CERVICAL CYTOLOGY

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Oxford Pathology Course 2010 for FRCPath

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Cervical Cytology

- **Aim of cervical screening**
  - To identify women at risk of developing cervical cancer
  - To eradicate the pre-invasive lesion

- **Identification**
  - Cytological recognition of dyskaryosis
    - Conventional microscopy
    - Immunocytochemistry
  - HPV testing (pre-pre-cancer!)
Dyskaryosis – abnormal nucleus

- Disproportionate nuclear enlargement
- Irregularity of form and outline
- Irregular thickness of nuclear membrane
- Irregular chromatin distribution
- Hyperchromasia (or hypochromasia)
- Abnormality in form & number of nucleoli
- Multinucleation
Dyskaryosis – irregular form & outline
Dyskaryosis
irregularity in nuclear membrane
Dyskaryosis – abnormal chromatin pattern
# Cytology results England 2005-6

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Call</th>
<th>Recall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3,940,194</td>
<td>119,832</td>
<td>1,881,734</td>
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<tr>
<td>Inadequate</td>
<td>7.2%</td>
<td>8.1%</td>
<td>6.5%</td>
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<tr>
<td>Negative</td>
<td>85.9</td>
<td>83.8</td>
<td>89.7</td>
</tr>
<tr>
<td>Borderline</td>
<td>3.6</td>
<td>3.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Mild dysk</td>
<td>2.1</td>
<td>2.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Mod dysk</td>
<td>0.6</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Severe dysk</td>
<td>0.5</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>?Invasive</td>
<td>0.0 (888)</td>
<td>0.1 (64)</td>
<td>0.0 (231)</td>
</tr>
<tr>
<td>?Glandular</td>
<td>0.1 (2066)</td>
<td>0.0 (50)</td>
<td>0.0 (678)</td>
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</tbody>
</table>
Mild Dyskaryosis \( ? \)CIN I

- Superficial/Intermediate cell types
- Mild nuclear enlargement
- Mild hyperchromasia
- Nucleus occupies less than half of cell area
Moderate Dyskaryosis ?CIN2

- Intermediate/ parabasal cell types
- Sizes of cells more variable
- Mild to moderate hyperchromasia
- Greater nuclear irregularity
- Occasional elongated cells
- Nucleus occupies less than two thirds of cell area
Severe Dyskaryosis ?CIN3

- Parabasal cell types
- Increased nuclear irregularity & hyperchromasia
- Elongated cells
- Thin rim of cytoplasm
- Nucleus usually greater than two thirds cell area
Severe Dyskaryosis - bland
Squamous dyskaryosis: Problems

- Small cell dyskaryosis
- Pale cell dyskaryosis
- Squamous metaplasia vs bland dyskaryosis
- Dysk in atrophy
- (Dysk with cytolysis)

- Gland crypt involvement in CIN vs glandular neoplasia
- Microbiopsies aka hyperchromatic crowded groups (HCCGs)
Severe small cell squamous dyskaryosis

- Scanty cells
- Dispersed cells
- Exclude:
  - Histiocytes
  - Lymphocytes
  - Metaplastic cells
  - Reserve cells
  - Endometrial cells
Immature metaplastic Histocytes cells/reserve cells
Pale dyskaryosis vs follicular cervicitis
Small cell dysk vs endometrial cells
Small cell dysk vs endometrial cells
Pale dyskaryosis

- Staining artefact?
- Other criteria for dyskaryosis unchanged
- May only be recognized on audit

Lookalikes:
- BNC with HPV
- Immature metaplasia
- Repair
Squamous carcinoma
Cytology

- Severe squamous cell dyskaryosis with:-
  - Bizarre nuclear & cytoplasmic morphology
    - Nuclear & cytoplasmic pleomorphism

- Cytoplasm
  - Fibre cells/ tadpole cells/ keratinisation

- Nuclei
  - Extreme chromatin clumping/ clearing
  - Irregular nuclear outline
  - Anisonucleosis
Squamous carcinoma
Cytology

- Bloodstained smears
  - Conventional cytology may be “inadequate”
  - LBC may see collections of altered blood
- Tumour diathesis (host response)
  - Necrotic debris
    - Fragments of leucocytes and nuclear material
  - LBC
    - Grey/blue amorphous debris
    - “Clinging” diathesis (SurePath)
Tadpole cell

Tumour diathesis
Sources of glandular cells in “cervical” samples

- Genital tract
- Cervix
- Endometrium
- Vagina
- Fallopian tubes
- Vulva

- Extra-uterine
- Metastatic to GT
  - Ovary
  - 1° peritoneal
  - 2° distant sites

- Trans-uterine
  - Ovary
  - 1° peritoneal
  - 2° distant sites
Glandular prediction in LBC Compared with Conventional

- Nuclear details more pronounced
- Nuclear enlargement is not a reliable indicator
- Architectural features more subtle
- Little or no feathering
- Dissociated normal & abnormal cells common

- Three most useful diagnostic criteria
  - Irregular nuclear membranes
  - Dissociated abnormal cells
  - Decreased cytoplasm (raised n/c ratio)
Cytological Prediction
HG-CGIN

- Rosettes
- Pseudostratification
- Feathering less prominent
- Maybe dense cytoplasm
- Nuclear distortion (SP)
- Raised n/c ratio
- Stippled chromatin
- Mitotic figures

- Often abundant
- 3D clusters & strips
- More cohesive
- Cytoplasm
  - Variable density
  - Better demarcation
  - Baso/ cyanophilic
- Well preserved
Pseudostratification

SurePath

ThinPrep

SP Common border
Snake & Egg SP & Conv
Non-neoplastic
- Tangential presentation (SP)
- Benign endometrial cells
- Lower uterine segment sampling (LUS)
- Tuboendometrioid metaplasia (TEM)
- Microglandular hyperplasia (MGH)

Neoplastic
- CIN with crypt involvement/
- hyperchromatic crowded groups
- Early invasive adenocarcinoma
- Endometrial neoplasia
- Extrauterine neoplasia
HG-CGIN pseudostratification
Common borders vs non-common borders
Benign endometrial cells
Lower Uterine Segment (Isthmic) Sampling
Tuboendometrioid metaplasia
Adenocarcinoma
Evidence of invasion

Features of HG-CGIN & invasion overlap

• Increasing degree of nuclear pleomorphism
• Increasing n/c ratio (nuclear crowding)
• Prominent +/- irregular nucleoli
• Abnormal or high number of mitoses
• Papillary fragments
• Tumour diathesis
Adenocarcinoma Caveats

- Microbiopsies more cohesive
  - Look in the background for discrete and small clusters of malignant cells

- Nucleo-cytoplasmic ratio unreliable
  - Moderate amount of cytoplasm in mucinous endometrioid & serous carcinomas
  - Abundant cytoplasm in clear cell & glassy cell carcinomas
Adenocarcinoma

Cervical origin
- Pseudostratification
- Snake & egg pattern

Non-cervical origin more likely
- Disorganised clusters
- “Bags” of polymorphs
- Acinar groups
Endocervical Adenocarcinoma
Endometrial adenocarcinoma
Adenocarcinoma in LBC
Non-cervical/extraterine lesions
Microbiopsies—
Histological fragments in cytological specimens

Benign

- Periphery well demarcated
- Architecture orderly

Pre-invasive/ invasive

- Periphery haphazard
- Architecture disordered
  - Central “piling up” of cells – (squamous lesions)
  - Subtle disturbance in honeycomb – (glandular lesions)
Borderline nuclear changes
Genuine doubt that the changes are neoplastic

- Holding category
- **NOT Necessarily** LOW GRADE
- Risk of neoplasia:
  - high grade <30%
  - low grade <46%
- Highest risk group: atypia in immature metaplasia
Borderline Changes

- Use only when there is increase in n/c ratio or koilocytes with no nuclear atypia

In the absence of cellular degeneration
In the absence of overt dyskaryosis

- Mild hyperchromasias in enlarged nuclei
- Chromatin slightly coarsened
Inflammatory changes (Not BNC)

- Nuclear enlargement with normal n/c ratio
- Minor variations in shape with smooth nuclear outline
- Regular nucleoli
- Condensation of chromatin under nuclear membrane
- Increased cytoplasmic density
- Metachromatic cytoplasm
Repair vs neoplasia
Degenerative change
Atrophy (Not BNC)

- High n/c ratio (parabasal cells)
- Small denser orangeophilic cells
- Blue blobs

- If irregular nuclei in orangeophilic cells ?? dyskaryosis ... report as BNC & ask for repeat after oestrogenisation
Koilocytes or not koilocytes?
Borderline ?glandular abnormality
Ask - Is it really abnormal?
Uncertain?

Likely reasons for uncertainty:

- LUS? But Absence of stromal component
- LUS? But mitotic figures late in cycle
- TEM? But absence of cilia with excessive nuclear crowding
Borderline Nuclear Change
Proposed BSCC terminology

BNC-NOS
Up to three such reports in 10 years before referral for colposcopy

BNC-?High grade  Immediate referral
BNC-?Glandular  Early repeat within 6 months. Refer on 2nd BNC-G

(Current BSCCP guidelines: Immediate referral)
“Rapid” screen the whole sample (30 secs) Make a note of:

- **Adequacy (= cellularity in LBC)**
  - For 15K cells
    - SurePath: 20 – 25 cells per x 40 field
    - ThinPrep: 10 – 12 cells per x 40 field

- **Hormonal pattern**
  - Appropriate for age & history

- **Cell types & entities present**
  - Abnormal cells/ pathogens/ repair/ regeneration
Tactics Beware
“satisfaction of search”

- The presence of one significant entity does not exclude the possibility of another
- All grades of dysk may be present in one sample
- 50% of CGINs are associated with CIN
- TEM & LUS are common in post-Rx samples – and so is residual pathology
- Microbiopsies can be benign, premalignant & malignant & are numerous in SurePath
- Awareness of look-alikes can cause false negatives – lack of awareness- false positives!
Resources

- Achievable standards, benchmarks for reporting and criteria for evaluating cervical cytology NHSCSP Publication No 1, 2000
- Histopathology reporting in cervical screening NHSCSP Publication No 10, 1999
- Colposcopy & Programme Management NHSCSP Publication No. 20, 2004
- [http://info.cancerresearchuk.org/cancerstats/types/cervix/incidence/?a=544](http://info.cancerresearchuk.org/cancerstats/types/cervix/incidence/?a=544) | [www.cancerscreening.nhs.uk](http://www.cancerscreening.nhs.uk)
**Resources**

- NHS Cervical Screening Programme
  Boxborough: Cytyc, 2003
- SurePath Slide Gyn Morphology Atlas.
  Burlington: TriPath Imaging © 2002
Acknowledgements

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