Cytopathology

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Learning objectives

At the end of this hour you will know:

1. What cytopathology is
2. How specimens are collected, processed, and diagnosed
3. What the major problems are
4. How to design a cytopathology study
5. Where to find additional information
What is cytopathology?

Histopathology

Cytopathology
Cytopathology is the morphological study of dissociated cells
Why not always histopathology?

- Histopathology requires fragments of tissue (biopsies)
- A biopsy is usually obtained through an invasive procedure
- A forceps (or similar instrument is needed)
- There may be bleeding or trauma
<table>
<thead>
<tr>
<th><strong>Histopathology</strong></th>
<th><strong>Cytopathology</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure and architecture</td>
<td>Detached cells</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Fluid, brushings</td>
</tr>
<tr>
<td>Large needle, forceps</td>
<td>Fine needle</td>
</tr>
<tr>
<td>Invasive procedure</td>
<td>Invasive procedure</td>
</tr>
<tr>
<td>30 min. - 2 hrs.</td>
<td>5 min. - 2 hrs.</td>
</tr>
<tr>
<td>Basic stain: H &amp; E</td>
<td>Basic stains: PAP - H &amp; E</td>
</tr>
<tr>
<td>Paraffin block</td>
<td>Slide and/or paraffin block</td>
</tr>
<tr>
<td>Special techniques possible</td>
<td>Special techniques possible</td>
</tr>
</tbody>
</table>
Exfoliative cytology
Aspiration cytology or Fine-needle aspiration
Aspiration

All superficial “lumps”
Breast growths
Thyroid nodules
Enlarged lymph nodes
Aspiration

Deep lesions may be aspirated under imaging guidance (US - CAT)
Exfoliation

All mucosal surfaces, particularly:

- Uterine cervix
- Oro-pharyngeal mucosa
- Gastrointestinal mucosa
- Urinary tract (brush or urine)
1928

George Papanicolaou
The Pap smear today

- Cervical dysplasia and cancer
- Herpes Virus Infection
- Other infections:
  - Candida
  - Fungi
  - *Trychomonas vaginalis* (hominis)
- Uterine carcinoma
Cervical cancer

- The most common cancer in women in most developing countries

- ~ 500,000 deaths per year worldwide
  - 80% in developing countries

Incidence related to:

HPV
Human Papilloma Virus
Circular double-stranded DNA, 8 kilobases, 70 documented types

Types 53, 54, 55, 70

Types 6, 11, 16, 18, 31, 33, 35, 39, 66
LSIL
prise en charge des patientes en utilisant le test HPV

LSIL (Thin Prep)

NORMALE

COLPOSCOPIE +/- biopsies

LSIL

HSIL

Test HPV

HPV haut risque NEGATIF

Cytologie q6m x2

TRAITEMENT

HPV haut risque POSITIF

Cytologie q6m x4

HPV haut risque NEGATIF

Cytologie q6m x4

TRAITEMENT

HPV haut risque POSITIF

Test HPV

### Preneoplastic lesions of the cervix

#### Classification Systems

<table>
<thead>
<tr>
<th>WHO Traditional</th>
<th>CIN</th>
<th>Bethesda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dysplasia</td>
<td>CIN 1</td>
<td>L SIL</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>CIN 2</td>
<td>H SIL</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>CIN 3</td>
<td>H SIL</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>CIN 3</td>
<td>H SIL</td>
</tr>
</tbody>
</table>
Cervical cancer after the “Pap test”

- USA: 1973 to 1994: from 14.2 to 7.8/100,000
- UK: 26% decrease 1995 - 2000
- UK: screening prevents ~2,000 - 4,000 cases/year
- USA: 50% of deaths occur in women who never had a Pap test
Normal
HPV - Mild dysplasia
Moderate dysplasia
Severe dysplasia
Carcinoma
Invasive carcinoma
Invasive carcinoma
Visual Analogue Scales

[Diagram showing changes in cervical epithelium from normal to high grade SIL (Squamous Intraepithelial Lesion), with corresponding Pap smears and histological images.]
These two guys are hopeless, they should learn to agree...
Who can recognize dysplasia and cancer?
Kappa statistics

- Excellent: ≥0.8
- Good: 0.6–0.8
- Fair: 0.4–0.6
- Poor: 0.2–0.4
- Perfect agreement: ≥0.8
- Chance agreement: <0.2
Performance of a group of cytologists

Chance agreement

Perfect agreement

Normal, no dysplasia
Performance of a group of cytologists

Invasive carcinoma

- Chance agreement
- Perfect agreement

- Poor
- Fair
- Good
- Excellent

Agreement levels: Excellent (.75), Good (.5), Fair, Poor (0.5)
Performance of a group of cytologists

Dysplasia (particularly low-grade)
Normal

Borderline lesions

Atypical Epithelium

Group III lesions

Dysplasia

Cancer
Major problems in histological and cytological assessment

- Distinction between non-dysplastic and dysplastic phenotype
- Grading of dysplasia and correlation with cancer risk
- Distinction between high-grade dysplasia and early invasive gastric cancer
Study A: patients

Four groups of 100 women each followed up yearly for 12 years
- Group 1: normal PAP
- Group 2: mild dysplasia/koilocytosis
- Group 3: moderate dysplasia
- Group 4: severe dysplasia

End point: invasive carcinoma
Study A: methods

- Patients followed by Research Nurse Florence Picky
- All PAP smears examined by famous cytopathologist Dr. Smartcell
- All histopathology reviewed by Prof. Goodeyes, an expert in uterine cancer
- All slides reviewed by a group of experts at the end of the study
Study A: results

- Normal
- CIS 1
- CIS 2
- CIS 3
- Cancer

Graph showing progression over time with different stages of CIS and Cancer.
Study A: conclusions

- Patients with a normal PAP smear do not develop cancer within 12 years.
- 11% of CIN 1 progress to CIN 3.
- 22% of CIN 2 progress to CIN 3.
- > 12% of CIN 3 develop invasive carcinoma.
- CIN 1 regresses more often than CIN 2, and more than CIN 3.
Study B: patients

- Four groups of 100 women each followed up yearly for 12 years
  - Group 1: normal PAP
  - Group 2: mild dysplasia/koilocytosis
  - Group 3: moderate dysplasia
  - Group 4: severe dysplasia

- End point: invasive carcinoma
Study B: methods

- Patients told to come once a year
- PAP smears examined by different cytopathologists
- Histopathology diagnosis at three local hospitals
- Slides not reviewed at the end of the study
Study B: conclusions

- More patients with CIN 1 progress to cancer than those with CIN 3
- Normal patients develop cancer more often than CIN patients
- Regression very common in patients with CIN 3, less common in CIN 1

These results are internally invalid
Lessons learned

- The design of a study is the most important key to its success

Beware of the pitfalls!
Study B: pitfalls

- Patients told to come once a year
- PAP smears examined by different cytopathologists
- Histopathology diagnosis at three local hospitals
- Slides not reviewed at the end of the study
# Meta-analysis

**Table 7.3** Natural history of CIN. A meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Regress</th>
<th>Persist</th>
<th>Progress to CIS</th>
<th>Progress to invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV lacking CIN</td>
<td>80%</td>
<td>15%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>CIN 1</td>
<td>57%</td>
<td>32%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN 2</td>
<td>43%</td>
<td>35%</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN 3</td>
<td>32%</td>
<td>&lt; 56%</td>
<td>-</td>
<td>&gt; 12%</td>
</tr>
</tbody>
</table>
Age of occurrence
Conclusions

Cytology is a valuable method to screen for and prevent cervical cancer.

Before programs are designed and implemented, a thorough knowledge of local conditions is indispensable.

Important studies in many populations remain to be performed.
A clinical study is a community effort: investigators, patients, health authorities, statisticians, consultants, must be involved from the planning stage.
Additional Information

http://www.cytopathology.org/
American Society of Cytopathology

http://pathology2.jhu.edu/cytopath/
Johns Hopkins Cytopathology

http://crsg.ubc.kun.nl/thesaurus/
Internet Thesaurus of Cytopathology