ES17: The new WHO classification of Lung tumours

Update on squamous cell carcinoma and neuroendocrine tumours of the lung

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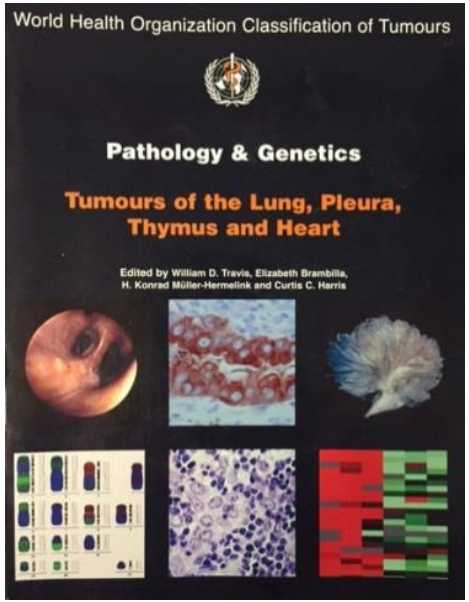
DISCLOSURES

Commercial Interest	Relationship(s)
Abbvie, Astra Zeneca	Advisory Board
UptoDate, European Society of Oncology	Educational activities

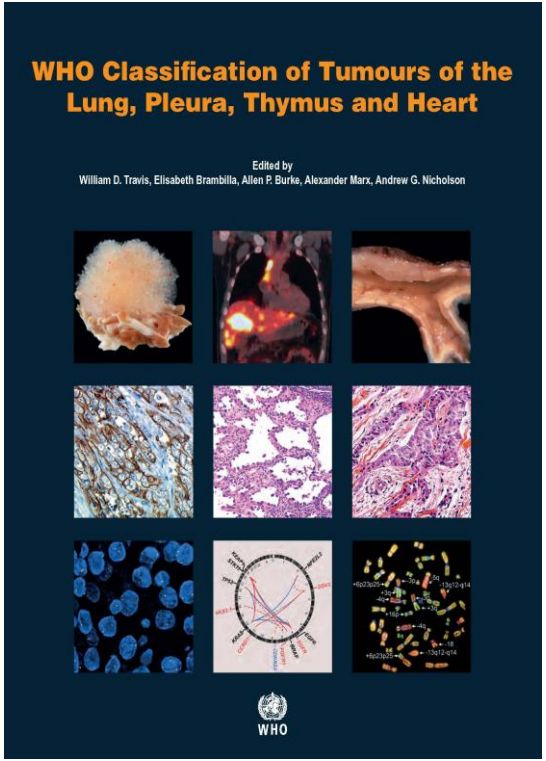
WHO CLASSIFICATION 2021

- A pathologic and genetic classification of human tumours designed to be accepted and used worldwide.

WHO classifications
1981
1999
2004
2015
2021



- Provides standard criteria for
  - *Pathology diagnosis*
  - *Clinical practice*
  - *Cancer registration*
  - *Epidemiologic studies*
  - *Clinical trials*
  - *Cancer research*



2015 WHO CLASSIFICATION OF NEUROENDOCRINE TUMOURS

- Small cell carcinoma
  - Combined SCLC
- Large cell neuroendocrine carcinoma
  - Combined LCNEC
- Carcinoid tumor
  - Typical carcinoid
  - Atypical carcinoid
- Pre-invasive lesion: Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)

A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Rindi G et al. *Mod Pathol.* 2018;31:1770-1786.

The classification of NETs differs between organ systems and currently causes considerable confusion. A uniform classification framework for NENs at any anatomical location may reduce inconsistencies and contradictions among the various systems currently in use.

Key feature of the new classification is a distinction between differentiated neuroendocrine tumors (NETs), also designated carcinoid tumors in some systems, and poorly differentiated NECs, as they both share common expression of neuroendocrine markers.

This dichotomous morphological subdivision into NETs and NECs is supported by genetic evidence at specific anatomic sites as well as clinical, epidemiologic, histologic, and prognostic differences.

In many organ systems, NETs are graded as G1, G2, or G3 based on mitotic count and/or Ki-67 labeling index, and/or the presence of necrosis;

NECs are considered high grade by definition.

A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Rindi G et al. *Mod Pathol.* 2018;31:1770-1786.

Site	Category	Family	Type	Grade	Current terminology
Lung	**Neuroendocrine neoplasm (NEN)**	**Neuroendocrine tumor (NET)**	**Pulmonary neuroendocrine tumor (NET)[a]**	**G1 G2**	**Carcinoid Atypical carcinoid[a]**
		Neuroendocrine carcinoma (NEC)	**Small cell lung carcinoma (Pulmonary NEC, small cell-type)[b]**		**Small cell lung carcinoma**
			Pulmonary NEC, large cell-type		**Large cell NE carcinoma**
Uterus (corpus and cervix)	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Uterine neuroendocrine tumor (NET)	G1 G2 G3	Carcinoid Atypical carcinoid Atypical carcinoid
		Neuroendocrine carcinoma (NEC)	Uterine NEC, small cell-type		Small cell carcinoma
			Uterine NEC, large cell-type		Large cell NE carcinoma
Pancreas	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Pancreatic neuroendocrine tumor (NET)	G1 G2 G3	PanNET G1 PanNET G2 PanNET G3
		Neuroendocrine carcinoma (NEC)	Pancreatic NEC, small cell-type		Small cell NE carcinoma
			Pancreatic NEC, large cell-type		Large cell NE carcinoma

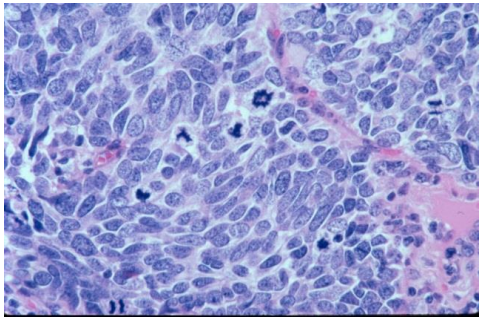
2021 WHO CLASSIFICATION OF LUNG NEUROENDOCRINE NEOPLASMS

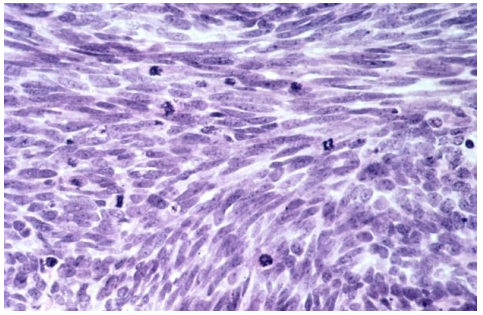
- Neuroendocrine carcinomas of the lung
  - Small cell carcinoma
    - Combined SCLC
  - Large cell neuroendocrine carcinoma
    - Combined LCNEC
- Neuroendocrine tumours of the lung
  - Carcinoid tumour/Neuroendocrine tumour of lung (NET)
    - Typical carcinoid
    - Atypical carcinoid
- Precursor lesion
  - Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)

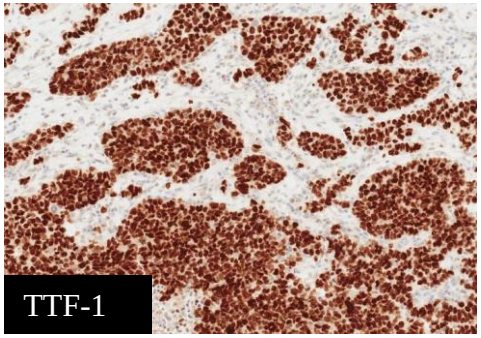
Neuroendocrine carcinomas of the lung

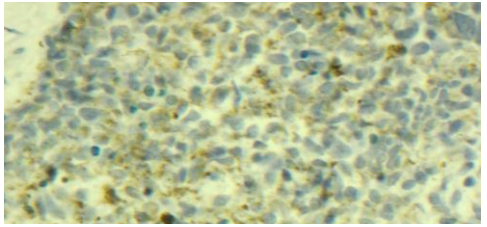
SMALL CELL LUNG CARCINOMA

- A malignant epithelial tumour composed of small cells with scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli, with a high mitotic count and frequent necrosis.
- Most SCLCs express neuroendocrine markers.
- Immunostains are of particular utility in excluding or confirming an alternate diagnosis.
- Up to 25% of SCLC are combined
- Increased recognition in the setting of acquired resistance to tyrosine kinase inhibitor therapy for adenocarcinoma with *EGFR* mutations.

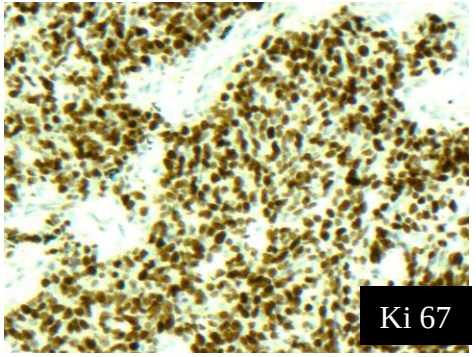


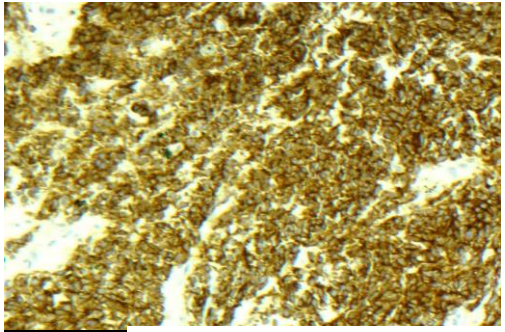






5% negative with HMWCK





CD56 <10% no reaction to NE markers

Neuroendocrine carcinomas of the lung

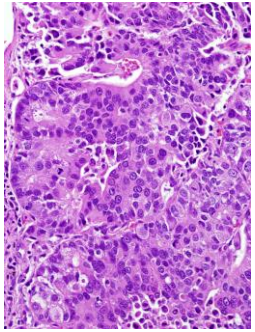
LARGE CELL NEUROEDOCRINE CARCINOMA

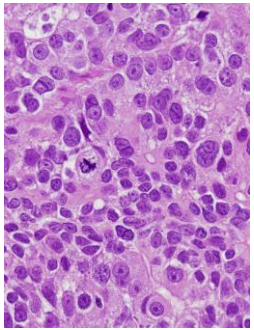
DIAGNOSTIC CRITERIA

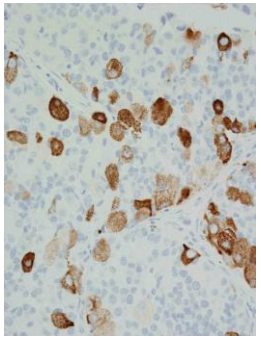
- NE Morphology: Organoid nesting, trabecular, palisading, rosette-like patterns
- Increased Mitoses (11 or more per $2mm^2$; Avg. 60)

- FEATURES OF A NON-SMALL CELL CARCINOMA
  - Large cell size (> diameter 3 lymphocytes)
  - Low N/C ratio (abundant cytoplasm)
  - Round to oval or polygonal shape
  - Nucleoli frequent and prominent (not every case)
  - Chromatin usually coarse or vesicular, may be finely granular

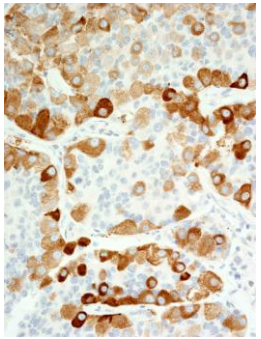
- NE Differentiation by immunohistochemistry (at least one NE marker staining >10% of the resected tumour)







CGA



SYN

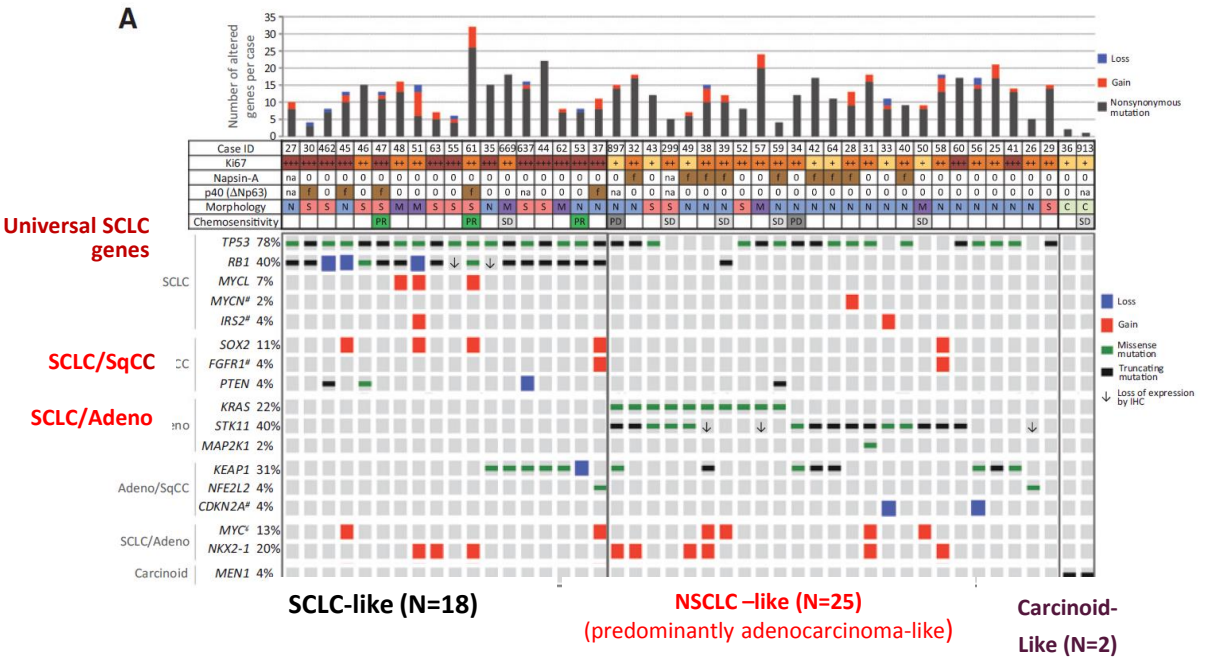
Slide courtesy of WD Travis

Neuroendocrine carcinomas of the lung

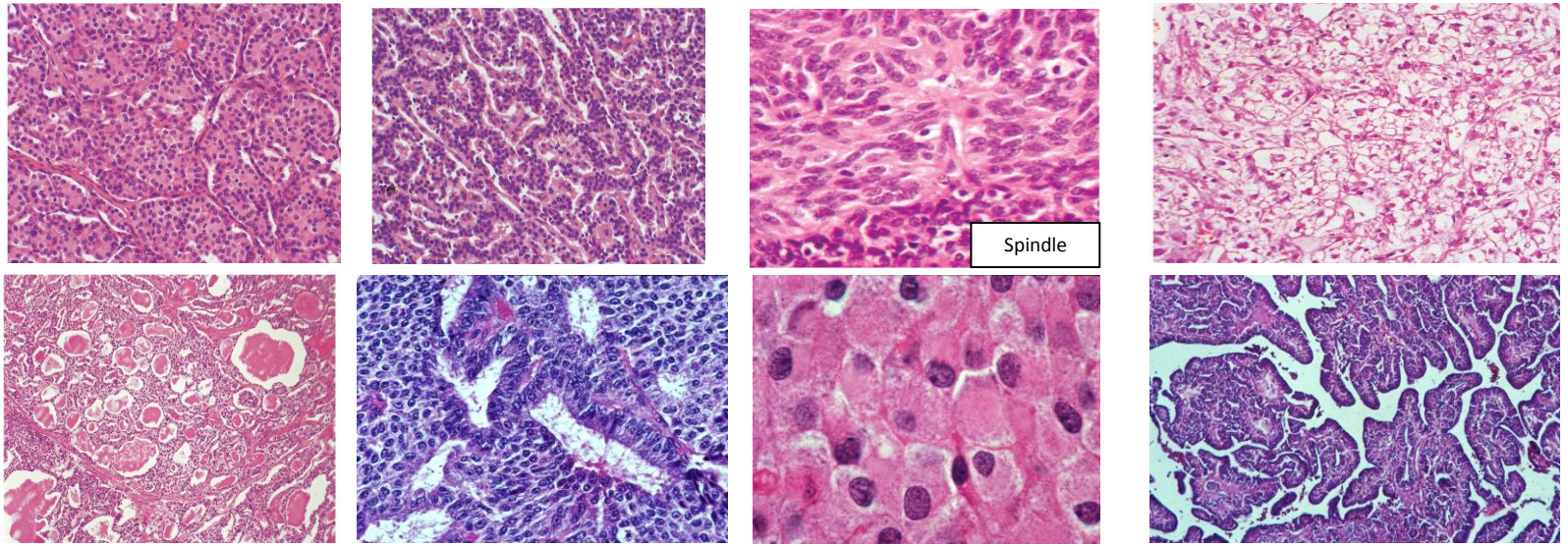
LCNEC – Molecular subdivisions

- Rekhtman N, Pietanza MC, Hellmann MD, et al. Next-Generation Sequencing of Pulmonary Large Cell Neuroendocrine Carcinoma Reveals Small Cell Carcinoma-like and Non-Small Cell Carcinoma-like Subsets. *Clin Cancer Res.* 2016;22(14):3618-3629.
- Miyoshi T, Umemura S, Matsumura Y, et al. Genomic Profiling of Large-Cell Neuroendocrine Carcinoma of the Lung. *Clin Cancer Res.* 2017;23(3):757-765.
- George J, Walter V, Peifer M, et al. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. Nat Commun. 2018;9(1):1048.
- Derks JL, Leblay N, Lantuejoul S, Dingemans AC, Speel EM, Fernandez-Cuesta L. New Insights into the Molecular Characteristics of Pulmonary Carcinoids and Large Cell Neuroendocrine Carcinomas, and the Impact on Their Clinical Management. J Thorac Oncol. 2018;13(6):752-766.

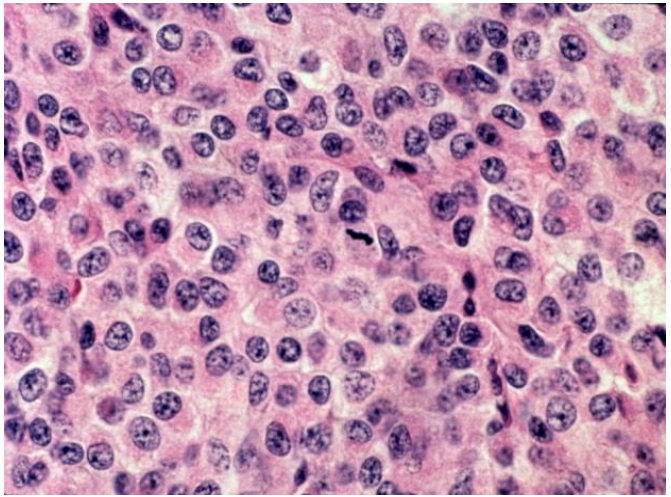
- High frequency of TP53 and RB1 inactivation has been identified
- Largely comprise two distinct genomic subsets.
  - SCLC-like genomic profile
  - NSCLC-like, similar to that found in adenocarcinoma
  - Transcriptomic analysis shows these subsets are distinct from SCLCs and NSCLCs

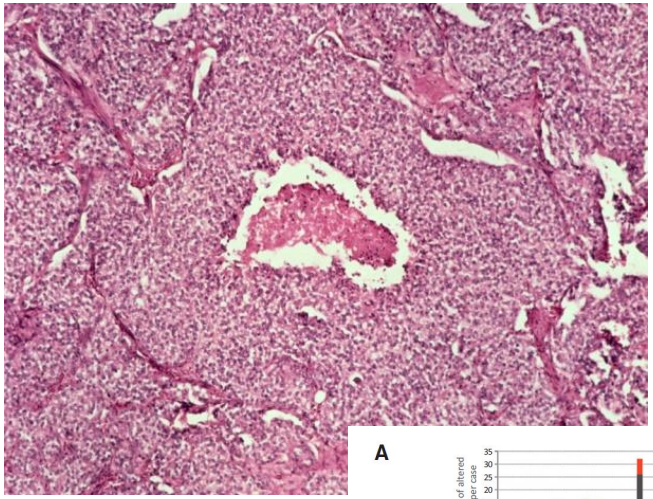


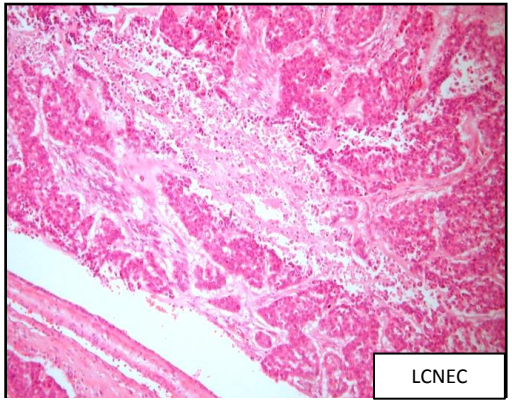
- Neuroendocrine tumours of the lung
- Carcinoid tumour/Neuroendocrine tumour of lung (NET)
  - Typical carcinoid
  - Atypical carcinoid
- NE tumours by definition >5mm
- Divided into typical and atypical on basis of mitotic count (+/- Ki-67) and/or necrosis



Atypical carcinoid

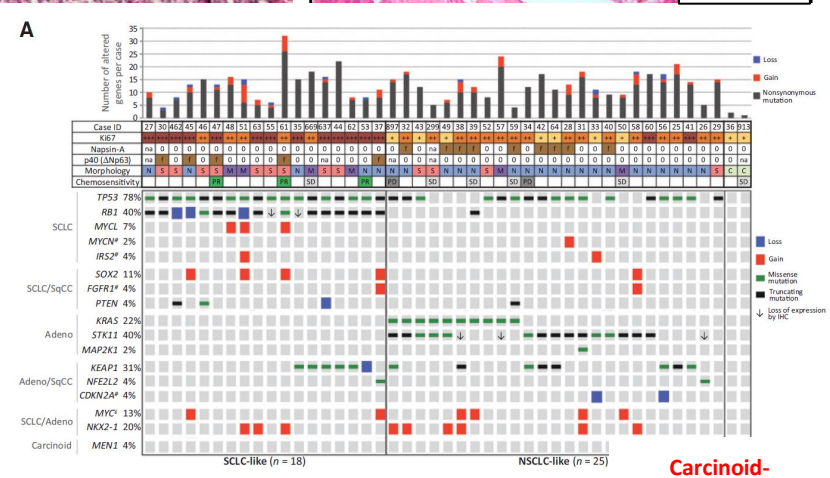






? further subdivision into 2-5 and 6-10 per 2mm^2

? Should there be a grade 3 NET (>10 per 2mm^2) but with CD-like morphology



Carcinoid-Like (N=2)

Pulmonary carcinoid tumours with elevated proliferation rates - should there be a grade 3 subgroup of neuroendocrine tumours (NET)?

Wright J et al. Presented at IAP-ESP meeting, December 2020

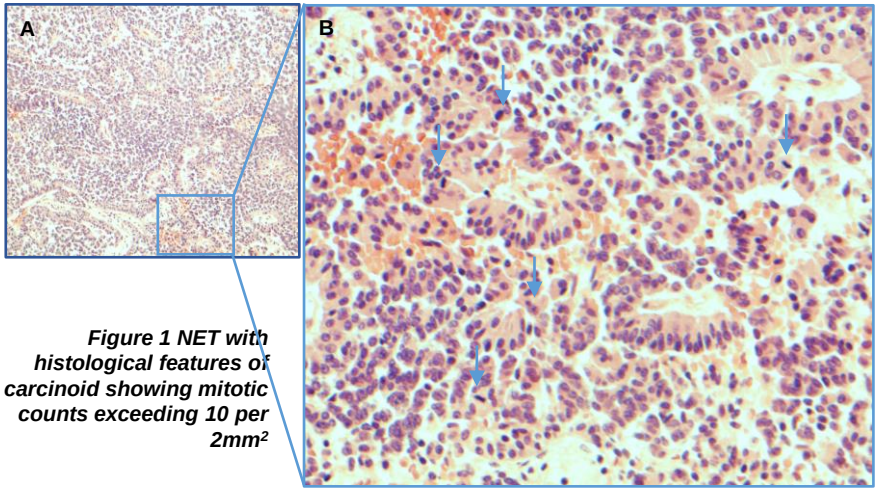


Figure 1 NET with histological features of carcinoid showing mitotic counts exceeding 10 per 2mm²

A: Low power image taken at x10 magnification
B: High power image taken at x40 magnification; five mitotic figures are present in one x40 microscopic field as indicated by the blue arrows. It is noted that mitotic counts should be evaluated over an area of 2mm²

Results

Of the 50 cases reviewed, 14 cases (28%) showed histological features of carcinoids but mitotic counts exceeding 10 per 2 mm². Three cases showed combined AC and LCNEC morphology and one case showed combined AC and SCC morphology. In all included cases, the highest mitotic count was >10 per 2mm². The median highest mitotic count was 19 (IQR 15.5-31.0). In eight

Conclusion

A subgroup of NETs exists with morphology closer to carcinoid than non-small cell carcinoma, but with a raised proliferation rate >10 per 2 mm². These may be better classified in alignment with carcinoids than LCNEC.

Multiple faces of pulmonary large cell neuroendocrine carcinoma: update with a focus on practical approach to diagnosis. Baine MK, Rekhtman N. Transl Lung Cancer Res. 2020;9:860-878.

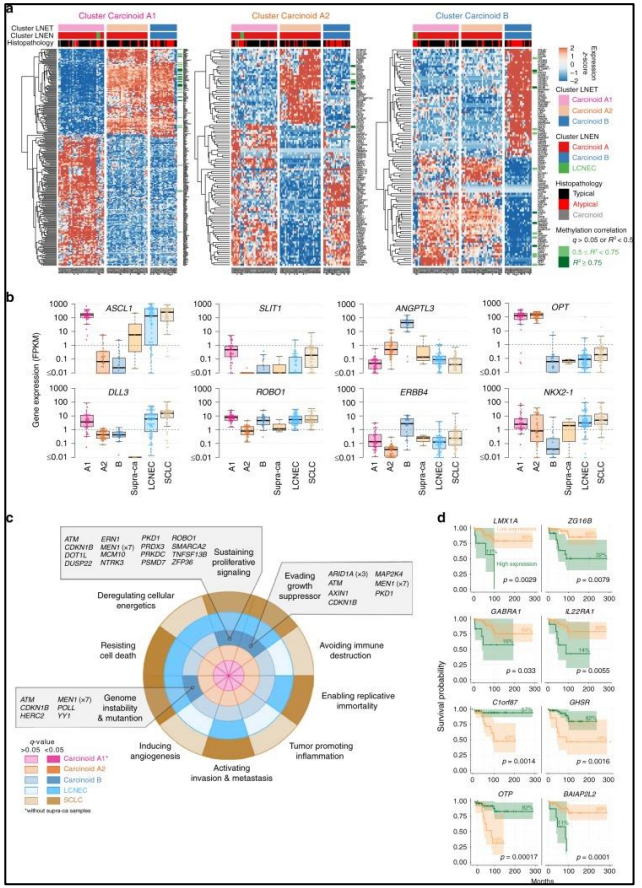
High-grade Neuroendocrine Carcinoma of the Lung With Carcinoid Morphology: A Study of 12 Cases. Quinn AM et al. Am J Surg Pathol. 2017;41:263-270.

Currently - classify these as LCNEC but to note carcinoid-like morphology and the mitotic rate/proliferation index.

Neuroendocrine tumours of the lung

Carcinoids – Molecular subdivisions

- Low mutation rates
- Recent publications have identified 3 molecular cell subgroups.
- Cluster A1 is mainly TCs and shows over-expression of *ASCL1* and *DLL3*.
- Cluster A2 is mainly TCs and show down regulation of *ROBO1* and *SLIT1* genes, along with somatic EIF1AX mutations and expression of *HNF1a* and *FOXA3*.
- Cluster B contains more ACs and is characterised by somatic *MEN1* mutations., again with expression of *HNF1a* and *FOXA3*.



Molecular groups of pulmonary carcinoids (from Alcala N et al).

Laddha SV, da Silva EM, Robzyk K, et al. Integrative Genomic Characterization Identifies Molecular Subtypes of Lung Carcinoids. Cancer Res. 2019;79(17):4339-4347.

Alcala N, Leblay N, Gabriel AAG, et al. Integrative and comparative genomic analyses identify clinically relevant pulmonary carcinoid groups and unveil the supra-carcinoids. Nat Commun. 2019;10(1):3407.

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) Available Literature (n>4).

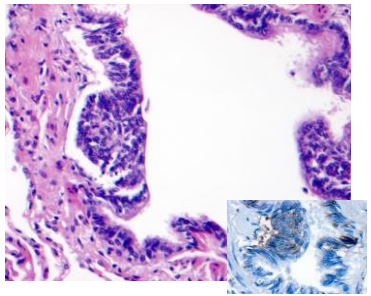
Aguayo et al	6	6 0	1/4/1	5/1/0	NECH+/−tumorlet +/−carcinoids
Lee et al	5	5 0	0/3/2	3/5/5	NECH+/−tumorlet +/−carcinoids
Davies et al	19	9 10	5/8/4	18/5/5	NECH+/−tumorlet +/−CB
Aubry et al	28	19 9	6/16/0	26/1/1	NECH+/−tumorlet +/−carcinoids
Gosney et al	7	4 3	7/NA/NA		NECH+/−carcinoids +/−CB
Gorshtein et al	11	6 5	2/7/NA	11/0/0	NECH
Marchevsky et al	30	22 8	7/4/2	28/0/0	NECH+/−tumorlet +/−carcinoids
Carr et al	30	30 0	0/26/4	26/25/21	NECH+/−tumorlet +/−carcinoids+/− CB
Chauhan and Ramirez	5	5 0	5/0/0		NECH+/−carcinoids
Baniak et al	6	6 0	NA/3/NA	4/NA/NA	NECH+/−tumorlet +/−carcinoids
Trisolini et al	13	7 6	2/4/1	7/0/7	NECH+/−tumorlet +/−carcinoids+/− C

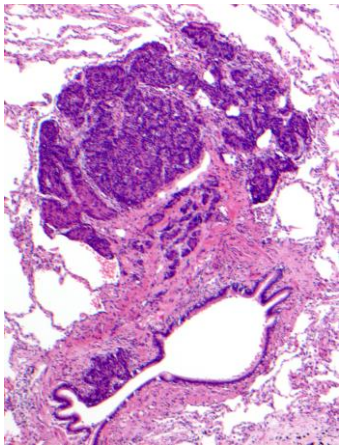
Mengoli MC et al. *AJSP* 2018;42:646-655

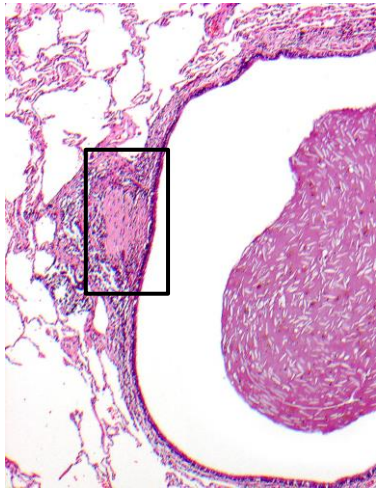
Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) Syndrome and Carcinoid Tumors With/Without NECH

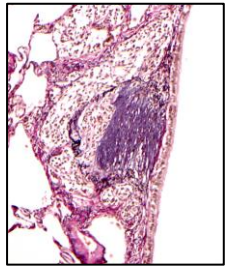
A Clinicopathologic, Radiologic, and Immunomolecular Comparison Study

Mengoli MC et al. *AJSP* 2018;42:646-655









151 cases (77F:74M), 19 with DIPNECH and 132 with carcinoids with/without NECH.

Patients with DIPNECH were more likely to be female individuals (P<0.0001), nonsmokers, (P=0.021), and symptomatic, and to have an obstructive/mixed respiratory defect, peripheral location of the lesions, and air trapping (P<0.0001) on CT and constrictive bronchiolitis on histology (P<0.0001).

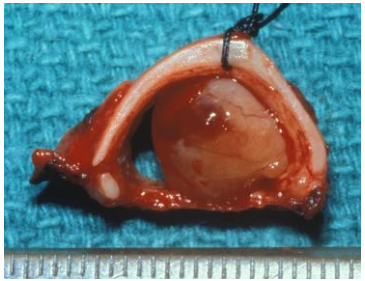
When limited to a purely histopathologic definition of DIPNECH, 40% of isolated carcinoids met diagnostic criteria for DIPNECH.

Associated with type 1MEN syndrome

Proposal: The term DIPNECH is limited to cases presenting with respiratory symptoms, functional and/or radiologic abnormalities, and OB on histology.

Frequency of NEH in patients with resected carcinoid tumours

	CD	Typical	Atypical	LCNEC	Central TC	Peripheral TC
Miller RR et al AJSP 1995;19:653-8	-	-	-	-	-	76
Rizvi SM et al. Histopathology. 2009 55:332-7.		46	36	39	43	62
Mengoli et al AJSP 2018; 42:646-655	68	61	8	-	15	96



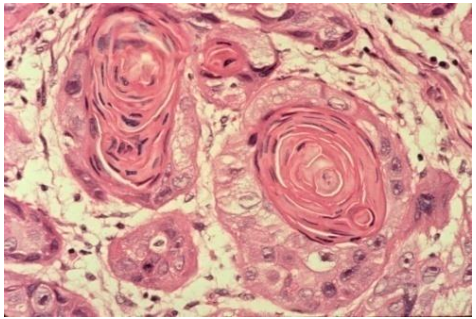
Colby TV, Koss MN, Travis WD: Tumors Lower Resp Tract, 1995

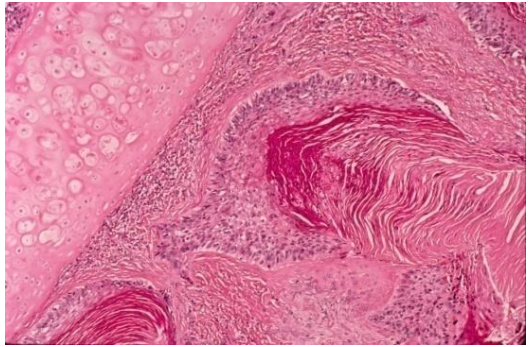
OTP and TTF-1 +ve associated with DIPNECH, peripheral location and spindle morphology
… 3 clusters with OTP/TTF-1 -ve more aggressive

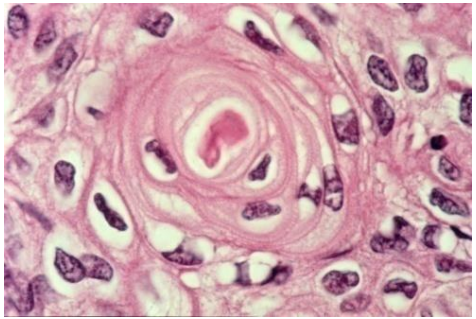
*Clinical and Pathologic Characteristics of Pulmonary Carcinoid Tumors in Central and Peripheral Locations. Papaxoinis G et al Endocr Pathol. 2018 29:259-268

SQUAMOUS CELL CARCINOMA (SQCC)

"A malignant epithelial tumour showing keratinization and/or intercellular bridges, or immunohistochemical markers of squamous cell differentiation.





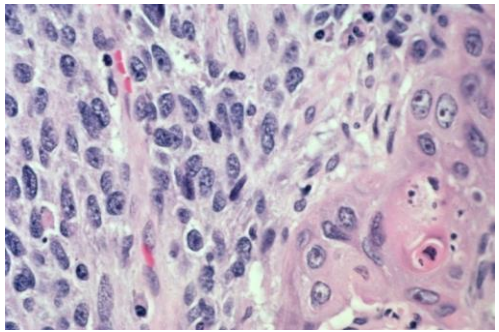


- THE REQUIREMENTS OF A CLASSIFICATION SYSTEM...
  - REPRODUCIBLE (strict and recognisable set of criteria…)
  - GLOBALLY APPLICABLE (…that everyone can apply…)
  - THOROUGH (…which can deal with atypical variants…
  - DYNAMIC (…adapts to recent advances) (CAN BECOME SIMPLER)

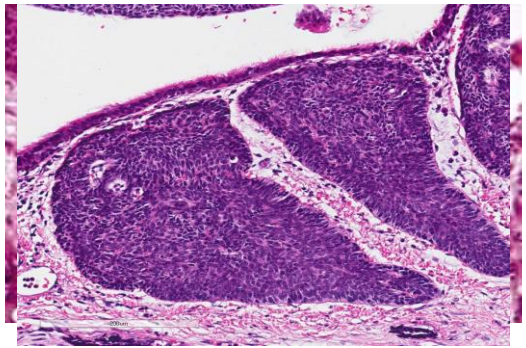
Images from WHO 2004 and 2015

Squamous cell carcinoma (WHO 2004)

- **Squamous cell carcinoma; variants:**
  - Papillary
  - Clear cell
  - Small cell
  - Basaloid



- **Adenosquamous carcinoma**

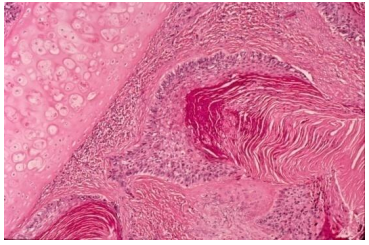


- **Large cell carcinoma:**
  - Basaloid carcinoma subtype

- **Pre-invasive lesions**:
  - Squamous cell carcinoma in situ

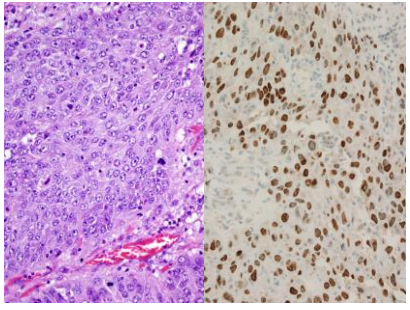
2015 WHO CLASSIFICATION
SQUAMOUS CELL CARCINOMA

- Keratinizing



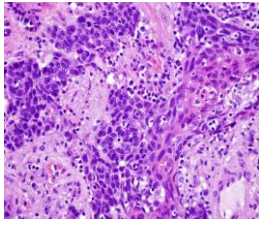
- Non-keratinizing

now need IHC –
P40 positive,
TTF-1 negative



- Basaloid carcinoma

now need IHC –
(+p40, -TTF-1 & NE markers)
r/o LCNEC & SCLC



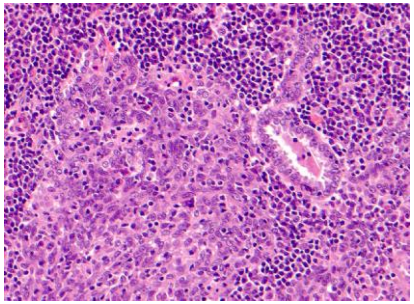
2021 WHO CLASSIFICATION

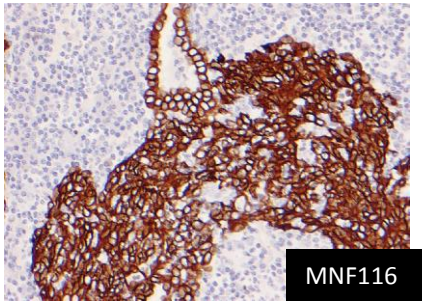
SQUAMOUS CELL CARCINOMA

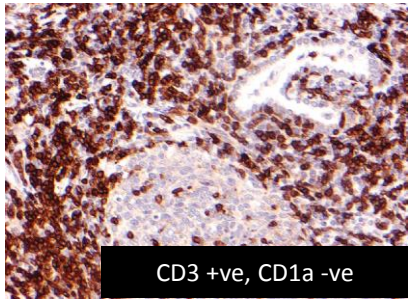
- Squamous precursor lesions
  - Squamous dysplasia and carcinoma in situ of the lung
- Squamous cell carcinomas
  - Squamous cell carcinoma of the lung
    - Basaloid variant of SQCC (if >50% of tumour shows basaloid features
  - Lymphoepithelial carcinoma of the lung

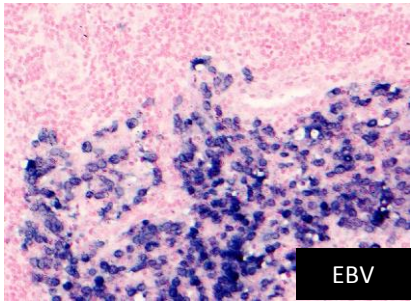
Lymphoepithelial carcinoma

- Poorly differentiated squamous cell carcinoma (SCC) admixed with variable amounts of lymphocytic infiltrate, frequently associated with EBV.
- > 90% of cases occurring in Asian patients, though lower rate in Europeans
- Survival better than for conventional NSCLCs









- **NUT carcinoma of the thorax**

- Poorly differentiated carcinoma
- Genetically defined by the presence of nuclear protein in testis (NUTM1) gene rearrangement.

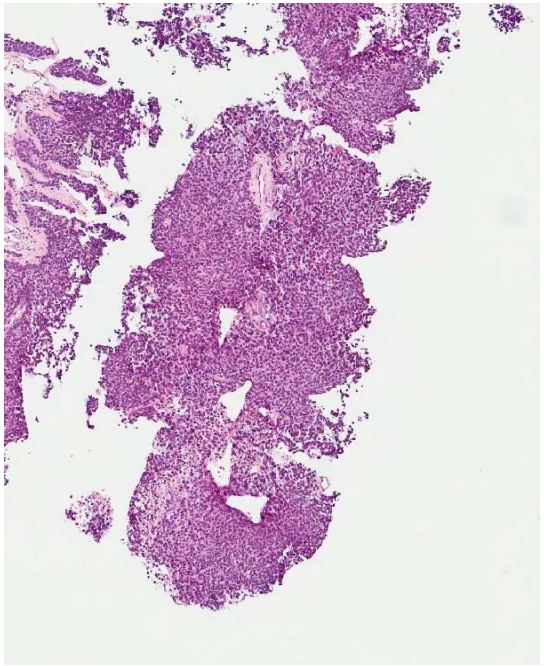
- Young adults and children

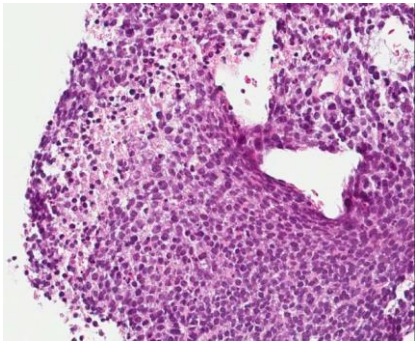
- P40/63 and CK positive

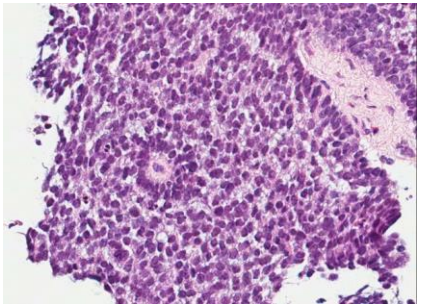
- NUT (Nuclear protein of the testis)-IHC and NUT-FISH to confirm diagnosis

- Very aggressive tumour, especially when intra-thoracic

- Drugs targeting BRD4 (of BET proteins (bromodomain and extra-terminal domain) in clinical trials.







TAKE HOME MESSAGE

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LUNG NEUROENDOCRINE NEOPLASMS

- Neuroendocrine carcinomas of the lung
  - Small cell carcinoma
  - Large cell neuroendocrine carcinoma
- Neuroendocrine tumours of the lung
  - Carcinoid tumour/Neuroendocrine tumour of lung (NET)
    - Typical carcinoid
    - Atypical carcinoid
- Precursor lesion
  - Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)

Structural changes for greater consistency (NENs at other sites)

Histopathological definitions remain largely the same

Significant advances in molecular subgroupings for NENs