The 2015 World Health Organization Classification for Lung Adenocarcinomas: A Practical Approach

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Objectives

• Discuss the history of the World Health Organization classifications for lung adenocarcinomas
• Define new terminology for low grade adenocarcinomas
• Review the evidence that the new classification for adenocarcinomas has prognostic significance

The 2015 WHO

• New emphasis on genetic/molecular studies
• Use of immunohistochemistry
• New classification for small biopsies and cytology
• Adenocarcinoma classification
• Large cell carcinoma: restriction of diagnosis
• Squamous cell carcinoma: keratinizing and non-keratinizing
• Neuroendocrine tumor: grouping into one classification
• Other changes to note
WHO Classification
Lung Adenocarcinoma
2015

- Adenocarcinoma in situ
- Minimally invasive adenocarcinoma
- Subtypes of adenocarcinoma
  - Lepidic
  - Invasive mucinous adenocarcinoma
  - Micropapillary
- Quantitation of subtypes
- Spread Through the Air Spaces (STAS)

Cleveland Clinic
2014 Total Carcinoma Surgical Specimens

WHO Classification
Lung Adenocarcinomas
1981

Adenocarcinoma:
- Acinar adenocarcinoma
- Papillary adenocarcinoma
- Bronchioloalveolar carcinoma
- Solid adenocarcinoma with mucin formation
Solid Adenocarcinoma: Mucicarmine Stain

Bronchioloalveolar

WHO Classification
Lung Adenocarcinomas
1999/2004

- Acinar
- Papillary
- Bronchioloalveolar carcinoma
  - Non-mucinous
  - Mucinous
  - Mixed mucinous and non-mucinous
- Solid adenocarcinoma with mucin
- Adenocarcinoma with mixed subtypes
Bronchioloalveolar, non-mucinous type

Predominantly BAC

Mixed with acinar and BAC
International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma


IASLC/ATS/ERS Lung Adenocarcinomas

2004
- Bronchioloalveolar carcinoma
  - Non-mucinous
  - Mucinous
  - Mixed mucinous/nonmucinous

2011
- Adenocarcinoma in situ
- Minimally invasive adenocarcinoma
- Lepidic predominant adenocarcinoma
- Invasive adenocarcinoma with lepidic component
WHO Classification
Lung Adenocarcinomas
2015

Adenocarcinoma in situ

- Minimally invasive adenocarcinoma
- Lepidic predominant adenocarcinoma
- Invasive adenocarcinoma with lepidic component

Adenocarcinoma in situ, non-mucinous type

CT scan of lung with suspected adenocarcinoma
Adenocarcinoma in situ, non-mucinous type

Adenocarcinoma in situ, non-mucinous type

Adenocarcinoma in situ, mucinous type

Adenocarcinoma in situ mucinous type
WHO Classification
Lung Adenocarcinoma
2004

- Precursor lesion: Atypical adenomatous hyperplasia (AAH)
- Adenocarcinomas:
  - Acinar
  - Papillary
  - Bronchioloalveolar
    - Mucinous
    - Non-mucinous
    - Mixed / indeterminate
  - Solid with mucin formation
WHO Classification
Lung Adenocarcinomas
2015

• Adenocarcinoma in situ
  ≥ 5 mm ≤ 3 cm

  Minimally invasive adenocarcinoma

  • Lepidic predominant adenocarcinoma

  • Invasive adenocarcinoma with lepidic component
Minimally invasive adenocarcinoma

Minimally invasive adenocarcinoma

Minimally invasive adenocarcinoma
WHO Classification
Lung Adenocarcinomas
2015

Minimally invasive adenocarcinoma (MIA)
Adenocarcinoma in situ with
≤5mm scar

2015 WHO Classification

Adenocarcinoma in situ
Minimally invasive adenocarcinoma

WHO Classification
Lung Adenocarcinomas
2015

- Adenocarcinoma in situ

- Minimally invasive adenocarcinoma

- Lepidic predominant adenocarcinoma

- Invasive adenocarcinoma with lepidic component
**Predominantly Lepidic Adenocarcinoma**

**Mixed adenocarcinoma with lepidic pattern**

**2015 WHO Classification**

- **Adenocarcinoma in situ**
- **Minimally invasive adenocarcinoma**
  - Lepidic predominant
  - Mixed with lepidic subtype
WHO Classification
Lung Adenocarcinoma
2015

- Adenocarcinoma in situ
- Minimally invasive lesions
- Subtypes of adenocarcinoma
  - Lepidic
  - Invasive mucinous adenocarcinoma
  - Micropapillary
- Quantitation of subtypes
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WHO Classification
Lung Adenocarcinoma
2015

- Adenocarcinoma in situ
- Minimally invasive lesions
- Subtypes of adenocarcinoma
  - Lepidic
  - Invasive mucinous adenocarcinoma
  - Micropapillary
- Quantitation of subtypes
- Spread Through the Air Spaces (STAS)
Micropapillary Lymphatic spread

Spread Through Airspaces (STAS)

- A pattern of invasion
- Tumor in airspaces beyond the edge of the tumor
  - Micropapillary, solid nests or single cells
- Not measured as part of tumor
- Reported separately like pleural and vascular invasion.
WHO Classification
Lung Adenocarcinoma
2015
• Adenocarcinoma in situ
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Acinar type
Interobserver Variability of Histopathological Subtypes in Lung Adenocarcinoma

![Image 1](Cribriform variant of Acinar type)

Typical cases

Difficult cases

Murakami S et al. Lung Cancer 2015;90:199-204

Stage 1A Lung Adenocarcinomas

Histologic Subtype and Prognosis

Murakami S et al. Lung Cancer 2015;90:199-204
**Therapeutic Implications**

- Can AIS, MIA and Lepidic predominant adenocarcinomas be treated less aggressively?
  - Minimal surgeries
  - Less or no adjuvant therapies

**Recurrence By Lepidic Predominant Subtypes**

![Graph showing recurrence by lepidic predominant subtypes with statistical data and p-values.](image-url)
Overall Survival
Stage 1 Adenocarcinomas
n=150 < 2cm

Years Post Surgery
Years

Therapeutic Implications

• Can AIS, MIA and Lepidic predominant adenocarcinoma be treated with less aggressive surgeries?
  —Cannot be diagnosed on biopsy
  —Wedge excision
    —Frozen section analysis requires entire tumor to be evaluated
    —Two step procedure

Therapeutic Implications

• Can AIS, MIA and Lepidic predominant adenocarcinomas be treated less aggressively?
  —Minimal surgeries
  —Less or no adjuvant therapies
Overall Survival
Stage 1 Adenocarcinomas
Retrospective Chemotherapy vs No Chemotherapy


The WHO Classification of Lung Adenocarcinomas

- Preinvasive lesions
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ (≤3cm)
    - Mucinous
    - Mixed mucinous or nonmucinous
- Minimally invasive adenocarcinoma (≤ 3cm)
  - Lepidic predominant with ≤5 mm invasion
    - Mucinous
    - Nonmucinous
    - Mixed

The WHO Classification of Lung Adenocarcinomas

- Invasive adenocarcinoma
  - Lepidic predominant
  - Acinar predominant
  - Papillary predominant
  - Micropapillary predominant
  - Solid predominant with mucin production
- Variants
  - Invasive mucinous adenocarcinoma
  - Colloid
  - Fetal (low and high grade)
  - Enteric
Summary

• The WHO classification for lung adenocarcinomas has introduced new terminology and categories for low grade adenocarcinomas
• Studies to date suggest these categories have prognostic implications
• Prospective studies are needed to evaluate the optimal therapies for these new categories

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