Lung Cytopathology
Irish Society of Surgical Pathology

Dr Stephen Crowther
Tallaght Hospital
SATURDAY: Lung Neoplasms

- 9.00 - 9.40: My Holidays Stephen Crowther (sponsored by British Airways)
- 9.40 - 10.20: Lung Tumours: Louise Burke (TBC)
- 10.20 - 11.00: Mesenchymal Lung tumours: Leona Doyle
Contents

- Specimens, preparation and adequacy
- Proposed classification system
- Common malignancies
- Pitfalls
What is the role of cytology

- Lung cancer presents at advanced stage
- Increased number of nodules sampled (screening)
- Diagnosis
- Staging
- Molecular testing
Specimens

- Sputum
- Bronchoscopic derived specimens
  - Bronchial brushings
  - Bronchial washings
  - Bronchoalveolar lavage (BAL)
  - Endobronchial ultrasound guided aspiration (lung, lymph nodes)
- Percutaneous trans-thoracic CT-guided FNA
- Pleural Fluid
Preparations

- Direct smears
  - Air dried (MGG)
  - Alcohol fixed (Pap, H&E)
- Touch imprints – core biopsy
- Concentration methods
  - Cytospin (Hanks)
  - Liquid-based preparations (Cytolyte)
- Cell block
Sputum

- Non invasive
- Early morning, induced, post Bronchoscopic
- Preparation
  - Pick and smear
- Adequacy
  - 2 smears with easily identifiable pulmonary macrophages
Bronchial Brush & Washings

- Central tumour exfoliating into the bronchi
- Squamous cell carcinoma and small cell most sensitive
- Washings
  - 5mls of salt solution instilled and then re-aspirated
- Brush
  - Rolled on a glass slide
  - Before biopsy
- Adequacy
  - Pulmonary macrophages, squamous cells, bronchial epithelial cells
  - Adequate if positive!
Bronchoalveolar Lavage

- Useful in benign disease
  - Cell differential
  - CD4:CD8 ratio
- Assessment of terminal air spaces
- 50-100 mls of warm saline
- Flood distal airspace and re-aspirated
- Adequacy
  - Alveolar macrophages (>10 per 10 HPF)
  - <5% BE or Squamous cells
Lung FNA

- Most effective cytological technique to diagnose pulmonary carcinoma
- Close radiological correlation required
- Onsite rapid assessment - triage material
- Direct smears (AD, IMS)
- Needle rinse
  - Hanks/PEG - ICC
  - RPMI - flow
  - Cell block – IHC, molecular
- Adequate if malignant!
EBUS Lymph node FNA

- Diagnose and Stage (N stage)
- Preparation
  - Rapid onsite assessment and smears
  - Cytolyte, Thinprep and cell block
- Adequacy
  - Minimum number of lymphocytes (>40 at x
  - Pigment laden macrophages
  - Germinal centre fragments
- Cellblock for molecular
Pleural Fluid

- Diagnose & Stage (M stage)
- No adequacy criteria
- Cytospins (2 PAP, 2 MGG)
  - Peg for immunocytochemistry
- Cell block for molecular
Standardized Terminology and Nomenclature for Respiratory Cytology

- I  Non diagnostic
- II  Negative (for malignancy)
- III  Atypical
- IV  Neoplasm, benign neoplasm, and low-grade malignancy
- V  Suspicious for malignancy
- VI  Malignant

The Papanicolaou Society of Cytopathology Guidelines
*Diagnostic Cytopathology*
## Risk of Malignancy

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy&lt;sup&gt;a&lt;/sup&gt;(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic</td>
<td>40</td>
</tr>
<tr>
<td>Negative for malignancy</td>
<td>24–43</td>
</tr>
<tr>
<td>Atypical</td>
<td>54</td>
</tr>
<tr>
<td>Neoplastic, benign neoplasm, low-grade carcinoma</td>
<td>N/A</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>82</td>
</tr>
<tr>
<td>Malignant</td>
<td>77–100&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on literature review.

<sup>b</sup>Depends on type and subtype of malignancy.
I. Non diagnostic

- Adequacy
  - Defined for sputum and LN EBUS-FNA
  - Not for brush, washing and Lung FNA (adequate if malignant!)
  - Doesn't mean lesion has been sampled

- Poor Sampling
  - Multidisciplinary approach
  - On-site evaluation

- Technical issues
  - Smearing, fixation, staining
II. Negative for malignancy

- Adequate
- Absence of cellular atypia
- Diagnose a lesion defined radiologically
  - Infection (abscess, TB, fungi, parasite, viral)
  - Infarction
  - Sarcoid
  - Aspiration
  - Amyloid
  - Lipoid
- Normal tissue – radiology vague (no definite lesion)
III. Atypical

- Limited use of this category – not a wastebasket!
- Two types
  - Abnormalities greater than inflam/repair but less than suspicious for malignancy
  - Highly suspicious for a benign neoplasm
    - Eg bland spindled cells suggestive of SFT
IV. Neoplasm, benign neoplasm and low-grade malignancy

- Allows discretion in treatment of elderly/medically unfit
- Adequately cellular and diagnostic
  - Solitary fibrous tumour
  - Pulmonary hamartoma
  - Squamous papilloma
  - Granular cell tumour
  - PEComa (clear cell sugar tumour)
  - Meningioma
  - Inflammatory myofibroblastic tumour
  - Langerhan’s cell histiocytosis
- Does not include neuroendocrine tumours (carcinoids)
V. Suspicious for malignancy

- Not diagnostic of malignancy – inform your clinicians!
- Carcinomas (NSCLC, SCLC, NEC), Carcinoids, Lymphoma, Metastases
- Inter-observer variability & experience
  - Scant cellularity
  - Peripheral sampling
  - Cavitation
  - Contamination of adjacent material
  - High level of differentiation in adca
VI. Malignant

- **Non small cell carcinoma** – need to further classify
  - Adenocarcinoma
  - Squamous cell carcinoma
  - *Large cell carcinoma*
- **Small cell carcinoma**
- Neuroendocrine (TC, AC, LCNEC)
- Adenoid cystic carcinoma
- Mucoepidermoid
- Lymphoma
- Metastases
Squamous cell carcinoma

- Single cell and flat sheets with well defined cell membranes
- Cytoplasm: polygonal, oval, spindled and irregular cell contours with dense or keratinised cytoplasm
- Nuclei: oval, rectangular, irregular contours, centrally situated, coarse to pyknotic like dark chromatin
- Nucleoli often inconspicuous
Washings
FNA
Pitfalls

- Upper RTI with reactive changes (sputum, washings)
- Reactive changes in cavities (aspergillus), bronchiectasis, infection, radiation
- Contamination – EBUS LN
- Necrosis can mimic keratinisation
- In situ v invasive
Adenocarcinoma

- Mostly flat to three-dimensional aggregates and variable number of individual tumour cells
- Acinar and glandular structures in aggregates
- Cytoplasm: abundant, delicate, granular to vacuolated, mucin
- Nuclei: eccentric round to oval structures with minor membrane irregularities and fine chromatin
- Prominent nucleoli
Washings
FNA
FNA
Pitfalls

- Reactive bronchial epithelium (washings)
- Pseudoglandular squamous cell
- Metastases
- Lepidic
Adenocarcinoma with lepidic pattern

- Adenocarcinoma-in-situ
- Minimally invasive adenocarcinoma
- Invasive adenocarcinoma with lepidic pattern

- Can you go any further on cytology??
- Adequate classification can require resection
Immunocytochemistry

- Tissue preservation important
- Cocktail of two markers
  - TTF1, ck5/6
  - P63(p40)Nap
- Special stains
  - Mucin for adenocarcinoma
Morphologic adenocarcinoma patterns clearly present
  • Adenocarcinoma
Morphologic adenocarcinoma patterns not present (supported by special stains)
  • Non-small cell carcinoma, favour adenocarcinoma
Morphologic squamous cell patterns clearly present
  • Squamous cell carcinoma
Morphologic squamous cell patterns not present (supported by stains)
  • Non-small cell carcinoma, favour squamous cell carcinoma
Large cell carcinoma

- Groups of large clearly malignant cells
- Pleomorphic single cell population
- High N/C ratio
- Necrotic background
- Immunos equivocal/negative
- Histological (resection) diagnosis
- Cyto dx – Non-small cell carcinoma, NOS
- Large cell neuroendocrine carcinoma – NE markers
Non small cell carcinoma NOS
Small cell carcinoma

- Single and loose clusters of cells
- Scant cytoplasm
- Granular/clumped chromatin
- Indistinct nucleoli
- Nuclear moulding
- Necrosis and Azzopardi affect
Washings
Washings
Washings
FNA
FNA
Pitfalls

- Degenerate bronchial cells (washings)
- Lymphocytes (washings)
- Poorly differentiated squamous cell carcinoma
- Lymphoma – CD56
Carcinoid

- Uniform small cells, rounded nuclei, stippled chromatin
- Palisades, trabeculae
- Bare nuclei
- Necrosis rare
- Brushings and FNA
- Rarely exfoliates into washings
Atypical carcinoid

- Neuroendocrine cytology
- Increased pleomorphism, mitoses, necrosis (v TC)
- No moulding, smearing, no abundant mitoses & necrosis (v SCC)
- Cell block – MIB 1 helps v SCC
FNA
Adenoid cystic

- Primary or metastatic
- Large acellular basement membrane spheres (MGG)
- Background of small cells with uniform nuclei
NA
FNA

Metastatic urothelial carcinoma
FNA
Pleural fluid
Pleural fluid

CD56

BerEp4
Pleural fluid – cell block
Concluding remarks

- Proposed new classification
- Terminology
  - Non small cell NOS!!
- Consider cellblock
- Think molecular