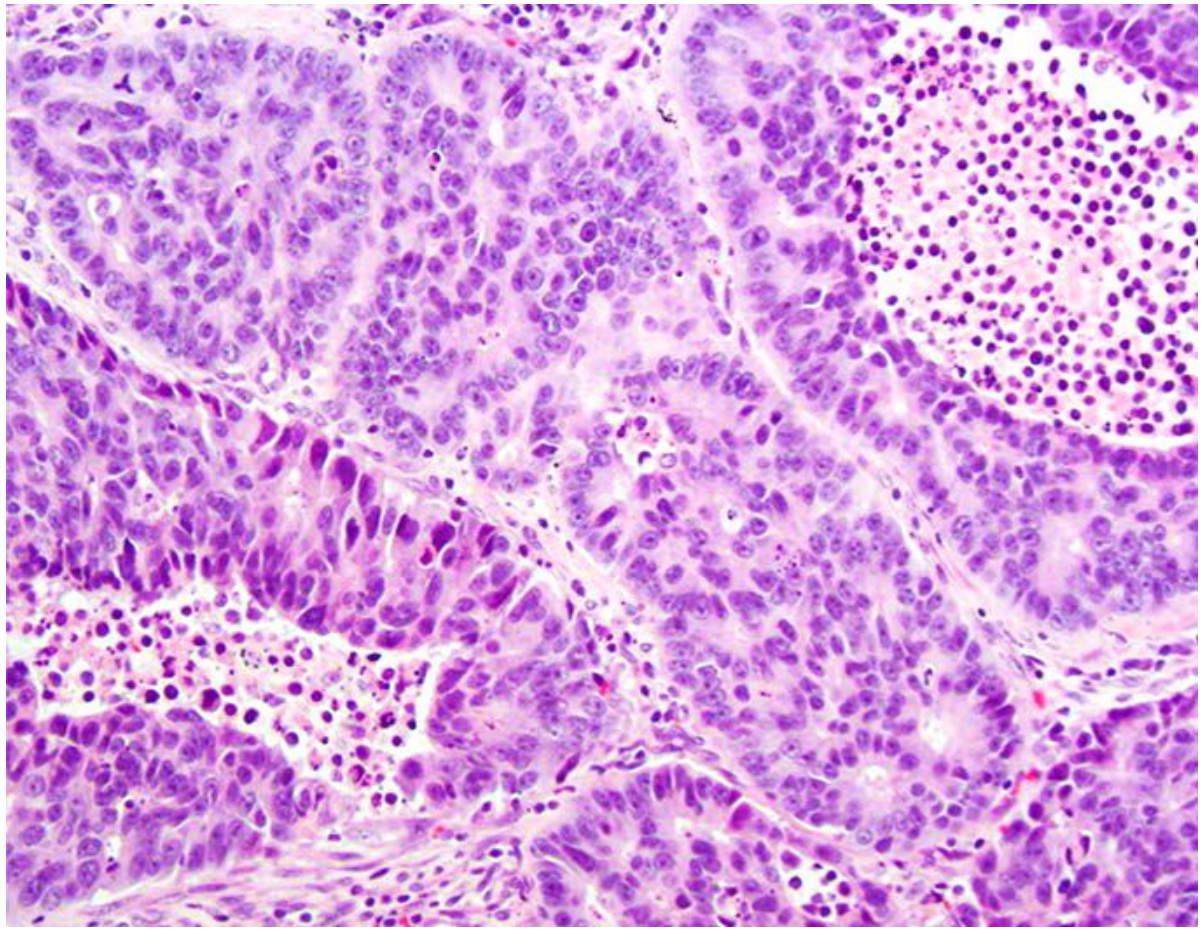
NSCLC with NE Differentiation

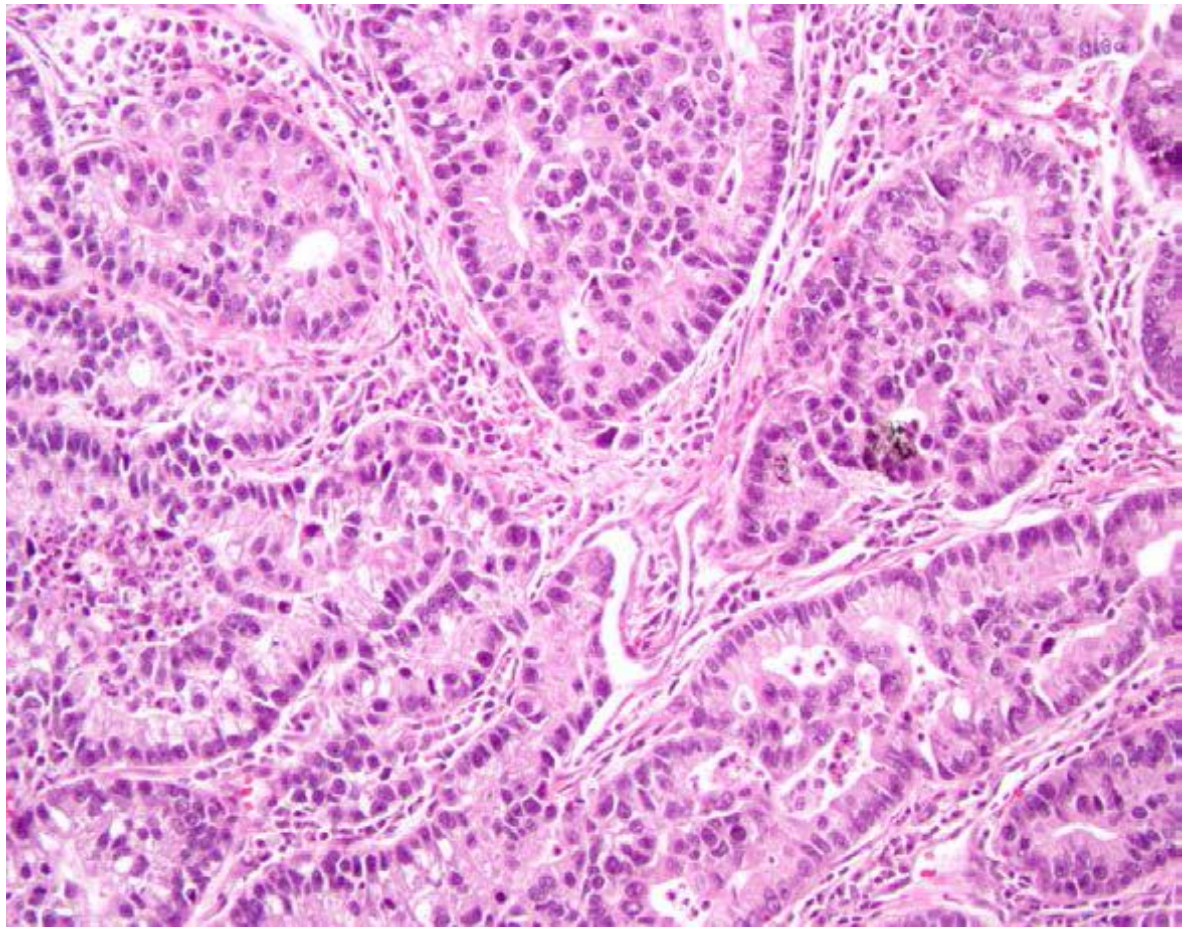
- Mostly those adenocarcinomas with a solid/nested or cribriform pattern
- LCNEC: presence of nuclear palisading and rosettes
- Expression of neuroendocrine markers in NSCLCs usually focal and limited to a single marker
- Napsin A expression is absent or very focal in LCNEC
- Caution: Staining for neuroendocrine markers in the absence of neuroendocrine morphology not recommended

LCNEC vs Adenocarcinoma

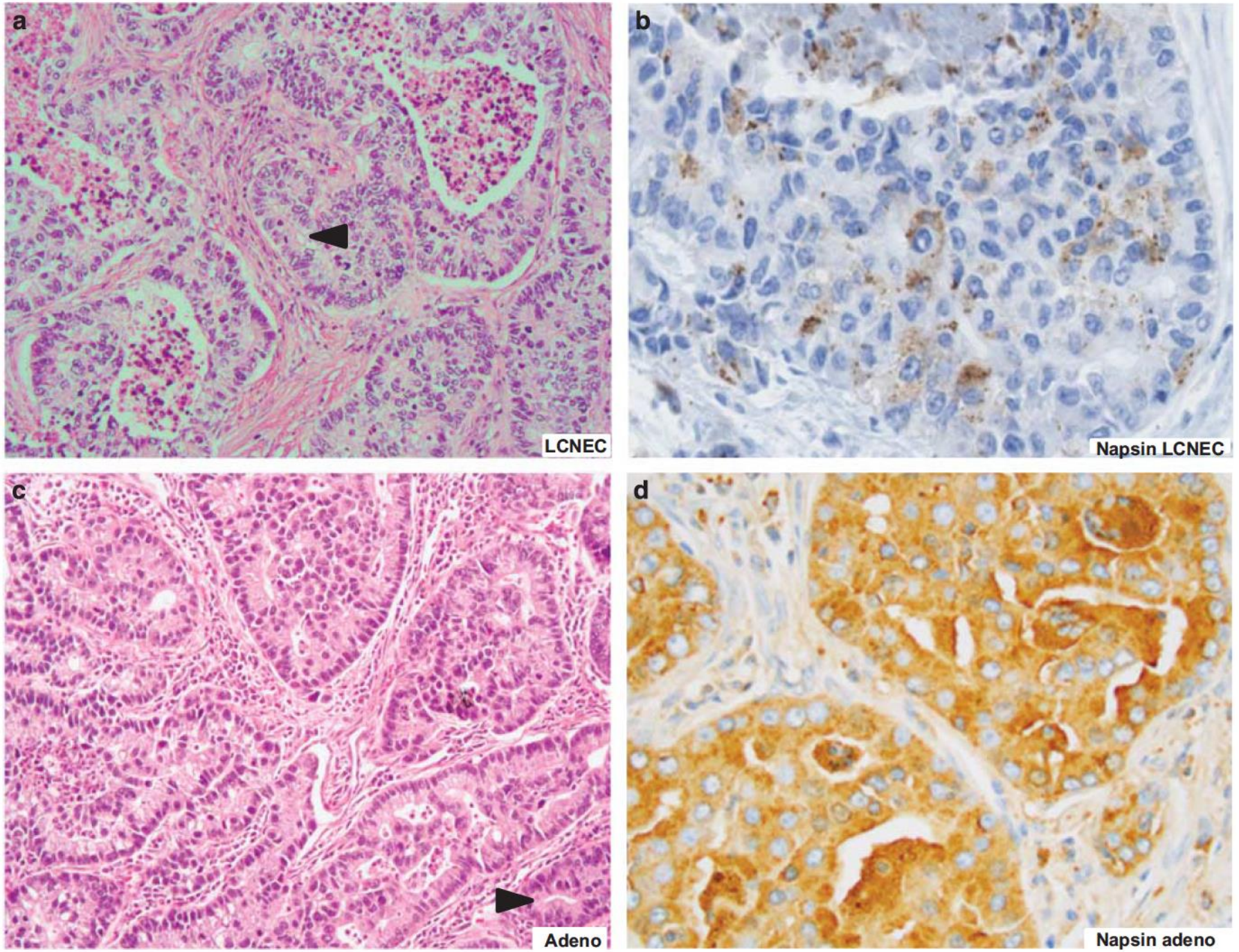
	LCNEC	Cribriform ADC
Growth pattern	Organoid nesting, rosettes, trabeculae, palisading	Solid, cribriform
Lumens	Punched-out, pin-pointed	Slit-like
TTF-1	Most positive, usually diffuse	Usually positive
Napsin A	Usually negative but can be focal (15%)	Usually positive
NE markers	Usually diffuse	Seen in 15%, often focal

LCNEC vs Adenocarcinoma





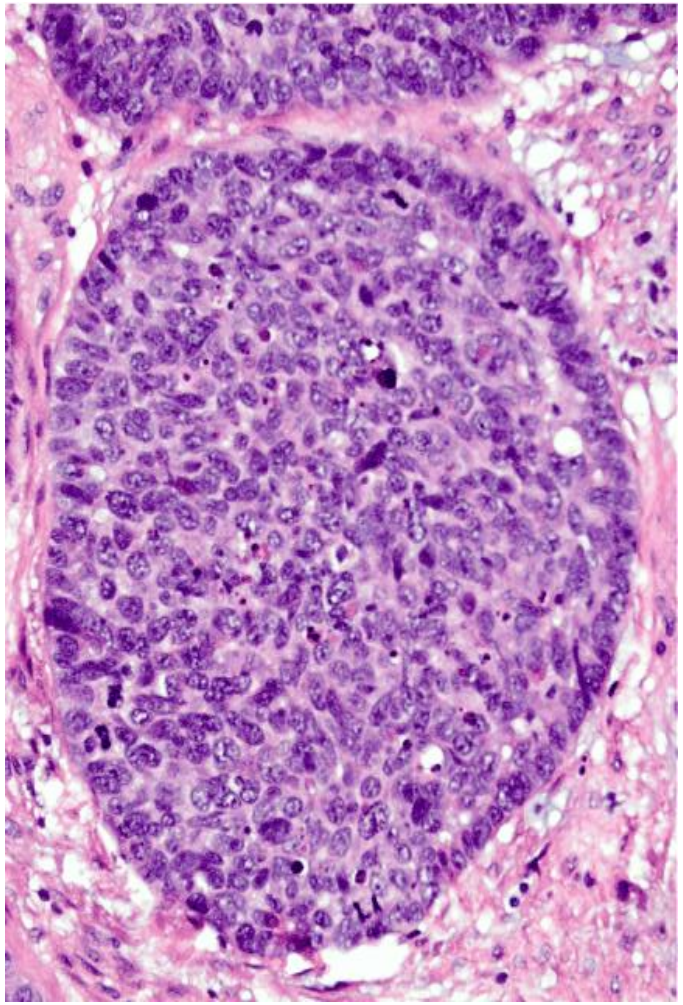
- *Rekhtman N, et al. Mod Pathol 2018; 31:111–121.*

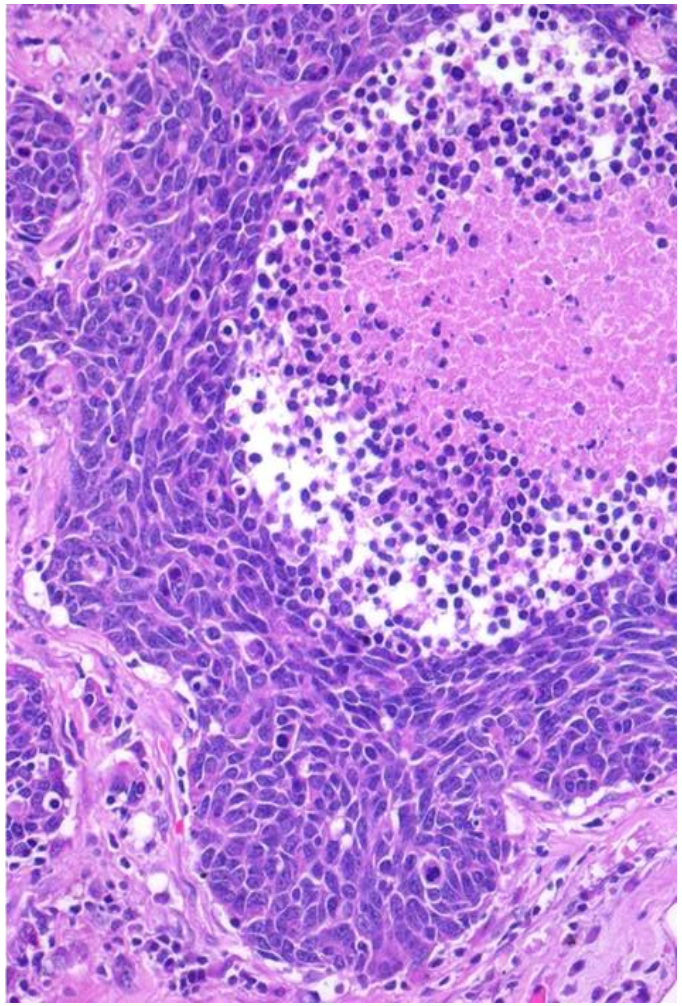

a
LCNEC
b
Napsin LCNEC
c
Adeno
d
Napsin adeno

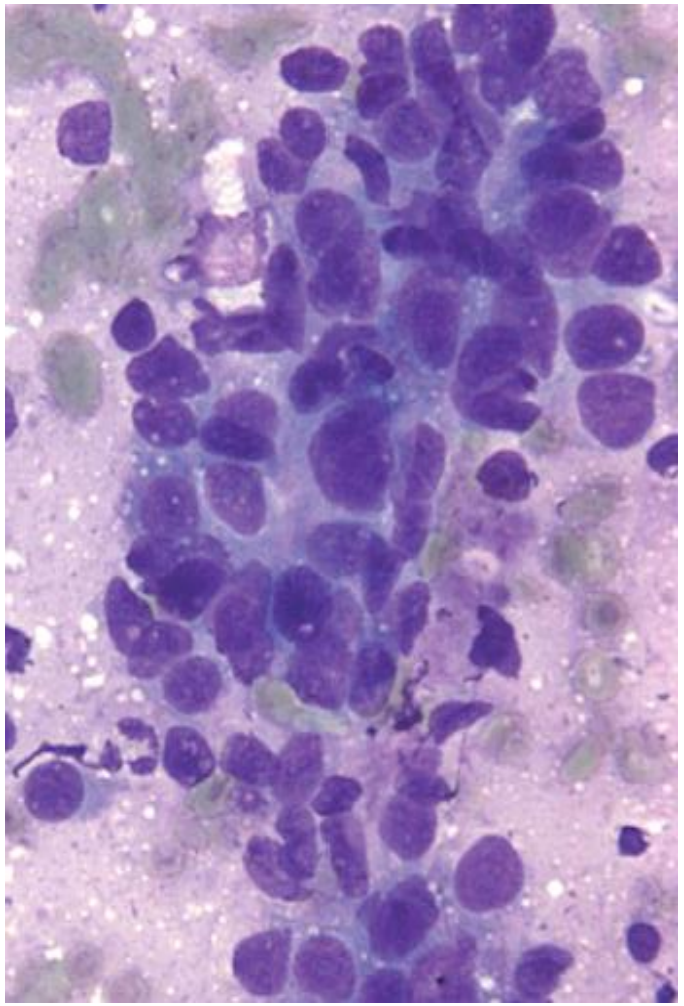
Small Cell Lung Carcinoma

- LCNEC: presence of prominent nucleoli and/or abundant cytoplasm, and in most cases by larger cell size
- Challenging in a subset of cases, no reliable immunocytochemistry or molecular markers
- In the absence of well-preserved areas to allow evaluation of cytological features, the diagnosis of “high-grade neuroendocrine carcinoma NOS” is appropriate
- Presence of any amount of SCLC in a predominant LCNEC called as combined SCLC and LCNEC

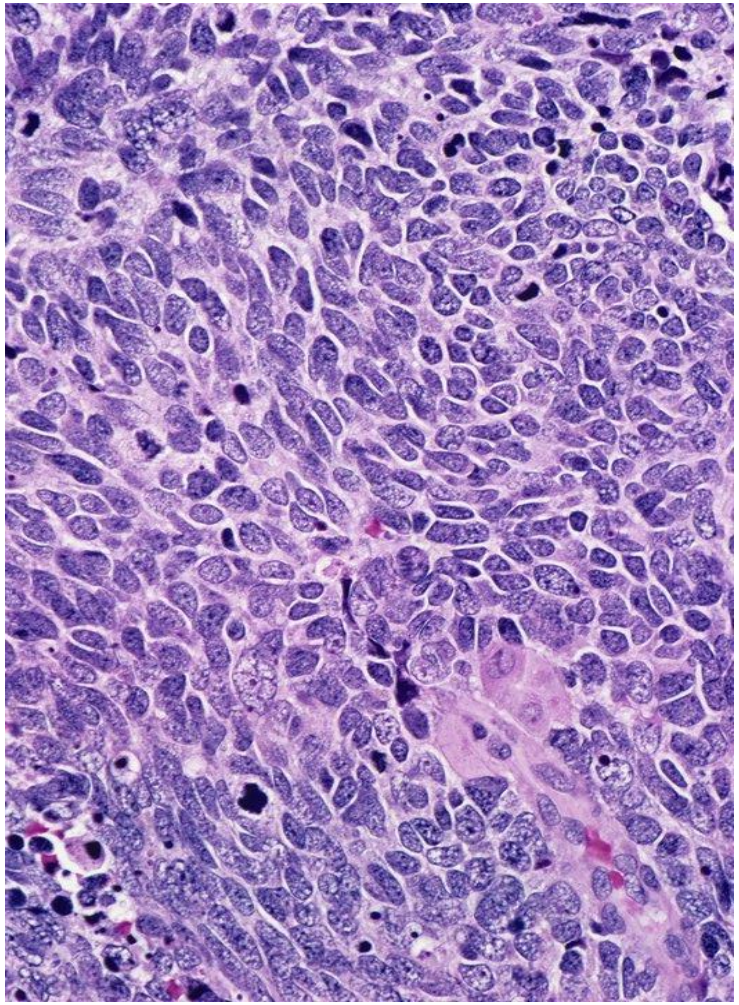
Large Cell Neuroendocrine Carcinoma

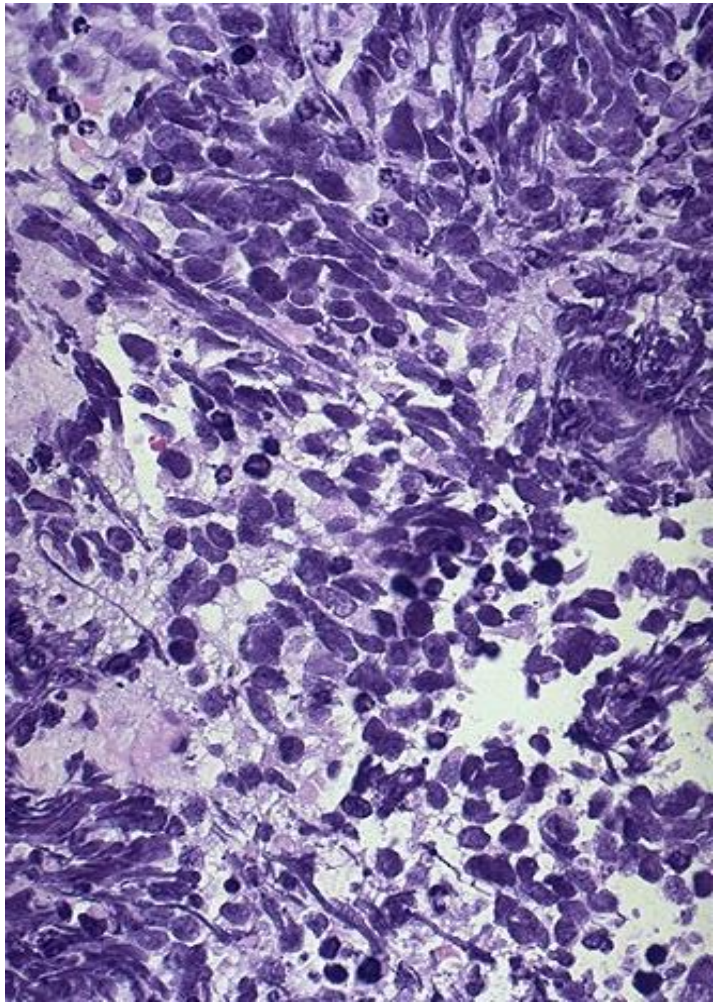


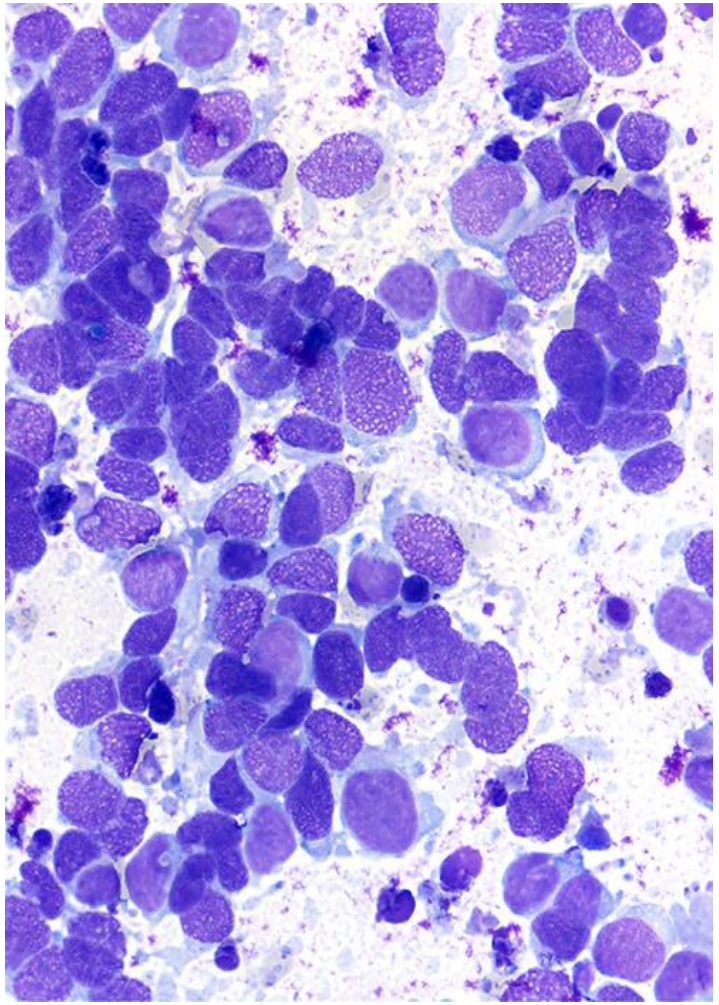




Small Cell Lung Cancer







LCNEC vs SCLC

	LCNEC	SCLC
Growth pattern	Organoid nesting, rosettes, trabeculae, palisading	Organoid nesting, rosettes, trabeculae, palisading
Mitotic rate	> 10 per 2 mm^2 (usually > 30, median 75)	> 10 per 2 mm^2 (median 60)
Necrosis	Frequent, often large zones	Frequent, often large zones
Cell size	Large, > 3 lymphocytes	Small, < 3 lymphocytes
Cytoplasm	Abundant	Scant
N:C ratio	High	Low
Chromatin	Vesicular or coarse	Fine granular
Nucleoli	Prominent	Absent or inconspicuous
Crush artifact	Absent or rare	Frequent

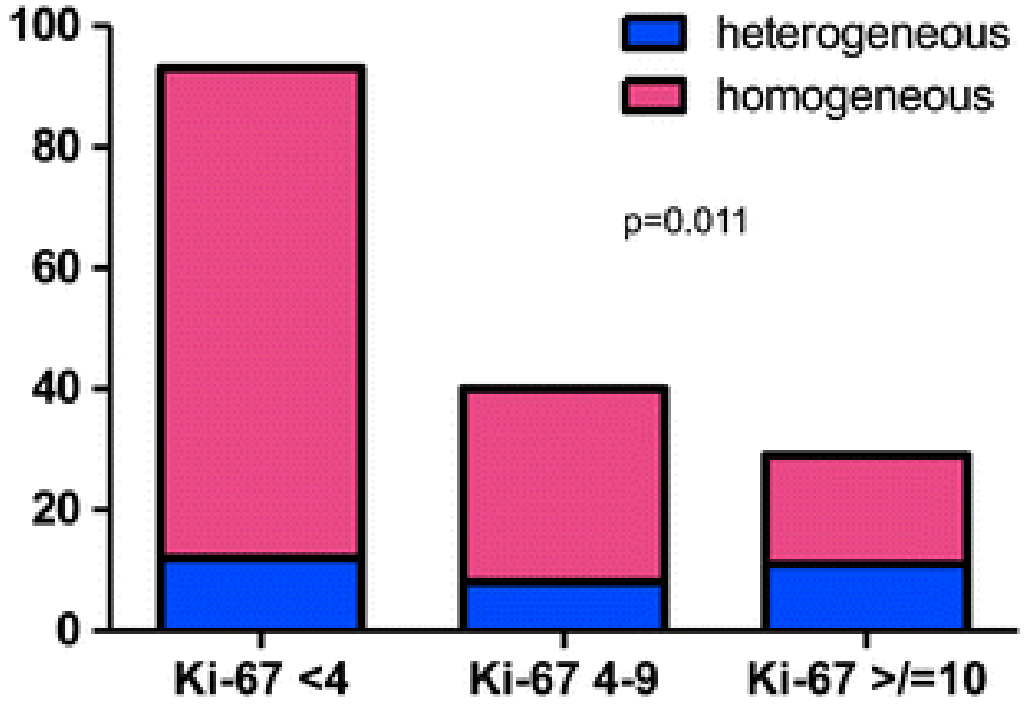
LCNEC vs SCLC

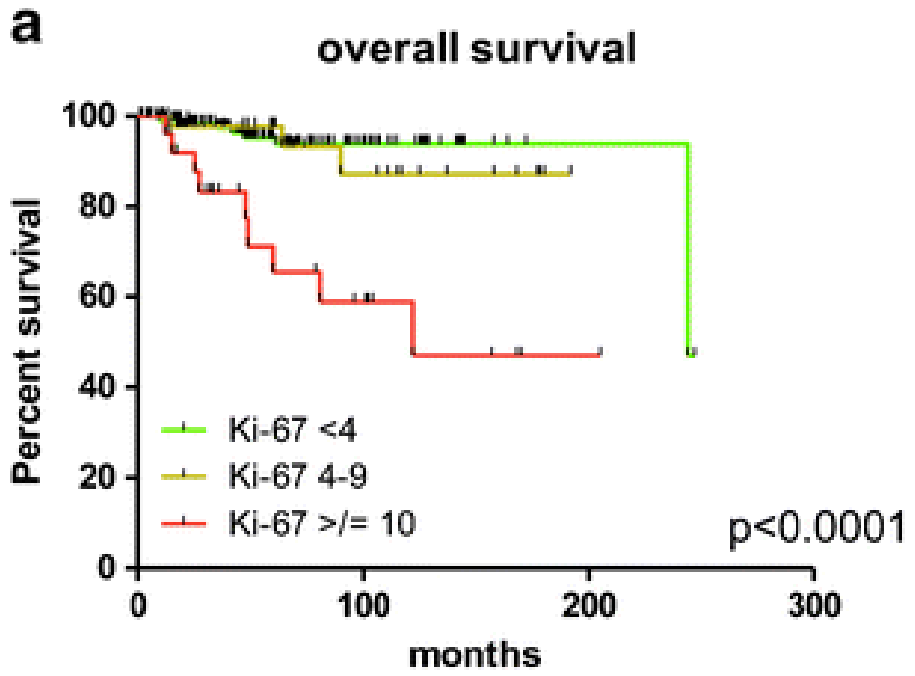
- Similar morphologic features: high mitotic rate and extensive necrosis
- Cell size:
  - Up to 30% of SCLC cases have predominant cell size >3 lymphocytes
  - Small cell size helps diagnosis of SCLC but large cell size does not reliably distinguish LCNEC vs. SCLC
- Cell morphology:
  - Cytoplasm, chromatin, nucleoli
- Regardless, there are still 5% of cases that are not difficult to classify and termed as high-grade neuroendocrine carcinoma

Atypical Carcinoid Tumor

- LCNEC: higher mitotic count/higher Ki-67 index, greater nuclear membrane irregularities, prominent nucleoli, and in most cases extensive necrosis
- Tumors with carcinoid morphology that qualify as LCNEC due to mitotic counts exceeding 10 mitoses/2 mm^2 – usually only mildly – occur rarely as lung primary tumors, but they are relatively common in the metastatic setting
- Emerging data suggest that such tumors have genomic and clinical characteristics similar to carcinoid tumors

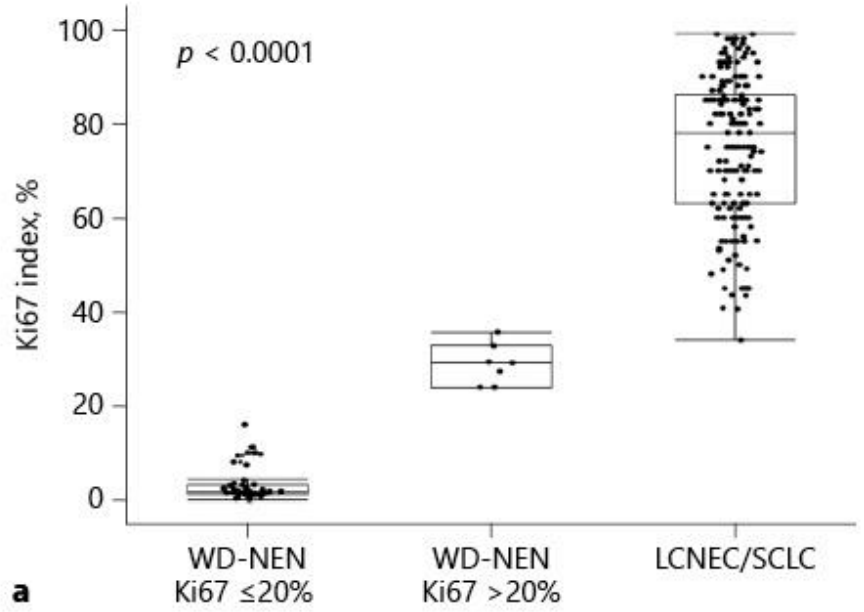
Lung Carcinoids with High Proliferation Index



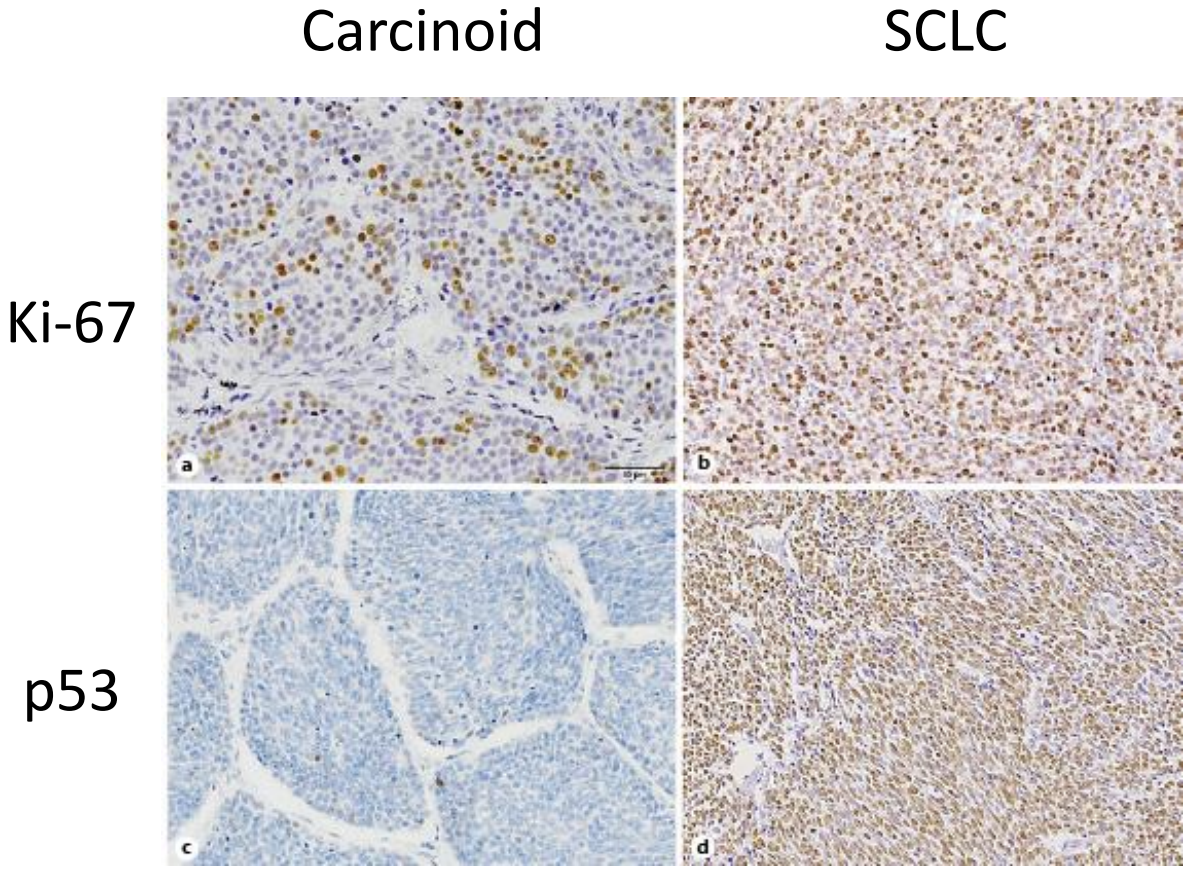


- Marchiò C, et al. Virchows Arch. 2017; 471(6):713-720.

Lung Carcinoids with Ki67 Index > 20%



All WD-NENs with Ki67 > 20% lacked abnormal p53 and loss of retinoblastoma 1 (Rb1) expression.



- Rekhtman N, et al. Mod Pathol. 2019; 32(8):1106-1122.

Carcinoids with Increased Proliferation Rate

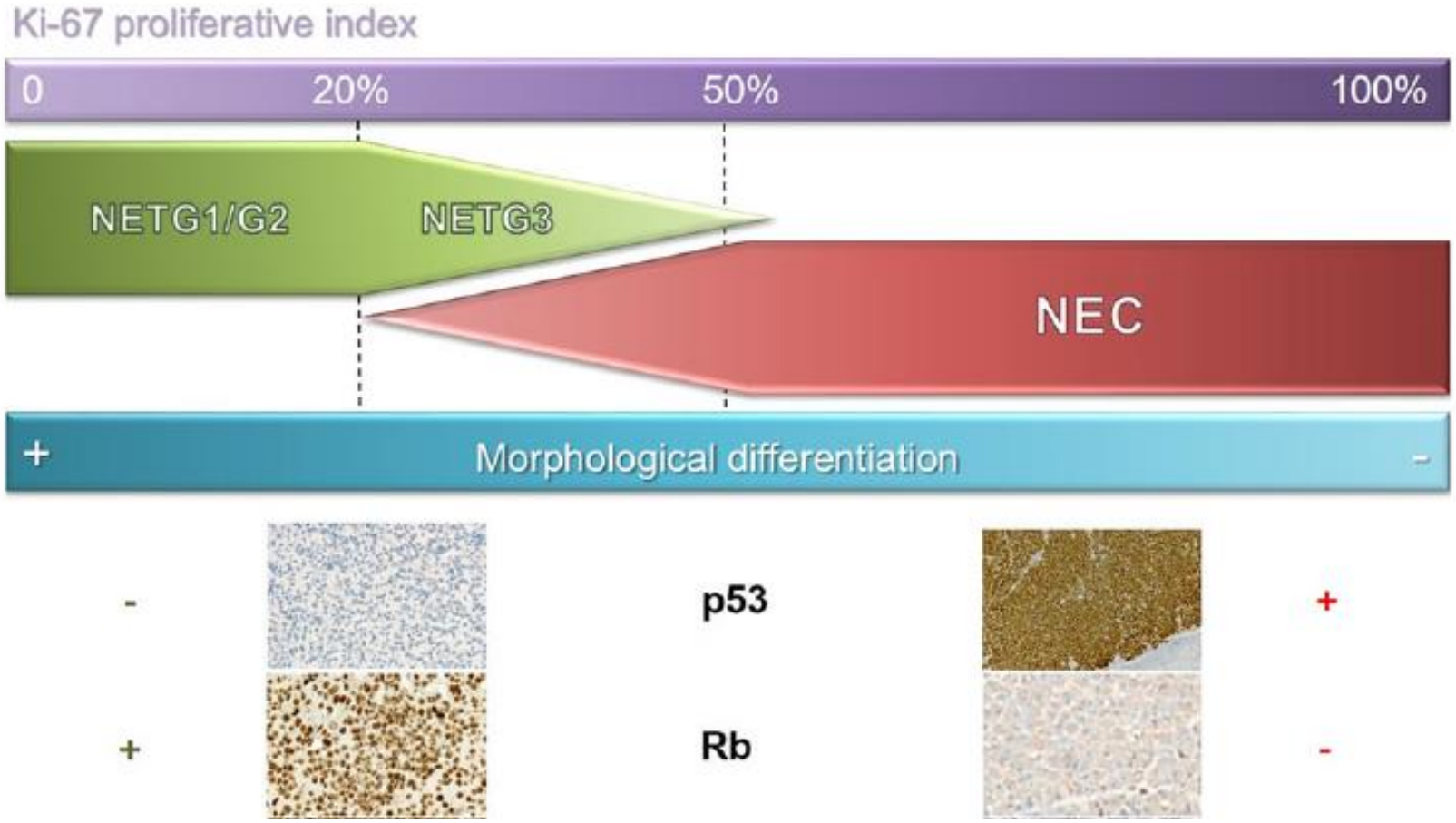
- In pancreas and other organ systems, NETs with typical morphology but higher mitotic counts (> 20 mitoses/2 mm^2) and/or a higher Ki-67 proliferation index than expected (> 20%) are regarded as G3 NETs.

- In lung, carcinoid tumors with typical morphology but higher mitotic counts (> 10 mitoses/2 mm^2) and/or a higher Ki-67 proliferation index than expected (> 30%) may currently be classified as large cell neuroendocrine carcinoma.

LCNEC vs Atypical Carcinoid

	LCNEC	AC
Growth pattern	Organoid nesting, rosettes, trabeculae, palisading	Organoid nesting, trabeculae
Mitotic rate	> 10 per 2 mm^2 (usually > 30, median 75)	< 10 per 2 mm^2
Necrosis	Frequent, often large zones	Focal, punctate
Cytoplasm	Abundant	Abundant
N:C ratio	Low	Low
Chromatin	Vesicular or coarse	Fine granular
Nucleoli	Prominent	Absent or inconspicuous

LCNEC vs Carcinoid Tumor



- *Uccella S, et al. Endocr Pathol 2018; 29:150-168.*

Lung Carcinoid Immunohistochemistry

- LMW cytokeratin positive but often lack reactivity to HMW cytokeratin.
- Neuroendocrine markers:
  - Chromogranin/Synaptophysin/ CD56/INSM1
- TTF-1 tends to positive in peripheral carcinoid.
- Ki-67 helps differentiating typical vs atypical carcinoid.
- ATRX, RB, p53 may help differential diagnosis from high-grade NEC.

- Prognostic/therapeutic markers
  - High coexpression of CD44 and nuclear OTP, mainly observed in TCs, was associated with a higher recurrence-free survival rate
  - Low CD44 and nuclear OTP expression and high RET expression were associated with a low 20-year survival rate.
  - Expression of SSTR2A could predict response to somatostatin analogue therapy.

➢ Papaxoinis G, et al. Endocr Pathol. 2017; 28(1):60-70.

➢ Swarts DR, et al. Clin Cancer Res. 2013; 19(8):2197-2207.

Take Home Messages

- Neuroendocrine neoplasms of the lung comprise of carcinoid, small cell lung carcinoma and large cell neuroendocrine carcinoma.
- Accurate cytologic diagnosis and precise classification of lung neuroendocrine neoplasms may be challenging:
  - Grading of carcinoid tumors
  - Separation of small cell carcinoma from large cell neuroendocrine carcinoma
- Ancillary tests are often needed in cytology specimens for diagnosis or differential diagnosis of lung neuroendocrine neoplasms.

Thank you

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