# The WHO Classification of Lung Tumours 5th edition What's New?


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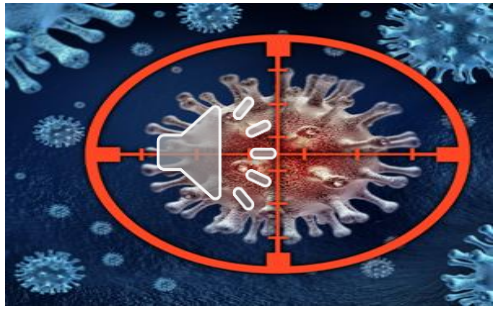

# WHO - 5th edition
# Classification of Tumours of the Lung

- The principles remain those of using morphology first, supported by immunohistochemistry, and then molecular techniques.
- In 2015, there was particular emphasis on using immunohistochemistry to make classification more accurate.
- In 2021, there is greater emphasis on advances in molecular pathology across all tumour types.
- Improved stratification of patient survival has also been revealed by using the 8th edition of the TNM staging classification for non mucinous adenocarcinomas (only the invasive size is used for T-factor size).
- As compared to the previous edition published in 2015, few new tumor types have been added to the 2021 classification; these are all low incidence tumors

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(1) Broader emphasis on genetic testing than in the 2015 WHO Classification;

(2) A section entirely dedicated to the classification of small diagnostic samples;

# Molecular Pathology of Adenocarcinoma

| Gene Altered | East Asia (%) | USA/Europe (%) |
|---|---|---|
| EGFR | 40–59 | 5–19.4 |
| ALK | 3–7 | 3–6 |
| ROS1 | 1–3 | 1–2 |
| ERRB2 | 2–3 | 2–3 |
| RET | 1–2.2 | 1–2 |
| BRAF V600E | 0.5–1 | 2–3 |
| Met ex14 | 2 | 3 |
| NTRK1/2/3 | <1 | 0.23 |
| KRAS | 7.4–11 | 20–30 |
| NRAS | 0.4 | 1.2 |
| MAP2K1 | <2 | 0.7 |
| TP53 | 36 | 42 |

# EGFR Mutation In 2 Lebanese Studies

Cancer Epidemiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

## EGFR mutation status in Middle Eastern patients with non-squamous non-small cell lung carcinoma: A single institution experience

Samah Naderi[a], Claude Ghorra[a], Fady Haddad[b], Hampig Raphael Kourie[b], Marc Rassy[a,*], Fadi El Karak[b], Marwan Ghosn[b], Gérard Abadjian[a], Joseph Kattan[b]

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**25 Positive Patients out of 201**

| Characteristics | | EGFR mutated patients, % (N) |
|---|---|---|
| Gender | Male | 33.3 (8) |
| | Female | 66.7 (16) |
| Smoking status | Smoker | 33.3 (8) |
| | Never-smoker | 66.7 (16) |

ONCOLOGY REPORTS 32: 2223-2229, 2014

## Epidermal growth factor receptor and *KRAS* mutations in lung adenocarcinoma: A retrospective study of the Lebanese population

NAJLA FAKHRUDDIN[1,3], RAMI MAHFOUZ[1], FADI FARHAT[4], ARAFAT TFAYLI[2], RABAB ABDELKHALIK[1], MARK JABBOUR[1], LAMIS YEHIA[6], ZIYAD MAHFOUD[5] and GHAZI ZAATARI[1]

**9 Positive Patients out of 106**

Table IV. Summary of the *EGFR* and *KRAS* mutations in primary adenocarcinoma.

| | Mutations | | |
|---|---|---|---|
| | *EGFR* n (%) | *KRAS* n (%) | Total n (%) |
| Cases | 9 (8.5) | 40 (37.7) | 49 (45.2) |

*KRAS*, Kirsten rat sarcoma viral oncogene; *EGFR*, epidermal growth factor receptor.

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- Testing of EGFR, ALK, ROS1, BRAF, and PD-L1 is recommended in the CAP/IASLC/ AMP/ ASCO, and ESMO guidelines;
- Simultaneous testing is encouraged to reduce the time between diagnostic testing and treatment.
- Unlike genomic driver alterations which should be present in all tumor cells, PD-L1 protein expression by IHC is often heterogeneous within a tumor, and it could be dynamic and influenced by previous treatment.
- In NSCLC, with a few exceptions, only the expression of PD-L1 on tumor cells is relevant as a predictive biomarker for immune checkpoint inhibitor (ICI) therapy (TPS : tumor proportion score; percentage of positive cells expressing membrane staining).

# Small Diagnostic Samples

- Knowing that 70% of lung cancers present in advanced stages and are unresectable, the diagnosis of these patients will be based primarily on small biopsy and cytology specimens.
- On these small samples we have to reach an accurate diagnosis, including specific histologic typing of non small cell carcinoma (NSCC) using ancillary techniques, such as immunohistochemistry, and allow the molecular testing.
- To spare enough tissue for molecular testing, it is recommended to use only a limited panel of immunohistochemical markers as well as mucin stains to diagnose and subtype NSCC.

# Current guidelines for NSCLC routine testing

To reach an accurate diagnosis, are needed :

- ✓A pre established **Workflow** for managing small biopsy samples is needed as well as a **multidisciplinary** strategy

- ✓A specific classification for lung cancer in small diagnostic samples which has been adopted in the 2015 WHO Classification and maintained in the 5th edition.

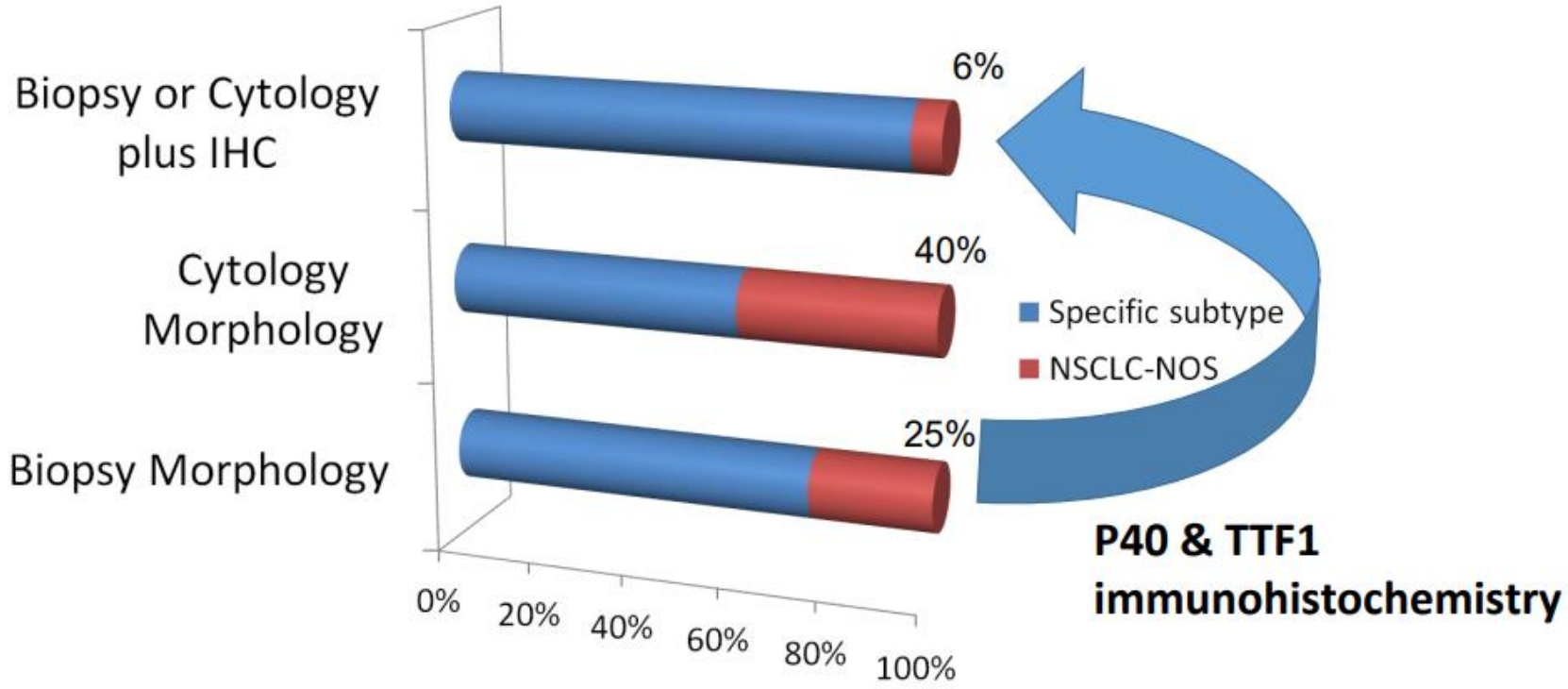
# Guidelines for Good Practice of Small Biopsies and Cytologic Preparations

1. For small biopsies and cytology, NSCC should be further classified into a more specific type, such as ADC or SQCC, whenever possible.

2. The term “non-small cell lung carcinoma-NOS (NSCLC-NOS)” should be used as little as possible (<10%).

3. In the final report, it should be clarified whether the diagnosis was established on the basis of light microscopy alone or if special stains were required.

# Small biopsy/Cytology: Thresholds of "certainty"




- Predictive IHC has 'levelled the playing field'
- Better diagnosis possible on poorer specimens

Loo PS et al, JTO 2010

# Guidelines for Good Practice of Small Biopsies and Cytologic Preparations

4. The terms AIS, minimally invasive ADC, Sarcomatoid Carcinoma and large cell carcinoma should not be used for diagnosis in small biopsy or cytology specimens and should be restricted to resection specimens where the tumor is **thoroughly sampled to exclude a differentiated component.**

5. In biopsies of tumors that reveal sarcomatoid appearance without any feature favoring ADC or SQCC, a comment on the sarcomatoid features should be precised.

| Morphology/Stains | Terminology for Small Biopsies and Cytology Specimens | Terminology for Resection Specimens |
|---|---|---|
| Morphologic squamous cell patterns clearly present | Squamous cell carcinoma | Squamous cell carcinoma |
| Morphologic adenocarcinoma patterns clearly present | | |
| | Adenocarcinoma (list the patterns in the diagnosis) | Adenocarcinoma, Invasive non mucinous<br><br>Predominant pattern : Lepidic Acinar/Papillary/Solid Micropapillary |
| | Adenocarcinoma with lepidic pattern (if pure, list the DD and add a comment that an invasive component cannot be excluded) → | Minimally invasive adenocarcinoma, Adenocarcinoma in situ, or Invasive adenocarcinoma with a lepidic component |
| | Invasive mucinous adenocarcinoma (list the patterns)<br>Mucinous adenocarcinoma with lepidic pattern (if pure lepidic pattern list the DD and add a comment that an invasive component cannot be excluded → | Invasive mucinous adenocarcinoma<br>Minimally invasive adenocarcinoma or adenocarcinoma in situ, mucinous type |

| Morphology/Stains | Terminology for Small Biopsies and Cytology Specimens | Terminology for Resection Specimens |
|---|---|---|
| | Adenocarcinoma with colloid features | Colloid adenocarcinoma |
| | Adenocarcinoma with fetal features | Fetal adenocarcinoma |
| | Adenocarcinoma with enteric features | Enteric adenocarcinoma |
| Morphologic squamous cell patterns not present, but supported by stains (i.e., p40+) | Non small cell carcinoma, favor squamous cell carcinoma | Squamous cell carcinoma (nonkeratinizing pattern may be a component of the tumor) |
| Morphologic adenocarcinoma patterns not present, but supported by special stains (i.e., TTF1+) | Non small cell carcinoma, favor adenocarcinoma | Adenocarcinoma (solid pattern may be just one component of the tumor) |
| No clear adenocarcinoma, squamous, or neuroendocrine morphology or staining pattern | Non small cell carcinoma NOS | Large cell carcinoma |

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(1) Broader emphasis on genetic testing than in the 2015 WHO Classification;

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**(3) Continued recommendation to document percentages of histologic patterns in invasive non mucinous adenocarcinomas.**

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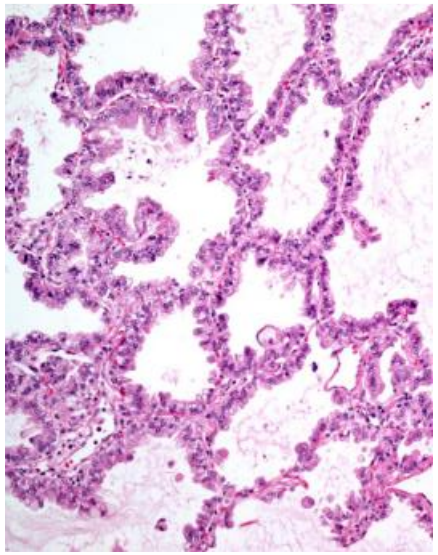
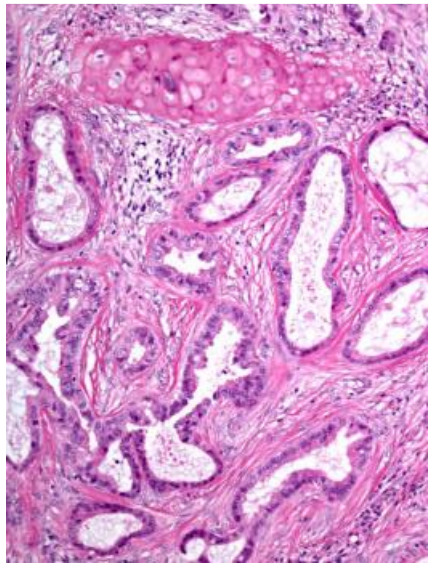
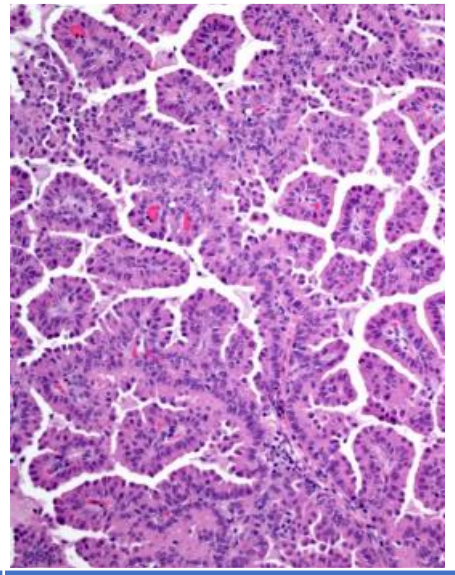
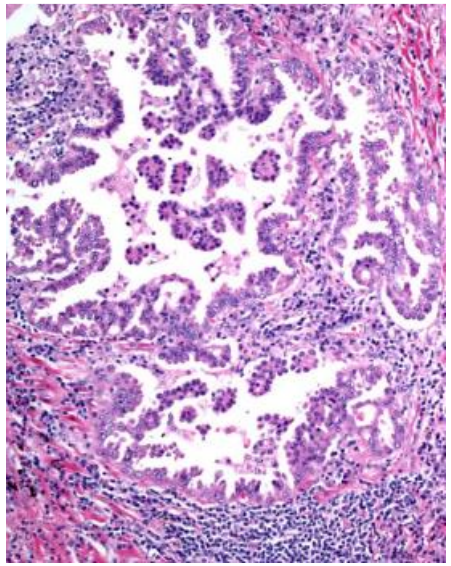
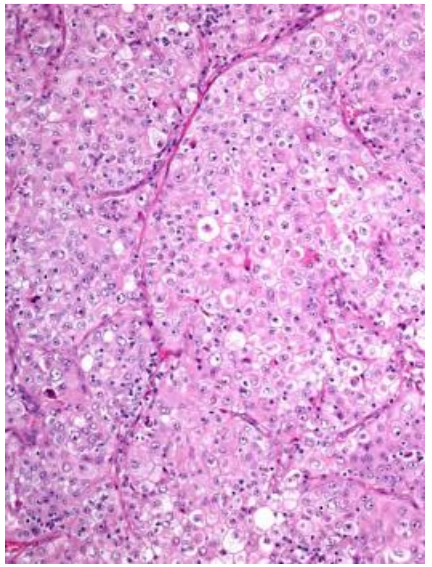
Subtyping invasive non-mucinous adenocarcinoma based on the predominant histological pattern is now standard.

| Lepidic pattern | Acinar pattern | Papillary Pattern | Micropapillary Pattern | Solid pattern G3 (Mucin and TTF1) |
|---|---|---|---|---|
|  |  |  |  |  |
| Grade 1<br>Better Prognosis | Grade 2<br>Intermediate prognosis | Grade 2<br>Intermediate prognosis | Grade 3<br>Poor prognosis | Grade 3<br>Poor prognosis |

# Grading of Invasive Nonmucinous Adenocarcinomas

In a study by the IASLC Pathology Committee, it was found that the presence of 20% or more of high-grade patterns (Solid, micropapillary and complex gland) on top of the primary pattern, can increase the risk of recurrence or death.

| Proposed IASLC Grading of Invasive Nonmucinous Adenocarcinomas | |
|---|---|
| Grade 1 (well differentiated) | Lepidic predominant with no or <20% high-grade pattern |
| Grade 2 (moderately differentiated) | Acinar or papillary predominant with no or <20% high-grade pattern |
| Grade 3 (poorly differentiated) | ✓ **Micropapillary, solid, cribriform, and complex glandular patterns**<br>✓ Or Any tumor with ≥ 20% high-grade pattern |

# Grading of Invasive Nonmucinous Adenocarcinomas

- The proposed IASLC grading system could accurately stratify prognosis and predict mediastinal nodal metastasis in patients with clinical stage I.
- This grading system appears to improve the stratification of the prognosis of early-stage non-mucinous adenocarcinoma patients compared to predominant pattern-based prognostication alone.
- Furthermore, the IASLC Grading System may possibly increase the percentage of patients (with grade 3 tumors) who might potentially benefit from adjuvant chemotherapy, although this requires additional supporting data.

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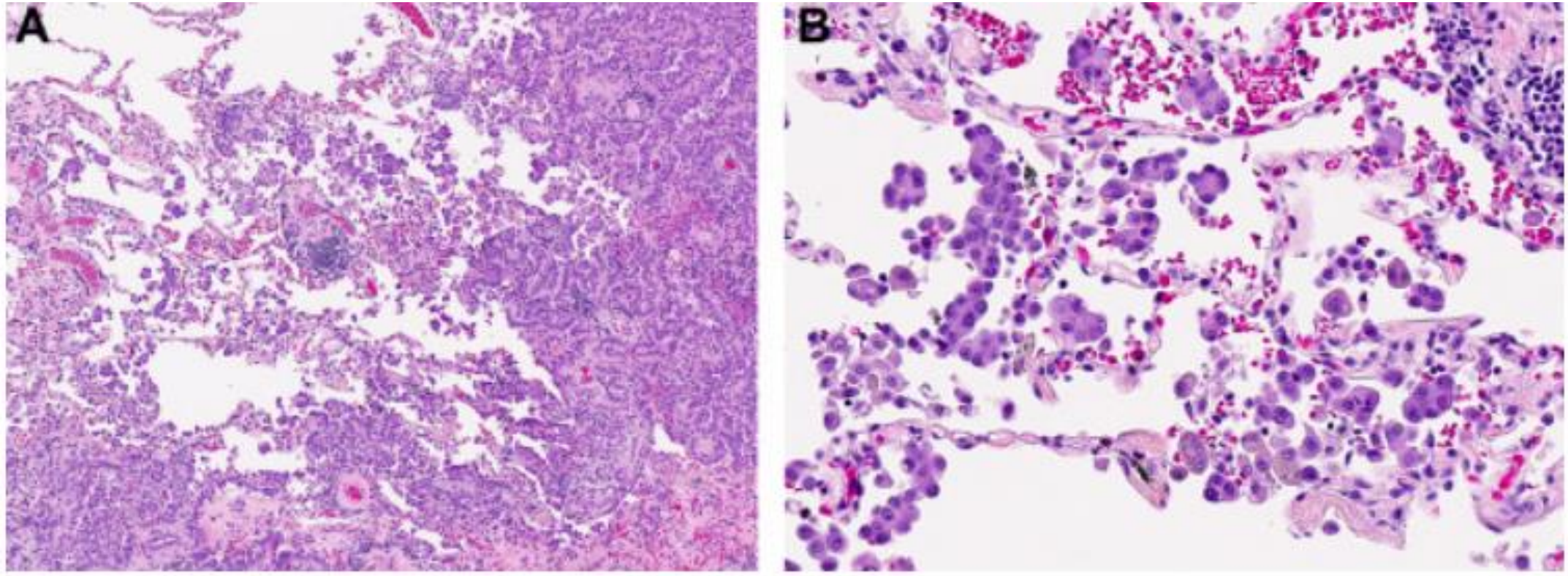
**(4) Recognition of spread through airspaces (STAS) as a histologic feature with prognostic significance**.

# Tumor STAS

= tumor cells within airspaces beyond the edge of the main tumor




STAS is associated with worse clinical outcome in resected lung ADC in all investigated major histologic lung cancer types

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(4) Recognition of spread through airspaces (STAS) as a histologic feature with prognostic significance.

**(5) Moving lymphoepithelial carcinoma to squamous cell carcinomas.**

**(6) Recognition of bronchiolar adenoma/ciliated muconodular papillary tumor as a new entity within the adenoma subgroup;**

**(7) Recognition of thoracic SMARCA4-deficient undifferentiated tumor.**

**(8) Update on evolving concepts in lung neuroendocrine neoplasm classification.**

# Epithelial tumours

**Papillomas**

Bronchial papillomas

**Adenomas**

Sclerosing pneumocytoma

Alveolar adenoma

Papillary adenoma of the lung

Bronchiolar adenoma / ciliated muconodular papillary tumour

Mucinous cystadenoma of the lung

Mucous gland adenoma of the lung

**Precursor glandular lesions**

Atypical adenomatous hyperplasia of the lung

Adenocarcinoma in situ of the lung

**Adenocarcinomas**

Minimally invasive adenocarcinoma of the lung

Invasive non-mucinous adenocarcinoma of the lung

Invasive mucinous adenocarcinoma of the lung

Colloid adenocarcinoma of the lung

Fetal adenocarcinoma of the lung

Enteric-type adenocarcinoma of the lung

**Squamous precursor lesions**

Squamous dysplasia and carcinoma in situ of the lung

**Squamous cell carcinomas**

Squamous cell carcinoma of the lung

Lymphoepithelial carcinoma of the lung

**Large cell carcinoma**

Large cell carcinoma of the lung

**Adenosquamous carcinoma**

Adenosquamous carcinoma of the lung

**Sarcomatoid carcinomas**

Pleomorphic carcinoma of the lung

Pulmonary blastoma

Carcinosarcoma of the lung

**Other epithelial tumours**

NUT carcinoma of the lung (see NUT carcinoma of the thorax)

Thoracic SMARCA4-deficient undifferentiated tumour

Lymphoepithelial like carcinoma

**Salivary gland-type tumours**

Pleomorphic adenoma of the lung

Adenoid cystic carcinoma of the lung

Epithelial-myoepithelial carcinoma of the lung

Mucoepidermoid carcinoma of the lung

Hyalinizing clear cell carcinoma of the lung

Myoepithelioma and myoepithelial carcinoma of the lung

**Lung neuroendocrine neoplasms**

- **Precursor lesion**

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

- **Neuroendocrine tumours**

Carcinoid/neuroendocrine tumour of the lung

- **Neuroendocrine carcinomas**

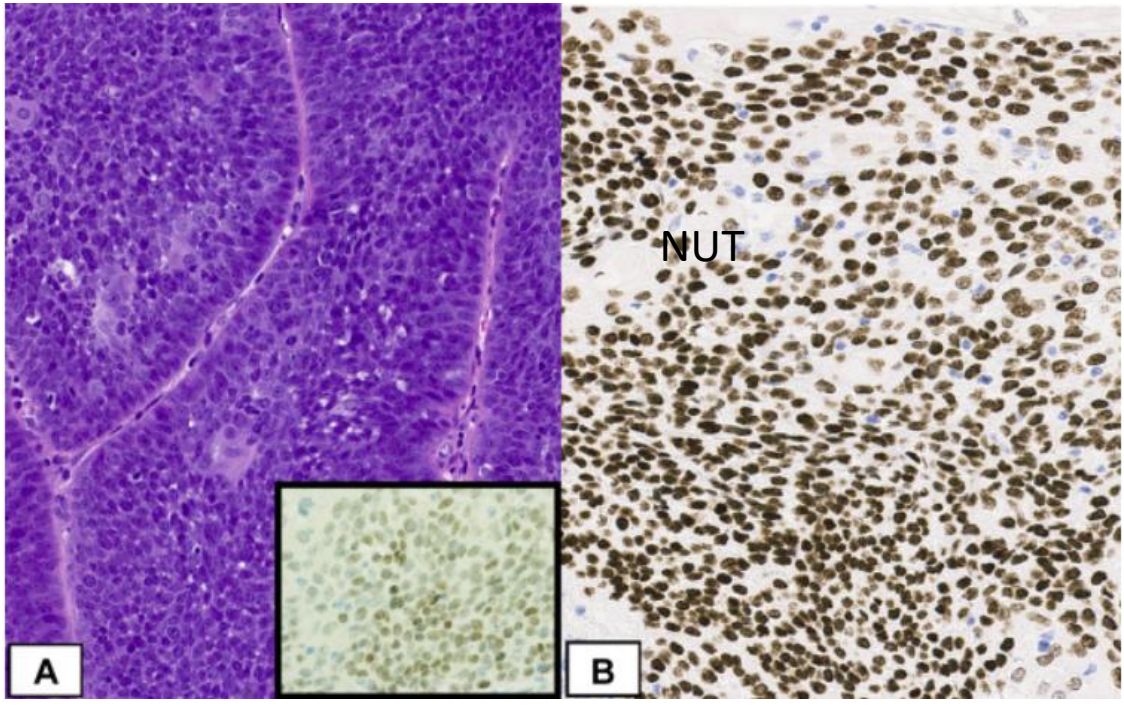
Small cell lung carcinoma

Large cell neuroendocrine carcinoma of the lung

# NUT Carcinoma

- NUT carcinoma is characterized by chromosomal translocation t(15;19) (q14;p13.1).
- Widely invasive at the time of diagnosis.
- Should be considered in young patients, light or never smoker, with malignant lung tumors with evidence of squamoid morphology.

Sheets and nests of poorly differentiated tumor cells with small squamous nests.



# Lung neuroendocrine neoplasms

➢ **Precursor lesion**

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

➢**Neuroendocrine tumours (NET) of the lung**

1. Carcinoid
2. Atypical Carcinoid

➢ **Neuroendocrine carcinomas (NEC) of the lung**

1. Small cell carcinoma of the lung
2. Large cell neuroendocrine carcinoma of the lung

In almost all other organs : NET/NEC

NET : G1; G2; **G3** ; “Proliferation index”

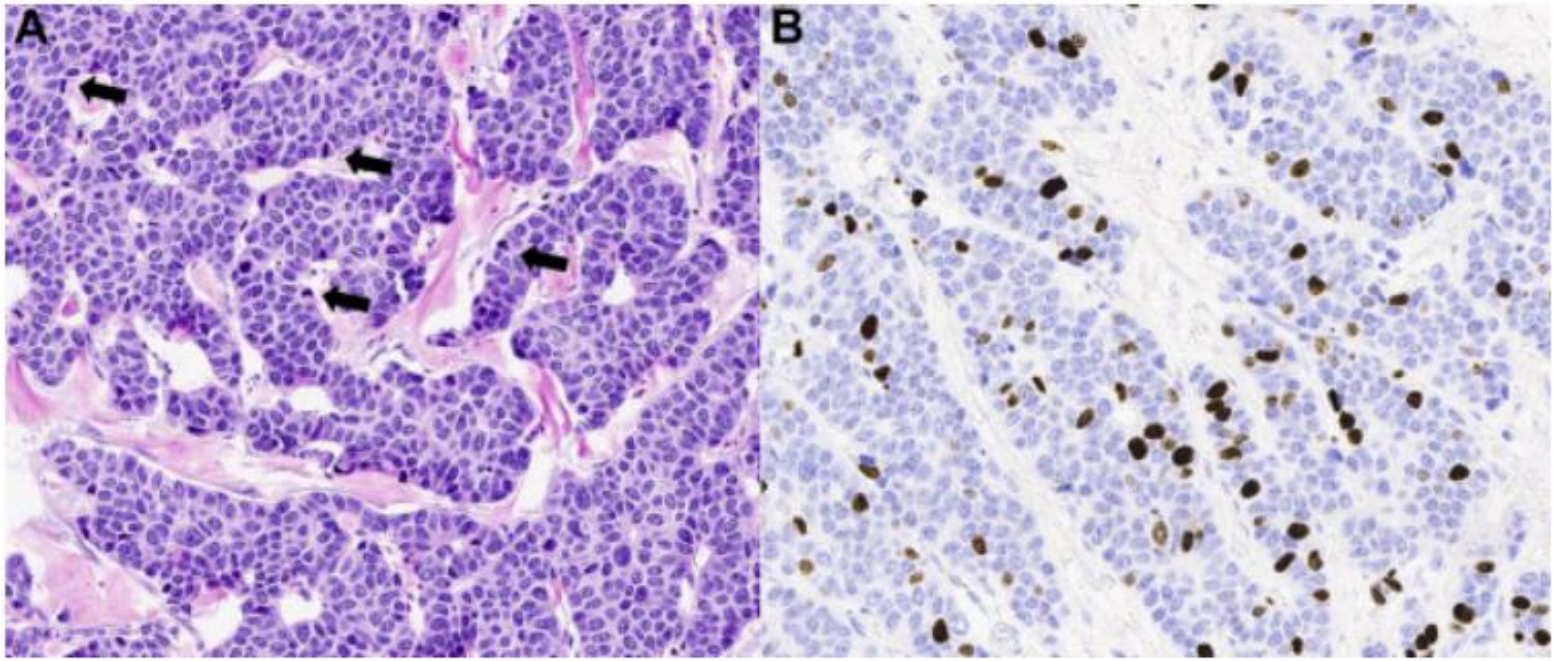
NEC : Large cell/small cell

# Carcinoid NOS and Metastatic Carcinoids Criteria and Terminology

- NEN subtypes are based on morphology alone, with **mitoses** and presence of **necrosis** representing the mainstay for classification
- These criteria have been validated in surgical specimens.
- Nevertheless, accurate mitotic counts and recognition of necrosis are often difficult in small biopsies or cytologic specimens, because the mitotic count can be heterogeneous.
- Therefore, the recommendation was made to use the term **“carcinoid tumor not otherwise specified (NOS)”** for small samples from primary or metastatic NETs and to record the mitotic count and the presence of any foci of necrosis

# Carcinoid Tumors With High Proliferation Index

Characterized by the well-differentiated, organoid morphology of carcinoids, but an elevated proliferative activity as documented by a mitotic count exceeding 10 per 2 mm2, thus meeting the criteria for a diagnosis of LCNEC rather than carcinoid




carcinoid-like morphology

Mitotic rate averaged 16 per 2 mm2
Ki-67 index was 20%.

# Emerging Genetic Data and Concepts

- Major clinical, epidemiologic, pathologic, and genetic differences are recognized between the NETs and the high-grade NECs.
- High-grade carcinomas have more genetic alterations than carcinoids, including mutations and amplifications.
- SCLC is consistently associated with biallelic TP53 and RB1 gene inactivation, but this does not mean that this tumor type is molecularly homogeneous.
- LCNECs have a also a heterogeneous molecular profile

# !!! Nonsmall Cell Carcinoma With NE Differentiation

- NE differentiation can be detected by immunohistochemistry in adenocarcinomas or squamous cell carcinomas lacking any NE morphology in 10% to 20% of cases.

- Nevertheless, this finding does not bear any clinical impact, and the routine use of immunohistochemistry in pathology practice is not recommended in the absence of a NE morphology.

# Future Work

➢ Future directions for work that might improve the classification , in terms of accuracy, reproducibility, and relevance to patient management:

(1) Validation of the proposed IASLC grading system of resected adenocarcinomas with development of grading for resected squamous cell carcinomas and NSCLC in small biopsies;

(2) Refining the classification of NENs with further study of ACs with high mitotic or proliferation rates;

(3) Better understanding of the clinical significance of the morphologic and genetic spectrum of both SCLC and LCNEC;

(4) Expansion of the role of diagnostic molecular testing for more tumor types.

# Do’s and Don’ts…….


- Don’t diagnose NSCC-NOS too often. Should be less than 10% of cases
- Indicate if IHC was used to make diagnosis
- Do not use the term non-squamous NSCC
- Be aware of terms you CANNOT use/accept in small samples

Adenocarcinoma-in-situ

Sarcomatoid carcinoma

Adenosquamous carcinoma

Large  cell carcinoma

# References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The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015

*Andrew G. Nicholson, DM ; Ming S. Tsao, MD; Yasushi Yatabe, PhD; Akihiko Yoshida, PhD;….. William D. Travis, MD*-Journal of thoracic oncology-November 19, 2021