Minimally invasive adenocarcinoma

5mm or less = microinvasion
No necrosis
No lymphatic or pleural invasion
No spread through air-spaces (STAS)
Kadota K et al. The cribriform pattern identifies a subset of acinar predominant tumors with poor prognosis in patients with stage I lung adenocarcinoma: a conceptual proposal to classify cribriform predominant tumors as a distinct histologic subtype. Mod Pathol. 2014;27:690-700.

How does this new classification help management of surgically resected ADC patients?

Not embarrassing ....(evidence-based and validated)

- Correlates with molecular abnormalities
- Reproducible amongst pathologists
- Predicts survival and recurrence
  - Defines AIS & MIA: 100% & near 100% survival if completely resected
  - Importance of histologic patterns
- Predicts survival benefit with adjuvant cisplatin based chemotherapy
ADENOCARCINOMA CLASSIFICATION

PREINVASIVE LESIONS
- AAH
- ADC-in-situ (formerly pure BAC) *most non-mucinous (NM)

INVASIVE ADC
- Minimally invasive (to be defined: < 5mm invasion, <10% invasion, <5mm scar)
- Lepidic pattern predominant
- Acinar pattern predominant/pure
- Papillary pattern predominant/pure
- Micropapillary pattern
- Solid pattern predominant/pure

Invasive mucinous adenocarcinoma
- Fetal (low and high grade)
- Colloid
- Enteric

Signet ring morphology

EGFR mutations
TTF-1 positive

K-ras mutations
TTF-1 negative

ALK and ROS gene rearrangements
## REPRODUCIBLE AMONGST PATHOLOGISTS

<table>
<thead>
<tr>
<th>Reference</th>
<th>ADC Subtypes</th>
<th>Statistics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thunnissen E: Mod Path 25:1574, 2012</td>
<td>Experts&lt;br&gt;Typical patterns&lt;br&gt;Difficult patterns</td>
<td>Kappa = 0.77&lt;br&gt;Kappa = 0.38</td>
<td>Selected images</td>
</tr>
<tr>
<td>Warth A: ERJ 40:1221-27, 2012</td>
<td>Experts&lt;br&gt;Residents</td>
<td>Kappa (0.44-.72)&lt;br&gt;Kappa (0.38-0.47)</td>
<td>Glass slides</td>
</tr>
<tr>
<td>Warth A: Virch Arch 461:185-93, 2012</td>
<td>Experts</td>
<td>Consensual votes: 59.6-75%</td>
<td>Digital Slides&lt;br&gt;educational session Ž disagreement (p&lt;0.001)</td>
</tr>
<tr>
<td>Duhig E JTO 20:673, 2015</td>
<td>Experts&lt;br&gt;Experts &amp; non-experts</td>
<td>Intraclass correlation coefficient ï 88-98%</td>
<td>Glass slides: High degree of concordance</td>
</tr>
<tr>
<td>Nakazato Y: JTO 8:736-743</td>
<td>Experts</td>
<td>5 class ï Kappa=0.46&lt;br&gt;2 class ï Kappa=0.66</td>
<td>LP/AC/Pap vs Sol/MP</td>
</tr>
<tr>
<td>Thunnissen E: Mod Path 25:1574, 2012</td>
<td>Invasive vs noninvasive&lt;br&gt;Typical patterns&lt;br&gt;Difficult patterns</td>
<td>Kappa = 0.55&lt;br&gt;Kappa = 0.08</td>
<td>Selected images</td>
</tr>
</tbody>
</table>

REPRODUCIBLE (strict and recognisable set of criteria...)

---

**Context:**
- **Typical patterns** vs **Difficult patterns**
- **Experts** vs **Residents**
- **Experts & non-experts**
- **Invasive** vs **noninvasive**

**Statistics:**
- **Kappa** measures inter-rater agreement.
- Higher Kappa values indicate better agreement.

**Comments:**
- Selected images
- Glass slides
- Digital Slides educational session
- High degree of concordance
- LP/AC/Pap vs Sol/MP
Predominant pattern - Validation...

A grading system of lung ADC based on histologic pattern is predictive in stage I tumors. Sica G AJSP 2010;34:1155


Prognostic significance of ADC patterns... Von der Thüsen JTO 2013;8:37-44

USA

Australia

Warth A, J Clin Oncol 2013; 30: 1438-46


UK
Solid and micropapillary histologic patterns predict survival benefit from cisplatin based adjuvant chemotherapy in resected lung adenocarcinoma patients

Tsao MS, et al: J Clin Oncol 2015; epub
SQUAMOUS CELL CARCINOMA (SQCC)

A malignant epithelial tumour showing keratinization and/or intercellular bridges that arises from bronchial epithelium.

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
2015 WHO CLASSIFICATION NEUROENDOCRINE TUMOURS

- Small cell carcinoma
  - Combined SCLC

- Large cell neuroendocrine carcinoma
  - Combined LCNEC

- Carcinoid tumor
  - Typical carcinoid
  - Atypical carcinoid

Diagnostic IHC, if appropriate
- TTF-1
- CD56
- Chromogranin
- Synaptophysin
- MNF116
- P40
LARGE CELL CARCINOMA

2004

- Large cell carcinoma
  - Large cell neuroendocrine carcinoma 8013/3
  - Combined large cell neuroendocrine carcinoma 8013/3
  - Basaloid carcinoma 8123/3
  - Lymphoepithelioma-like carcinoma 8082/3
  - Clear cell carcinoma 8310/3
  - Large cell carcinoma with rhabdoid phenotype 8014/3

2015

- Large cell carcinoma
  - Null phenotype on IHC
  - Unclear phenotype on IHC
  - No IHC available
Figure 1-05 4 Large cell carcinoma. (A-C) A resected morphologically undifferentiated non-small cell carcinoma, that would hitherto have been classified as large cell carcinoma, stains for TTF-1 but not for p40, with subsequent classification as an adenocarcinoma, solid subtype (B i p40; C i TTF-1). (B-F) A resected morphologically undifferentiated non-small cell carcinoma, that would hitherto have been classified as large cell carcinoma, stains for p40 but not for TTF-1, with subsequent classification as a non-keratinising squamous cell carcinoma (E i p40; F i TTF-1). (G-I) A resected morphologically undifferentiated non-small cell carcinoma does not stain for P40 or TTF-1. The tumour cells also did not contain mucin, with subsequent classification as a large cell carcinoma, null phenotype (H i p40; I i TTF-1). Courtesy of Dr L Sholl
Subtyping of resected morphologically undifferentiated non-small cell carcinomas (formerly large cell carcinoma)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma, solid subtype</td>
<td>Positive TTF-1 and/or Napsin A and/or mucin</td>
</tr>
<tr>
<td></td>
<td>Negative (or focal staining in scattered tumour cells) p40, p63* and/or CK5/6</td>
</tr>
<tr>
<td>Non-keratinising squamous cell carcinoma</td>
<td>Negative TTF-1, Napsin A, mucin</td>
</tr>
<tr>
<td></td>
<td>Diffusely positive p40, p63* and/or CK5/6</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>Positive adeno- and squamous markers in geographically-distinct cell populations, each representing &gt;10% of tumour cells</td>
</tr>
<tr>
<td>Large cell carcinoma with null immunohistochemical features</td>
<td>Positive cytokeratins</td>
</tr>
<tr>
<td></td>
<td>Negative lineage-specific markers and mucin stain</td>
</tr>
<tr>
<td>Large cell carcinoma with unclear immunohistochemical features</td>
<td>Positive cytokeratins</td>
</tr>
<tr>
<td></td>
<td>Unclear Immunoprofiles and negative mucin stain</td>
</tr>
<tr>
<td>Large cell carcinoma with no stains available</td>
<td>No Immunohistochemical or mucin staining available</td>
</tr>
</tbody>
</table>

*p63 (4A4) can rarely be more diffusely positive in some TTF-1 positive tumours. These should be classified as adenocarcinomas.

In cases where there is morphological evidence of either squamous cell carcinoma or adenocarcinoma, then immunohistochemistry is not required to assess undifferentiated areas.
## A Genomics-Based Classification of Human Lung Tumors

The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM)¹

### A

<table>
<thead>
<tr>
<th>Carc</th>
<th>SCLC</th>
<th>AD</th>
<th>SQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>LC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NkX2-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF/ERBB/KRAS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SOX2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDR2/NFE2L2</td>
<td></td>
<td></td>
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</table>

### B

<table>
<thead>
<tr>
<th>HE</th>
<th>TTF-1</th>
<th>p63</th>
<th>CD56</th>
<th>Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD-like</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ-like</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NEC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOS</td>
<td></td>
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</tr>
</tbody>
</table>

- **AD-like**
  - KRAS G12C
  - STK11 P321fs
  - TP53 L265_N268del
- **SQ-like**
  - FN1CA E542K
  - TP53 R273L
  - CCND1 amp
  - FGFR1 amp
- **NEC**
  - TP53 splice 6-1
  - RB1 loss
- **NOS**
  - EGFR K714N
  - KRAS G12C
  - TP53 R213Q
  - CDKN2A del
  - SOX2 amp

Note: The diagram and table illustrate the genomics-based classification of human lung tumors, detailing specific markers and alterations for different subtypes. The CLCGP and NGM projects are referenced for this classification.
SEER data on incidence of non-small cell carcinomas (Lewis DR et al. Cancer. 2014;120(18):2883-92)
2015 WHO CLASSIFICATION

1-9: Salivary gland-type tumours
   1-9A Mucoepidermoid carcinoma
   1-9B Adenoid cystic carcinoma
   1-9C Epithelial-myoepithelial carcinoma
   1-9D Pleomorphic adenoma

1-10: Papillomas
   1-10A: Squamous papilloma
   1-10B: Glandular papilloma
   1-10C: Mixed squamous and glandular papilloma

1-11: Adenomas
   1-11A: Sclerosing pneumocytoma
   1-11B: Alveolar adenoma
   1-11C: Papillary adenoma
   1-11D: Mucinous cystadenoma
   1-11E: Mucus gland adenoma

1-12: Mesenchymal tumours
   1-12A: Hamartoma
   1-12B: Chondroma
   1-12C: PEComatous tumours (LAM, PEComa)
   1-12D: Congenital peribronchial myofibroblastic tumour
   1-12E: Diffuse lymphangiomatosis
   1-12F: IMT
   1-12G: Epithelioid haemangioendothelioma

1-12: Mesenchymal tumours, cont'd
   1-12H: Pleuropulmonary blastoma
   1-12I: Synovial sarcoma
   1-12J: Pulmonary artery intimal sarcoma
   1-12K: Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation
   1-12L: Myoepithelial tumours
   1-12M: Others

1-13: Lymphoproliferative disorders
   1-13A: Marginal zone B-cell lymphoma of MALT origin
   1-13B: Diffuse large B-cell lymphoma
   1-13C: Lymphomatoid granulomatosis
   1-13D: Intravascular lymphoma
   1-13E: Langerhans cell histiocytosis
   1-13F: Erdheim Chester disease

1-14: Tumours of ectopic origin
   1-14A: Germ cell tumours
   1-14B: Intrapulmonary thymoma
   1-14C: Melanoma
   1-14D: Meningioma

1-15: Metastases to the lung
HAMARTOMA
SCLEROSING HEMANGIOMA
CLEAR CELL TUMOUR
GERM CELL TUMOURS
THYMOMA
MELANOMA
OTHERS

Mesenchymal (1-12)
(Adenoma) Sclerosing pneumocytoma (1-10)
Mesenchymal (1-12)
Ectopic origin (1-14)
Ectopic origin (1-14)
Ectopic origin (1-14)
<table>
<thead>
<tr>
<th>Clear cell tumour</th>
<th>Lymphangioleiomyomatosis</th>
<th>“PEComatosis”</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Clear cell tumour" /></td>
<td><img src="image2" alt="Lymphangioleiomyomatosis" /></td>
<td><img src="image3" alt="“PEComatosis”" /></td>
</tr>
</tbody>
</table>

**1.12C PEComatous tumours**

**Mutations in the TSC gene**
NUT-carcinoma

- Young adults and children
- P63 and CK positive
- NUT (Nuclear protein of the testis)-IHC and NUT-FISH to confirm diagnosis
- BETi (bromodomain and extra-terminal domain inhibitor) and HDACi (histone deacetylase inhibitor) in clinical trials.
New tumoursé

IHC ï Negative other than vimentin

Resembles extraskeletal myxoid chondrosarcoma but histochemically differenté.
Primary pulmonary myxoid sarcoma with EWSR1-CREB1 fusion: a new tumor entity.
Thway K et al. AJSP 2011;35:1722-32

- 10 pulmonary myxoid sarcomas - Recurrent fusion gene, that appear to represent a distinct tumor entity at this site.
- 7 were shown to harbor a specific EWSR1-CREB1 fusion by RT-PCR and direct sequencing, with 7 of 10 showing EWSR1 rearrangement by FISH.
- This gene fusion has been described previously in two different sarcomas: clear cell sarcoma-like tumors of the gastrointestinal tract and angiomatoid fibrous histiocytomas;
- Novel finding in tumors with the morphology we describe and that occur in the pulmonary region.
Endobronchial pulmonary angiomatoid fibrous histiocytoma: two cases with EWSR1-CREB1 and EWSR1-ATF1 fusions.
Thway K et al. AJSP 2012;36:883-8

Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue neoplasm of intermediate biological potential, predominantly occurring in the extremities of children and young adults.

2 cases arising endobronchially harboring EWSR1 gene rearrangements by FISH and, respectively, EWSR1-CREB1 and EWSR1-ATF1 gene fusions by RT-PCR
MOLECULAR ABNORMATLITIES IN “RARE LUNG TUMOURS”

1-8 Other carcinomas
   1-8A NUT-carcinoma

1-9: Salivary gland-type tumours
   1-9A Mucoepidermoid carcinoma

1-12: Mesenchymal tumours
   1-12C: PEComatous tumours
   1-12D: Diffuse lymphangiomatosis
   1-12F: Inflammatory myofibroblastic tumour
   1-12G: Epithelioid haemangioendothelioma
   1-12H: Pleuropulmonary blastoma
   1-12I: Synovial sarcoma
   1-12J: Pulmonary myxoid sarcoma
   1-12L: Myoepithelial tumours
   1-12M: Others
       Localized fibrous tumour

1-13: Lymphoproliferative disorders
   1-13E: Langerhans cell histiocytosis
   1-13F: Erdheim Chester disease