Problem Areas in Thoracic Malignancy Diagnosis

Prof Keith M Kerr
Department of Pathology
Aberdeen University Medical School
Aberdeen Royal Infirmary
Foresterhill
Aberdeen, UK

Problem Areas in Thoracic Malignancy Diagnosis

• Many potential areas to discuss
• Wide range of tumours
• Relatively difficult to access
  – Anatomical considerations
  – Respiratory function & other co-morbidities
• Small sample size
  – Decreasing size → Increasing problem
  – Less invasive sampling techniques
Thoracic malignancy: The WHO system of Classification

- Complex and comprehensive
- Reflects tumour variety
  - Lung, pleura, thymus
- Assumes whole tumour is available
- Acknowledges heterogeneity
  - 10% rule
  - Undifferentiated tumour
- Does NOT account for small biopsy / cytology diagnosis

Histologic subtyping of Lung Tumours: WHO 2004

- Squamous cell carcinoma
- Small cell carcinoma
- Adenocarcinoma
- Large cell carcinoma
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
- Carcinoid tumour
- Salivary Gland tumours
- Squamous dysplasia / CIS
- Atypical adenomatous Hyperplasia
- DIPNECH
Is diagnosis ‘Fit for Purpose’?

- **Pathologist**
  - Complete diagnosis
  - Useful report

- **Clinician**
  - Treatment focused
  - Prognostic data
  - Predictive information

Clinical requirements of diagnosis

**Surgical resections**
- Fewer patients
- Pre-op diagnosis & staging
- Post-op full diagnosis
- Staging TNM

**Adjuvant treatment**
- Stage
- Histology
- Biomarkers

**Non-surgical cases**
- Most patients
- Hierarchy of diagnosis
- Refine as much as possible

- Identify malignancy as carcinoma
- Metastatic
- Primary
  - SCLC
    - Platinum - Etoposide
  - NSCLC
    - Platinum Doublet
**Diagnostic algorithm for lung cancer**

- **Identify Malignancy**
  - **Metastatic**
  - **Primary**

- **SCLC**
  - Diagnostic accuracy is good
  - Variable reported use of IHC
  - 88-91%

- **NSCLC**
  - 98%

- Interobserver consistency is excellent
  - $K = 0.86$

**References**
- Burnett RA et al, J Clin Pathol, 1994
- Gutterman F et al. Diagnosis and Treatment of Lung Cancer. 2008
- Schreiber G & McCrory DC, Chest 2003; 123, 115-128

---

**Clinical requirements of diagnosis**

- **Identify malignancy as carcinoma**
  - **Metastatic**
  - **Primary**

- **SCLC**
  - Platinum - Etoposide

- **NSCLC**
  - Selected Options

Different therapeutic choices determined by Differences in pathology
5 studies reported 'non-squamous' or adenocarcinoma did better

2 studies reported squamous cell carcinoma did better

Different regimens

Small numbers of cases

Poor histological review

Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer

Various 'standard' Cytotoxic combination chemotherapies
**Therapeutic issues in Squamous Cell carcinoma**

**Bevacizumab – Anti-VEGF agent**

No evidence for patient selection

Contraindicated in Squamous cell carcinoma

Fatal haemoptysis

[Sandler A. Clin Cancer Res 2007; 13, 483-486]

---

**Histological selection for Molecular Analysis**

1. Identify Malignancy
   - Metastatic
     - SCLC
   - Primary
     - NSCLC
     - NSCLC, NOS
     - Large cell carcinomas
     - Sarcomatoid carcinomas
     - Mixed with adenoca?

2. Tested?
   - Adenocarcinomas
   - NSCLC, NOS
   - Large cell carcinomas
   - Sarcomatoid carcinomas
   - Mixed with adenoca?

3. Not tested?
   - Squamous cell carcinomas
   - Large cell neuroendocrine carcinomas
   - Carcinoid tumours
   - Mucinous adenocarcinomas
eesp ‘MBAC’ pattern
   - Salivary types?

---

**The Insulin-Like Growth Factor Pathway in Lung Cancer**

Rafał Dziadziuszko, MD, PhD,* D. Ross Camidge, MD, PhD,† and Fred. R. Hirsch, MD, PhD†‡

J Thorac Oncol 2008; 3, 815-818

---

**Phase II Paclitaxel/Carboplatin +/- CP751,871**

Suggestion of better response in Squamous cell carcinoma Small numbers
Histological subtyping of NSCLC: the big ‘small sample’ problem

Identify malignancy as carcinoma

Metastatic

Primary

SCLC

NSCLC

WHO NSCLC subtypes
- Squamous cell carcinoma
- Adenocarcinoma
- Large cell carcinoma
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
- Carcinoid tumour
- Salivary Gland tumours

Inconsistency
Poor interobserver agreement
Inaccuracy
Squamous Cell (36-97% accuracy)
Adenocarcinoma (32-93% accuracy)
Large cell carcinoma (<50% accuracy)

Reporting Bias
Variable accuracy
Few good at both squamous and adenoca

Morphologic Heterogeneity
Let’s admit we sometimes cannot be specific!

Poor accuracy, especially for Large Cell carcinoma
Use NSCLC-NOS if differentiation absent

25% Bronchial biopsy
40% Cytology

NSCLC-NOS

Specific typing Accuracy
Squamous Cell - 87%
Adenocarcinoma – 80%

Still not perfect
Still some inaccuracy

Diagnostic reproducibility of squamous cell carcinoma in the era of histology-directed non-small cell lung cancer chemotherapy: A large prospective study
Grilley-Olsen JE et al. ASCO 2009; 8008, 409s

- Surgically-resected lung tumours
- Full WHO to simple Squamous / Non-squamous
- Expert vs ‘general’ histopathologists
- Inter-observer agreement

- Experts did better but…..
- Squamous vs Non-squamous – $\kappa=0.64$

- Strict diagnostic criteria
- Use of ‘confirmatory’ immunohistochemistry
Non-small cell carcinoma, NOS:  
- **Diagnosis in resected cases?**

- **All small samples** (bronchial and transthoracic biopsy and cytology diagnoses)

  64% **Adenocarcinoma**

- **Bronchial biopsies only**

  46% **Squamous cell carcinoma**  
  24% **Adenocarcinoma**  
  16% **Large cell carcinoma**  
  14% **Others**

  (Loo PS et al, JTO, in press 2010)
Good predictive performance in suggesting Squamous Cell Ca by cytology

Prediction of surgical histology subtype on undifferentiated biopsies

Most published papers do NOT validate IHC predictive value of small samples
Reporting categories in small biopsy samples and cytology

Restricted version of WHO

- Small cell carcinoma
- Squamous cell carcinoma
- Adenocarcinoma
- Non small cell carcinoma
  - Probably squamous cell
  - Probably adenocarcinoma
  - NSCLC-NOS
- Others - occasionally

More realistic classification
IHC suggests rather than confirms diagnosis
Use in future trials
Therapeutic significance of ‘diagnostic shift?’

Morphological & Molecular Heterogeneity

Anti-EGFR DAKO PharmDx kit
Heterogeneity is present....

- At a molecular as well as morphological level
- May involve differences in
  - gene expression (mutation, translocation)
  - Transcription (mRNA levels)
  - Translation (protein levels)
- Seems to be marker dependent

Heterogeneity within the lesion

- Multiple tumour samples
- Small biopsy vs resected tumour

Variable correlation between biopsy and whole tumour

How representative of the patients tumour burden is the processed sample?
Heterogeneity between lesions

- Differences between primary and metastases
  
- Primary and Recurrent disease
  - Emergence of T790M EGFR resistance mutation in patients relapsing after TKI therapy

Predictive and Prognostic Markers?

- EGFR
- KRAS
- EML4-ALK
- BRAF
- HER2
- cMET
- ERCC1
- P27
- BRCA-1
- Serpin B3
- RAP80
- IGFR
- Hedgehog
- PTEN
- pAKT
- Thymidylate Synthase (TS)
- MTAP
- RRM1
- β tubulin
Targeted Molecular Profiling

- Is there enough tissue?
- What is the best technique to assess the marker?
- Does the result truly reflect the patients tumour burden?
- Histological – Molecular correlation

Problem Areas in Thoracic Malignancy Diagnosis

- Classification ‘fit for purpose’
- Strategies to improve value of diagnosis
- Shrinking tissue resources
- Expanding need for tissue
- Therapeutic decisions based on detailed diagnosis