The place of Colposcopy in Cytology and HPV based screening: What is going to change?

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Disclosures

• No financial relationships or conflict of interest to disclose
The outcome will remain the histologic diagnosis

- The biopsy should be obtained under colposcopy
- The biopsy should be taken around the squamous-columnar junction
- The performance of the histologic diagnosis will depend of the expertise of the colposcopist and the pathologist
HPV infection and precancerous lesions

Initial latent Infection with Papilloma virus

First year

Cervical cancer

Clearance of infection

Persistent infection

Productive infection CIN1 / LSIL

5 years

Transforming infection CIN2/3/HSIL

10 years and more

Cancer
LSIL / HSIL

- Low grade squamous intraepithelial lesion (LSIL): productive infection
- High grade squamous intraepithelial lesion (HSIL): transforming infection
Infectious cycle of HPV

1. Viral penetration

2. Rare event: transforming infection
   - Expression of E6 and E7 genes
   - Assemblage of virions: L1, L2

3. Frequent event: replication of viral DNA
   - E1, E2, E4

4. Frequent event: productive infection

Inactivation of pRB by HR-HPV E7 results in marked overexpression of p16

Promoter p16^{INK4a}

Persistent HPV infection
p16 immuno-positive in HSIL
If morphologic interpretation is w/o doubt
- NILM
- -IN 1
- -IN 3

no p16 stain

LAST Dx
- NILM
- LSIL
- HSIL

If morphologic interpretation is
- -IN 2 vs NILM mimic
- -IN 3 vs NILM mimic
- -IN 2
- < -IN 1 with HSIL cytology

p16 stain should be performed

If p16 stain is negative (patchy, focal)
LAST Dx
- NILM
- LSIL
- non-HPV pathology

If p16 is positive : strong block staining
LAST DX   HSIL

any identified p16-positive area must meet H&E morphologic criteria for a high grade lesion

Darragh et al, 2012  LAST of the American Society of Colposcopy and Cervical Pathology
CIN 1: p16 focal staining = negative
WHO Histologic Terminology 2003

- Condyloma
- CIN I, II, III (with koilocytosis)
- Adenocarcinoma in situ
- Micro-invasive squamous carcinoma
- Invasive squamous or glandular carcinoma
WHO Terminology 2014

- LSIL
- HSIL (CIN2 or 3 in young patients)
- Adenocarcinoma in situ
- Superficially invasive squamous carcinoma
- Invasive squamous or glandular carcinoma

Do p16 IHC for differential diagnosis between LSIL and HSIL
ASC-US: The Issues

ASC-US cytology
- Represents 2-5% of all cytology interpretations
- 6-10% of ASC-US harbors underlying CIN2+

Management options
- Repeat testing
- Direct to colposcopy
- Triage with HR-HPV testing

HPV triage in ASC-US Cytology Results
- 40 - 50% rate of HR-HPV positivity for ASC-US in women ≥ 30 and even higher in younger women
Initial ASC-US after 30 ys

- HPV Test
  - Negative
  - Positive
    - Colposcopy with biopsy if abnormal

3 yrs Pap smear

French National Cancer Institute recommandations 2016
Ki 67 in normal squamous epithelium

p16 and Ki67 in transforming infection
Dual staining  p16/Ki-67
# p16/Ki67 performance ASC-US

<table>
<thead>
<tr>
<th>Age Group</th>
<th>P16/Ki67 Sens</th>
<th>P16/Ki67 Spec</th>
<th>HR-HPV Sens</th>
<th>HR-HPV Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>92.2%</td>
<td>80.6%</td>
<td>90.9%</td>
<td>36.3%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>96.8%</td>
<td>72.4%</td>
<td>100%</td>
<td>23.8%</td>
</tr>
<tr>
<td>≥ 30</td>
<td>89.1%</td>
<td>85.5%</td>
<td>84.8%</td>
<td>43.6%</td>
</tr>
</tbody>
</table>

Initial ASC-US before 30 ys

HPV Test

- Negative
- Positive

Positive:

Colposcopy with biopsy if abnormal

p16/ki67

Positive

Negative

Pap smear

1 y

Pap smear

3 y

French National Cancer Institute recommandations 2016
LSIL: The Issues

LSIL cytology
- Represents 2-3% of all cytology interpretations
- 15-20% of LSIL harbors underlying CIN2+

Management challenge
- Direct colposcopic intervention based on cytology alone leads to huge over-intervention and false positive results
- HR-HPV positivity of 85% on LSIL leads to ineffective triage

Existing management options are sub-optimal
- Direct to colposcopy
- Repeat Pap testing until colposcopy
## p16/Ki67 performance in LSIL

<table>
<thead>
<tr>
<th></th>
<th>P16/Ki67</th>
<th>HR-HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens</td>
<td>Spec</td>
</tr>
<tr>
<td>all ages</td>
<td>94.2%</td>
<td>68.0%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>96.4%</td>
<td>62.1%</td>
</tr>
<tr>
<td>≥ 30</td>
<td>92.7%</td>
<td>70.7%</td>
</tr>
</tbody>
</table>

PALMS Trial Data in LSIL
Rates of Positive Test Results per Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>LSIL Cases</th>
<th>P16/ki67</th>
<th>HR-HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>529</td>
<td>52.4%</td>
<td>83.9%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>250</td>
<td>54.8%</td>
<td>88.0%</td>
</tr>
<tr>
<td>≥ 30</td>
<td>279</td>
<td>50.2%</td>
<td>80.3%</td>
</tr>
</tbody>
</table>

Bergeron C et al Cancer Cytopathol 2015
Initial Cytologic LSIL

Colposcopy

+ p16/Ki67

- Pap smear or HPV test

1y
Relative incidence of CIN3+ after a negative result with HPV vs cytology based screening

<table>
<thead>
<tr>
<th>Study</th>
<th>Detection rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbyn et al, Vaccine 2012</td>
<td>0.53</td>
<td>(0.29, 0.98)</td>
</tr>
<tr>
<td>Naucler, 2007</td>
<td>0.53 (0.29, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Kitchener, 2009</td>
<td>0.52 (0.28, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Ronco, 2010*</td>
<td>0.34 (0.15, 0.75)</td>
<td></td>
</tr>
<tr>
<td>Rijkaart, 2012</td>
<td>0.39 (0.27, 0.56)</td>
<td></td>
</tr>
<tr>
<td>Overall (I²=0.0%, p=0.681)</td>
<td>0.43 (0.33, 0.56)</td>
<td></td>
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</tbody>
</table>
Risk of invasive carcinoma after a negative entry test (HPV- in HPV arm and cytology- in cytology arm)

Solid lines: HPV group.
Dotted lines: cytology group

Pooled RR
0.30 (0.15-0.60)

<table>
<thead>
<tr>
<th></th>
<th>3.5 years</th>
<th>5.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>cytology</td>
<td>15.4 (CI 7.9-27.0)</td>
<td>36.0 (23.2-53.5)</td>
</tr>
<tr>
<td>HPV</td>
<td>4.6 (1.1-12.1)</td>
<td>8.7 (3.3-18.6)</td>
</tr>
</tbody>
</table>

Ronco et al. Lancet 2014
Guidelines can be downloaded at:
Primary screening HPV with cytological triage: Organized screening programme

- **Test HR HPV**
  - **Negative**
  - **Positive**
    - **Cytology**
      - **Normal**
      - **Abnormal**
        - **Colposcopy**
      - **cyto and/or HR HPV 1 yr**
        - **Normal/ Neg**
        - **Abnormal/ Pos**
          - **Colposcopy**
      - **Test HPV 5 ys**
Primary screening HPV with triage strategies
Combinations of different tests? Interval between tests if negative?

- Test HR HPV
  - Positive
    - Cytology
      - Normal or ASC-us or LSIL
        - Test HPV 3ys?
        - HSIL
          - COLPOSCOPY
          - Test HPV 3ys?
          - Negative
            - p16 / Ki 67
              - COLPOSCOPY
              - Test HPV 3ys?
              - Positive
        - HSIL
          - COLPOSCOPY
          - Test HPV 3ys?
          - Negative
            - p16 / Ki 67
              - COLPOSCOPY
              - Test HPV 3ys?
              - Positive
  - 16 / 18
    - Negative
      - Test HPV 3ys?
    - Positive
      - COLPOSCOPY
      - Test HPV 3ys?

Test HPV 5ys
Cervical screening in the XXI century

Need cytological expertise: primary or triage
Need molecular testing: HPV testing, genotyping, p16/Ki67
Need good colposcopists
Colposcopy in the context of primary HPV screening

- Smaller lesions?
- Different staining appearance?
- Will need education and training of the colposcopists