Role of pathology in Diagnosis and Management of Cancer

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Cancer – from Latin word for “crab”
Cytology interpretation and rapid-review FNA

Screening programmes – cervical, breast, bowel

Biopsy and resection histology – classifying, grading staging

Role of Pathology in the diagnosis and management of cancer

Diagnosing familial cancers

Ancillary studies

Predictive and prognostic markers
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Cervical Screening Programme

• British society cervical cytology 1986
• Replaced by British Association Cytopathology 2011
• Estimated to reduce cervical cancer deaths by 4500 per year
Mild Dyskaryosis

Koilocytes

Moderate and Severe Dyskaryosis

Moderate and Severe Dyskaryosis
Cervical Screening Programme

Sample taken – liquid based cytology

Slide made and reviewed by screener 4-5 minutes

Review by checker 1.5 mins

Routine recall

Advise GP refer Gynae

Glandular Abnormality

Consultant Review

abnormal

High grade dyskaryosis

Direct referral by lab to colposcopy

Borderline/low grade dyskaryosis

HPV test

positive

negative

normal

routine recall
Proposed National Switch to primary HPV testing

Smear taken as usual with LBC – no slide made – primary HPV testing from pot

- negative: Routine recall 3 years
- positive: Cytology triage (slide made)
  - Cytology normal: Rescreen 12 months
  - Colposcopy
Potential problems

- Miss HPV negative dysplasias and cancers
- Difficulty commissioning services
- Lack of staff
- Potential for different strains of HPV to increase with introduction of vaccine
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Cytology for malignant cells

- Urine cytology for renal cell tumours 30-50% sensitive (Piscioli et al)
- Sputum – pre-bronchoscopy sputum 50%, bronchial washings 63%, post-bronchoscopy sputum 89%, bronchial brushings 52% sensitivity (combined specificity 87%)(Jay et al)
- Ascitic cytology 50-60% sensitive (Karoo et al 2003)
Immediate on-site interpretation cytology

Advantages

• Immediately alert clinician of need for repeat aspirate
• Advise if additional samples needed for special stains, etc.
• If confident in diagnosis can speed up further investigation
• If reassuring, reduce waiting times and anxiety for patient
• Head and neck cancers 4.6% difference in preliminary and final cytology diagnosis in large study (biggest difficulty distinguishing reactive nodes from lymphoma) (Sauer et al 1992)
• 95% accuracy immediate interpretation breast FNA (Lieuw et al 2011)
• FNAs lung 96% sensitive and almost 100% specific and found to reduce mortality from repeat procedures
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Identifying/grading/staging of cancers on biopsies and resection specimens

- Morphology
- Architecture
- Ancillary Studies
Ancillary Studies – intermediate filament family

Cytokeratins – epithelium
Vimentin – mesenchyme (also epithelium)
GFAP (glial fibrillary acidic protein) – Glia
Desmin – Muscle
Neurofilament - neurons
Cytokeratins

- Moll et al. designated system “Moll’s catalogue”

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<thead>
<tr>
<th>Basic (Type B/Class 2)</th>
<th>Acidic (Type A/Class 1)</th>
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<tbody>
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<td>CK1</td>
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“Squamous keratins”
Ab: CK903, CK5/6 -

“Simple/non-squamous keratins”
Ab: Cam 5.2 – LMWCK cocktail
Uses:

- Identify poorly diff. malignancy as carcinoma – pancytokeratin e.g. AE1/AE3 or MNF116 + Cam 5.2
- Narrow down organ of origin – e.g. CK7, CK20
Other epithelial markers

- EMA – present in majority of non-squamous carcinomas – strongest in secretory epithelium e.g. eccrine, breast, pancreas) – not specific for epithelium
- CEA – specific but not sensitive for carcinoma. Positive in HCC, colorectal, stomach, lung adenocarcinomas, pancreatobiliary
- Ber-EP4 – positive most adenocarcinomas – useful to differentiate lung adenoca from mesothelioma
Mesothelial Markers

- Cyokeratins AE1/3 and Cam 5.2 positive (perinuclear accentuation), can be CK5 positive
- Calretinin
- WT1
- D2-40
- (BerEP4 = negative!)
66 year old man with 50 pack year hx and previous dock yard worker
IHC:
CK5 positive
Calretinin positive
WT1 positive
BerEP4 negative
CEA negative
Melanocytic markers:
Melan A, S100

Endocrine Markers:
CD56, chromogranin A, Synaptophysin

Renal Cell Markers:
PAX 8, RCC
Unexpected/incidental findings of cancer and use of ancillary studies to locate origin
Immuno

• MNF116 positive
• CK7 and CK20 negative
• Endocrine markers (chromogranin and synaptophysin) negative
• Melan A and S100 negative
• RCC and PAX8 negative
• PSA focal positivity
• Hx of prostate cancer – treated at another hospital
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Identifying treatment response – steroid hormone receptors

In 1980s and 1990 lots of effort went into studying prognostic and predictive biomarkers – ER, PR and herceptin are now in routine use

ER negativity – better response to conventional chemo (complete response 21-33%) vs ER positive tumours (7-8%) (Colleoni et al 2004)

• ER positivity – indication for oestrogen receptor modifying drugs
• Use of Oestrogen receptor modifying drugs drugs first example of selective targeted therapy in oncology
• Tamoxifen – active metabolites competitively inhibit AR2 sites on oestrogen receptor – antagonist in breast, partial agonist in uterus
• Reduces death in ER positive women by 31% per year
• Aromatase inhibitors block the conversion of precursor molecules to oestradiol (e.g. anastrazole)
Differences in AI and Tamoxifen Mechanism of Action

Androgens

Aromatase

Tamoxifen

Estrogens

ERE (estrogen response elements)

ER (estrogen receptor)

ER target genes

↑ Proliferation

AI (e.g., exemestane)

EREs = estrogen response elements.

Johnston SRD et al. Nat Rev Cancer. 2003;3:821-831. Adapted with permission:

http://www.nature.com.
PR receptor positivity

• Strongly related to oestrogen so rarely expressed in ER negative tumours

• PR positive and PR negative patients show same relative benefit from endocrine treatment (tamoxifen/aromatase inhibitors) (Dowset et al 2006)

• However patients with higher expression PR worse outcome in groups of hormonally treated patients
Molecular Genetics

Identifying oncogenes in patients more likely to benefit from targeted therapies

HER-2 – breast cancer
EGFR and ALK1 – non-small cell lung cancer
BRAF – melanoma
KRAS – colorectal cancer

Dowsett M, Houghton J, Iden C. Benefit from adjuvant tamoxifen therapy in primary breast cancer patients according to oestrogen receptor, progesterone receptor, EGF receptor and HER2 status. Ann Oncol. 2006;17:818–826


