The impact of the new 2015 WHO classification of lung cancer: Pathologist’s view

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Disclosures

• I have acted as consultant for Roche Genentech, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, Clovis, Bristol Myers Squibb, Merck Sharp Dohme

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Background

• Reviewed approx. every 10 years
• Traditionally a classification for surgically resected lung cancers
• For pathologists.............

• Multidisciplinary team working.....and awareness
• Evolving therapy diversity
  • Need to do better with small samples
• Molecular data on lung cancer
WHO classification of lung cancer: what is it?

• A list
• A classification
• A biologically and clinically meaningful division of lung cancers according to their
  – Morphological features
  – Biological features
  – And their molecular features
• Practical and widely applicable
What has changed?

• Definitions of Large cell carcinoma
• Several issues with adenocarcinoma
• Little change for squamous cell carcinoma
• New category of ‘neuroendocrine tumours’
• Consolidate recommendations for small sample diagnosis
Large cell carcinoma

Largely a diagnosis of exclusion
Well Differentiated Squamous Cell Ca  
Poorly Differentiated Squamous Cell Ca

Well Differentiated Adenocarcinoma  
Poorly Differentiated Adenocarcinoma

Morphologically Large Cell Carcinoma

Pathologists will differ  How they call marginal cases
**A Genomics-Based Classification of Human Lung Tumors**

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

Well Differentiated Squamous Cell Ca
Poorly Differentiated Squamous Cell Ca
Non-keratinising Squamous Cell Ca

Morphology & Immunohistochemistry
Large Cell Carcinoma

Well Differentiated Adenocarcinoma
Poorly Differentiated Adenocarcinoma
Solid-pattern Adenocarcinoma

Pathologists will still differ how they call marginal cases !!!!

Tumour progression and de-differentiation

IHC profile
Adenocarcinoma: Solid subtype

Non-keratinizing Squamous cell carcinoma
Diagnosis of Large Cell Carcinoma: 2015

Definition
Large cell carcinoma is an undifferentiated non-small cell carcinoma (NSCC) that lacks the cytological, architectural, and immunohistochemical features of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma. The diagnosis requires a thoroughly sampled resected tumour, and cannot be made on non-resection or cytology specimens.

The diagnosis of large cell carcinoma is only made when additional staining (Immunohistochemistry and/or mucin stains) is negative, unclear, or not available.
Clinical impact

• Large cell category gets smaller
• Classification shift may reduce post-operative 5YS for squamous cell and adenocarcinomas
• No impact on molecular testing practice
• New nomenclature
Adenocarcinoma: changes

• Bronchiolo-alveolar cell carcinoma is no more!
  – BAC becomes AIS (adenocarcinoma in situ)
• Minimally invasive adenocarcinoma (MIA)
• Surgically resected adenocarcinomas classified by predominant pattern
Post operative survival vs **predominant pattern** in pulmonary adenocarcinoma – five patterns

Yoshizawa A et al. Mod Pathol 2011; 24, 653-664  
Russell P et al. J Thorac Oncol 2011; epub June  
Warth A et al. J Clin Oncol 2012; Mar 5 epub
Adenocarcinoma: changes

• Bronchiolo-alveolar cell carcinoma is no more!
  – BAC becomes AIS (adenocarcinoma in situ)
• Minimally invasive adenocarcinoma (MIA)
• Surgically resected adenocarcinomas classified by predominant pattern
  • Promote better understanding of relationship between the lepidic pattern and ground glass change on CT
• Invasive mucinous adenocarcinoma
Formerly ‘mucinous BAC’

Invasive mucinous adenocarcinoma

KRAS mutations very common
Spread Through Alveolar Spaces: STAS
Clinical impact

• More biologically meaningful classification
  • AIS rather than BAC, MIA
• Pattern predominance and prognosis
  • Adjuvant therapy?
• Histology – Molecular correlates?
  • Signet ring cells and ALK
  • Invasive mucinous and KRAS
• Histology – radiology correlates
• MIA, STAS, recurrence and sub-lobar resection?
Squamous Cell Carcinoma

1-3A  Keratinizing and Non-keratinizing SCC
Squamous cell carcinoma is a malignant epithelial tumour that either shows keratinization and/or intercellular bridges, or is a morphologically undifferentiated non-small cell carcinoma that expresses immunohistochemical markers of squamous differentiation.

1-3B  Basaloid Carcinoma
Basaloid carcinoma is a poorly differentiated malignant epithelial tumour that presents in its pure form as a proliferation of small cells with lobular architecture and peripheral palisading. These cells lack squamous morphology, but show immunohistochemical expression of squamous markers. Tumours with a keratinizing or non-keratinizing squamous cell component, but a basaloid component of > 50%, are also classified as basaloid carcinoma.

1-3C  Pre-invasive disease
Squamous dysplasia and Carcinoma in situ
Clinical relevance

• None, other than classification migration and possible effect on post-op survival statistics
Neuroendocrine tumours

High Grade Neuroendocrine tumours
• 1-4A: Small cell carcinoma
• 1-4B: Large cell neuroendocrine carcinoma (LCNEC)

Low Grade Neuroendocrine tumours
• 1-4C: Carcinoid tumours
  – Typical Carcinoid
  – Atypical Carcinoid

Precursor lesion
• 1-4D: Diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH)

Diagnostic criteria have NOT CHANGED for any of these tumours
LUNG NE TUMORS: SURVIVAL

Survival Functions

Cumulative Survival vs. follow-up (yrs)

Diagnosis
- AC
- LCNEC
- SCLC
- TC

Surgically resected

510 AFIP Cases: TC-92; AC-127, LCNEC – 152, SCLC – 139; p<0.0001. Data courtesy of WD Travis.
Clinical Impact

• Can LCNEC now be regarded more like SCLC, rather than NSCLC?
Clinical requirements of diagnosis: Advanced Disease

Advanced disease, small samples

• WHO 2004 *et prev*
  ➢ inapplicable
  ➢ inaccurate

• NSCLC-NOS problematic

• NSCLC subtype matters

Now a critical determinant of Therapy Choice
Subtyping NSCLC greatly improved by IHC

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

Loo PS et al, J Thorac Oncol 2010
Diagnosis of NSCLC in small biopsy & cytology

- Squamous cell carcinoma
- NSCLC, probably squamous cell (IHC – p40, p63, CK5/6)
- Adenocarcinoma
- NSCLC, probably adenocarcinoma (IHC – TTF1)
- NSCLC-NOS – cannot be resolved (null IHC)
- Occasionally, rare specific types may be suggested
Clinical Impact

• Substantial
• Therapeutic selection – efficacy and toxicity
• Triage for molecular testing
• Incorporation into clinical trial data collection?
Genetic profiles, Liquid biopsies & Molecular microscopes?

Oncogene ‘drivers’ in Adenocarcinoma

Oncogene ‘drivers’ in Squamous carcinoma

Somatic mutation rate

C>T
C>A
C>G
T>C
T>A
T>G
Clinical impact of the WHO 2015 classification

- Case reassignment might impact post-operative survival data
- Better prognostication in resected adenocarcinoma
- Possible challenges posed by pathological factors which could influence surgery
- Better ‘home’ for Neuroendocrine tumours
- Better diagnosis on small samples
- Assimilation of genetic data into the way we regard individual patients and their lung cancers