PATHOLOGY OF THE UTERINE CERVIX

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DEPARTMENT OF PATHOLOGY
PATHOLOGY OF THE UTERINE CERVIX

- Anatomy and physiology
- Benign diseases
  1. Infections
  2. Benign tumors and tumor-like lesions
- Premalignant lesions
- Malignant tumors
UTERINE CERVIX

- Lower part of the uterus
- Exocervix and Endocervix
- Stratified nonkeratinizing squamous epithelium and Simple columnar mucin-secreting epithelium
- Fibrous, muscular and elastic tissue
Exocervix
Endocervix
• Location of **squamocolumnar junction** in relation to the external os varies *depending upon* age, menstrual status, pregnancy and oral contraceptive use.

• **Ectropion** = eversion of the columnar epithelium onto the ectocervix, when the cervix grows rapidly and enlarges under the influence of *estrogen*, after menarche and during pregnancy.
- **Squamous metaplasia** = physiological replacement of the everted columnar epithelium on the ectocervix by a newly formed squamous epithelium from the subcolumnar reserve cells.

- **Transformation zone** = region of the cervix where squamous metaplasia occurs.

- Identifying the transformation zone is of great importance in colposcopy, as almost all manifestations of cervical neoplasia occur in this zone.
Squamocolumnar junction (SCJ)

The point where the squamous epithelium meets the columnar epithelium.
Location of the squamocolumnar junction and transformation zone

(a) Before menarche

(b) After puberty / early reproductive age
(c) women in her 30s

(d) Perimenopausal

(e) Post-menopausal
Normal cervix
Cervical ectopion
Diseases of The Uterine Cervix

• **Infections**: Bacterias, Viruses (HPV, HSV), Others

• **Benign Tumors and Tumor-like Lesions**: Polyp / Microglandular Hyperplasia

• **Premalignant and Malignant Lesions**
Classification of HPVs

**Low risk HPV**
- HPV types: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

**High risk HPV**
- HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82

*Baseman and Koutsky JCV 32S, 2005, S16-S24 REVIEW*
Human Papillomavirus

72 Capsomers

HPV Particle

HPV Genome

L1 protein ----> HPV genotyping
-----> Prophylactic HPV vaccine
The Relationship

HPV is *An Infection*

Lesion is *A Disease*

No HPV *No Cervical Cancer*
How does HPV cause cervical precancer & cancer?

• Persistent infections with high-risk HPV types

Premalignant Lesions

- Squamous lesion
  1. Dysplasia- Carcinoma in situ (CIS)
     (mild / moderate / severe) - CIS
  2. Cervical Intraepithelial Neoplasia (CIN)
     (CIN 1 / CIN 2 / CIN 3)
  3. Squamous Intraepithelial Lesion (SIL)
     (Low- / High-grade SIL)
- Adenocarcinoma in situ (AIS)
## Classification of Precancerous Lesions

<table>
<thead>
<tr>
<th>Dysplasia System</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>CIS</th>
<th>CA</th>
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<tbody>
<tr>
<td>CIN System</td>
<td>CIN 1</td>
<td>CIN 2</td>
<td>CIN 3</td>
<td>CA</td>
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<tr>
<td>Bethesda System</td>
<td>LSIL</td>
<td>HSIL</td>
<td></td>
<td>CA</td>
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</table>
Tumorigenesis

Host factors
Environmental factors

The three steps of cervical carcinogenesis

1. Initial infection
   - Normal cervix
   - HPV-infected cervix
   - Clearance

2. Persistent HPV infection
   - Mild cytologic abnormalities
   - Progression
   - Regression
   - Precancerous lesion
   - Invasion

3. Cancer
Disease progression

Normal epithelium

HPV infection; koilocytosis

CIN I

CIN II

CIN III

Carcinoma

Low-grade squamous intraepithelial lesions (LSILs)

High-grade squamous intraepithelial lesions (HSILs)

Screening

Treatment

Time

Months

Years
Squamous Intraepithelial Lesions

- The Bethesda System (TBS)
- Current concepts of pathogenesis and clinical behavior
- Two grades
  - Low-grade SIL / low-risk HPV / Follow
  - High-grade SIL / high-risk HPV / Treat
- Use for both “cytologic (Pap Smear) and histologic diagnosis”
Criteria for Grading SIL

• Degree of nuclear abnormality
• Location of mitotic figures and undifferentiated cells
• Abnormal mitotic figures
• Koilocytes
CONDYLOMA ( LSIL )

HPV infection

- HPV 6, 11 (exophytic lesion)
- HPV 16,18,31,33 (flat lesion)
- Koilocytes – frequently present
- Mostly diploid / polyploid
- No abnormal mitotic figures
- Undifferentiated cell / mitosis : Lower third
- Natural history : Spontaneous regression
High-grade SIL = Precancer

- High risk types of HPV (16, 18, 58, 52, 33, 45,)
- Koilocytes - occasionally present
- Usually aneuploid
- Abnormal mitotic figures
- Undifferentiated cells / mitosis : upper two thirds
- Natural history : Persistence / Progression
Age and disease severity correlation

34.9 ± 9.8  43.2 ± 8.5  46.4 ± 9.8
Age (X±SD) Yrs.

P <0.001, p for trend
Squamous Intraepithelial Lesion
Squamous Intraepithelial Lesions

- Age 36-42 years
- No abnormal symptoms (Bleed / Leukorrhea)
- Diagnosis
  1. Screening (Cytology / HPV test / VIA)
  2. Colposcopy
  3. Biopsy
Screening

- **Conventional pap smear (CP)**: กรมการแพทย์ / สปสช
- **Liquid-based cytology (LBC)**
- **HPV test** (Hybrid Capture 2, Cervista, Cobas 4800) aged 30 years or older with HPV genotyping (HPV16/18)
- **Tumor markers** (P16 / Ki67 / DNA methylation)
- **VIA (visual inspection aided by acetic acid)** ใช้ในประเทศกำลังพัฒนา (เอเชีย / อัฟริกา) / กรมอนามัย (อายุไม่เกิน 45 / บ้านใกล้)
Sensitivity for Detection of HSIL & Cancer

- Conventional Pap: 53%
- Liquid-based cytology (LBC): 74%
- HPV testing (HC 2): 96-99%
- HPV testing + Liquid-based cytology: 100%***

***Negative predictive value ~ 99-100%

PAP Smaer
Comparison between LBC and Conventional Pap
Fixation for cytologic smear

- 95% alcohol
Colposcope

Biopsy forceps are used to sample the cervix.

Colposcope illuminates the cervix for biopsy.
Adenocarcinoma In Situ (AIS)

- **Precursor** of invasive adenocarcinoma
- Associated with SIL (30-60% of cases)
- Invasive carcinoma must be excluded by deep CONE biopsy (Conization)
1. Insert forceps in the os gently
2. Cut through 12 o’clock or other
3. Avoid touching on the mucosa and lesion
Fixative for tissue specimens

• Formalin
  – The best = 10% “Buffered” formalin
• Use “true” 10% formalin
  – If false = Disaster
• How much is formalin volume?
  – 10 x volume
• How fast is the penetration rate?
  – 1 mm / hour
FOR LABORATORY USE ONLY

Specimen Adequacy (see optional comment)
- Satisfactory for evaluation
- Unsatisfactory for evaluation
  - Specimen rejected/not processed
  - Specimen processed and examined

General Categorization
- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality: (see interpretation)
- Others: (see interpretation)

CYTOLOGICAL INTERPRETATION

NEGATIVE FOR MALIGNANCY
Organism
- Trichomonas Vaginalis
- Fungus consistent with Candida spp
- Suggestive of bacterial vaginosis
- Bacteria consistent with Actinomyces spp
- Consistent with Herpes simplex virus
- Other (specify)

Other non-neoplastic findings
- Reactive changes associated with
  - inflammation
  - radiation
  - intrauterine contraceptive device (IUD)
- Glandular cell status post hysterectomy
- Atrophy

OTHERS
- Endometrial cells (in 40 year-old woman or older)
- (specify)

Comment:

EPITHELIAL CELL ABNORMALITIES

Squamous cell
- Atypical squamous cells
  - of undetermined significance (ASC-US)
  - cannot exclude HSIL (ASC-H)
- Low grade squamous intraepithelial lesion (LSIL)
- High grade squamous intraepithelial lesion (HSIL)
  - with features suspicious for invasion
  - Squamous cell carcinoma

Glandular cell
- Atypical cells (see comment)
- Atypical cells favor neoplastic (see comment)
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma (specify)

Other malignant neoplasms:
- (specify)
Microinvasive Squamous Cell Carcinoma

- Age 44-48 years
- No abnormal symptoms (Abnormal bleed / Leukorrhea)
- Diagnosis 1. Screening (cytology +/- HPV test)
  2. Colpolscopy
  3. Definite Dx. need Conization (LEEP) / Hysterectomy
A = Horizontal spread $\leq 7$ mm
B = Depth $\leq 5$ mm
Measurement of invasion
Invasive Squamous Cell Carcinoma (80%)

- Mean age 45 years
  (CMU data 2556: 22-90, mean 54)
- Abnormal bleeding or Leukorrhea (minority of asymptomatic cases)
- Diagnosis: Biopsy
- Treatment: Surgery/ Radiation / Chemotherapy
Invasive Squamous Cell Cercinoma

- **Gross features**
  1. Exophytic mass
  2. Ulcerative infiltrative
  3. Noduloinfiltrative

- **Histologic subtypes**
  1. Keratinizing SCC / Nonkeratinizing SCC
  2. Well / Moderately / Poorly Differentiated SCC
Histologic Classification: WHO 2014

Epithelial Tumors

- Squamous cell carcinoma (75-80% / 80%)
- Adenocarcinoma (20-25% / 15%)
- Other Epithelial tumors
  - adenosquamous carcinoma (2%)
  - adenoid cystic
  - adenoid basal
  - neuroendocrine carcinoma (2%)
  - undifferentiated
Histologic Classification: WHO 2014

Squamous tumors

• (Early invasive) Microinvasive SCC (MICA) or Superficially invasive SCC

• Squamous cell carcinoma
  
  Typical
  
  Keratinizing (well differentiated)

  Non-keratinizing (moderately / poorly)

  Variants
  
  Basaloid*
  
  Verrucous
  
  Warty
  
  Papillary
  
  Lymphoepithelioma-like
  
  Squamotransitional*
มะเร็งปากมดลูกในประเทศไทย : จากอดีตสู่ปัจจุบัน

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<th>ศ./พศ.</th>
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มะเร็งปากมดลูกในจังหวัดต่างๆในประเทศไทย พ.ศ. 2553

- Thailand: 18.1
- Chiang Mai: 25.1
- Lampang: 23.8
- Khon Kaen: 23.3
- Nakhon Phanom: 16.8
- Ubon Ratchathani: 24.8
- Udon Thani: 20.9
- Bangkok: 22.4
- Chon Buri: 30.6
- Lop Buri: 21.7
- Prachuap Khiri Khan: 22.8
- Rayong: 36.6
- Songkhla: 16.2
- Surat Thani: 22.8

***
ผู้หญิงไทยเป็นมะเร็งปากมดลูกมากที่สุดเมื่ออายุเท่าไร?
(สถิติที่จังหวัดเชียงใหม่ พศ 2540-2553)

<table>
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<th>Age (yrs)</th>
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<td>≤ 20</td>
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<td>21-30</td>
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<td>≥ 61</td>
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<td>Total</td>
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*Min - Max = 17 - 91 years, mean = 50 yrs*
Etiology and risk factors

- Human papillomavirus (HPV)
- Others
Cervical Cancer Prevention

• Primary prevention (Risk reduction): Avoid exposure, HPV vaccine

• Secondary prevention (Early detection) Screening (HPV testing, Cytology)

• Tertiary prevention (Treatment)
1. [http://screening.iarc.fr](http://screening.iarc.fr) (Training material)
2. Pictures of gross lesion & histopathology
3. [eslide.med.cmu.ac.th](eslide.med.cmu.ac.th)
   Registration : Name / Surname
   : email add.
   : Activation key repro2016
Thank You for your attention