Neoplastic lesions of the uterine cervix

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### Squamous and Glandular lesions by TAH&CONE Bx.(2541-2545)

<table>
<thead>
<tr>
<th>Age</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIL (40-67)</td>
<td>805</td>
<td>56.73</td>
</tr>
<tr>
<td>MIB (44-75)</td>
<td>210</td>
<td>16.21</td>
</tr>
<tr>
<td>SCC (45-60)</td>
<td>384</td>
<td>27.06</td>
</tr>
<tr>
<td>1,419</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>AIS (45-56)</td>
<td>32</td>
<td>18.39</td>
</tr>
<tr>
<td>EIA (40-55)</td>
<td>12</td>
<td>6.89</td>
</tr>
<tr>
<td>ACA (37-67)</td>
<td>130</td>
<td>74.71</td>
</tr>
<tr>
<td>174</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

### WHO Classification of tumors of the uterine cervix (2003)

- **Epithelial tumors**
  - Squamous tumors and precursors
  - Glandular tumors and precursors
  - Other epithelial tumors
- **Mesenchymal tumors**
- Mixed epithelial and mesenchymal tumors
- **Germ cell tumors**
- **Lymphoid and hematopoietic**
- **Secondary tumors**

### Epithelial Tumors(malignant)

- Squamous cell carcinoma (75-80% / 80%)
- Adenocarcinoma (20-25% / 15%)
- Other epithelial tumors:
  - adenoid cystic
  - adenoid basal
  - neuroendocrine tumors (2%)
  - undifferentiated

### Squamous tumors and precursors

- Squamous cell carcinoma (SCC)
- Early invasive (microinvasive) SCC
- Squamous intraepithelial neoplasia
  - Cervical intraepithelial neoplasia (CIN) 3
  - Squamous cell carcinoma in situ
- Benign squamous cell lesions
  - Condyloma acuminatum
  - Squamous papilloma
  - Fibroepithelial polyp
Glandular tumors and precursors

- Adenocarcinoma (ACA)
- Early Invasive Adenocarcinoma (EIA)
- Adenocarcinoma In Situ (AIS)
- Glandular dysplasia
- Benign glandular lesions
  - Mullerian pilloma
  - Endocervical polyp

Glandular dysplasia

Squamous cell carcinoma

- (Early invasive) Microinvasive SCC (MICA)
- Squamous cell carcinoma
  - Typical Keratinizing
  - Non-keratinizing
- Variants Basaloid*
  - Verrucous
  - Warty
  - Papillary
  - Lymphoepithelioma-like
  - Squamotransitional*

Microinvasive SCC (MICA)

- Diagnosis must be based on
  1. Cone Bx. or TAH (entire lesion)
  2. Cervix is entirely sampled for microscopic evaluation
- Overdiagnosis (41-50%) and Underdiagnosis
- Frequency of MICA
  <1-50% / 16-19% (HSIL patients; Cone bx./TAH)
  12% / 14% (1997)-24% (2000) (stage I)
  7% / 2% (1997)-10.8% (2000) (all invasive)
- Age 35-46 (mean 44, range 17-75)
- 92.5% multicentric lesions

Criteria for invasion

1. Desmoplastic response in stroma
2. Focal eosinophilic maturation of epithelium with prominent nucleoli or pearl formation (better differentiation)
3. Blurring of the epithelial-stromal interface / Scallop margins
4. Loss of polarity of nuclei at epithelial-stromal border with absence of palisaded pattern characteristic of CIN

DDx of invasion (mimics of invasion)

1. Tangentially sectioned epithelium
2. Prior biopsy sites
3. Inflammatory or reparative changes in CIN, including pseudoepitheliomatous changes
4. Obscuring of epithelial-stromal interface by inflammation or other artifacts
5. Gland involvement that is inflamed or tangentially sectioned
6. Cautery or crush artifact
7. Misinterpretation of CA in ECC, including implantation site and floaters from other sites

Pitfalls in interpretation of stromal invasion

- HSIL involving endocervical clefts vs HSIL-like pattern of SCC
- HSIL (with papillary architecture) vs SCC
- HSIL with microinvasion mimics
  - Decidua
  - Placental site nodule
Immunohistochemistry (IHC) for ass. Basement Membrane in MICA

- Type IV collagen
- Laminin
- Fibronectin
- IHC appears to be of limited value in assessing early stromal invasion

Measurement of invasion

Lateral extension
More than one focus of invasion = measure lateral spread of each individual invasive lesion and add together to give a total horizontal spread (Fox 2002)

Common dilemmas and their management

Multifocal lesions, none of which exceed the microinvasive criteria
- These should be described in detail.
- These should be reported in a narrative.
- These should be more likely to mandate LN dissection.
Follow up of stage Ia cervical carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Depth of invasion</th>
<th>+ LVSI (%)</th>
<th>(+) Node (%)</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia1</td>
<td>&lt;3mm</td>
<td>&lt;1mm=3</td>
<td>0.6</td>
<td>0.9-1.4</td>
</tr>
<tr>
<td>Ia2</td>
<td>3.1-5mm</td>
<td>25</td>
<td>9.8</td>
<td>2.5-19 (5.4)</td>
</tr>
</tbody>
</table>

Reporting for Microinvasive SCC

- Biopsy: Greatest dimension
- Cone Bx.: Depth (mm.): Horizontal dimension or width (mm.)
  - multiple foci or single
  - LVSI (+/-, number if + as 1-9 or ≥10)
  - Margins esp. endocervical margin (+/-, not able to evaluate)
- Do not use term “MICA” in pathology report
- Dialogue between pathologist & clinician
- Reviewed by 2 or more pathologists

Squamous cell carcinoma

- (Early invasive) Microinvasive SCC (MICA)
- Squamous cell carcinoma
  - Typical: Keratinizing
  - Non-keratinizing
- Variants: Basaloid*
  - Warty
  - Papillary
  - Lymphoepithelioma-like
  - Squamotransitional*

Squamous Cell Carcinoma

- Subtype: Keratinizing / Non-keratinizing
- Small cell carcinoma is used for neuroendocrine carcinoma only
- Grade: Modified Broder's (WD, MD, PD)
- Prognostic significance of subtype and grade is not confirmed: tumor heterogeneity
  - Subjectivity

Significance of columnar cell differentiation in squamous cell carcinoma

- 5% contained sufficient mucin to warrant reclassification as adenosquamous carcinomas, suggesting that mucin stains may in some cases aid in classification
- 87 SCC: 39% were mucin positive which was associated with a high risk of LN metastases

Other prognostic features

- C-erbB-2 (proto-oncogene)
  - Positive staining in cervical tumors identifies a poor prognostic group that is most apparent in those without nodal metastases
- Epidermal growth factor receptor
- CD44
  - (Speiser, et al. Int J Cancer 1997;185-8)
- Degree of angiogenesis (microvessel density)
Reporting for Invasive SCC (Bx./RH)

- Subtype (variants) / Grade
- Tumor size (greatest dimension, cm.)
- Extent of invasion (proportion relative to wall thickness, inner/middle/outer third) or % or tumor depth / thickness (mm.) and residual uninvolved stroma (mm.)
- LVSI (+/−, number if + as 1-9 or ≥ 10)
- Pelvic, extrapelvic organs?
- Parametrium (direct invasion / LN / LVSI) / margin
- Vagina (positive for HSIL or SCC / neg.) / margin
- Lymph nodes (specify group and no. of positive / total)

Squamous tumors and precursors

- Squamous cell carcinoma (SCC)
- Early invasive (microinvasive) SCC
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  - Fibroepithelial polyp

Classification of HPV-associated intraepithelial lesions of the cervix

<table>
<thead>
<tr>
<th>Terms</th>
<th>HPV risk category</th>
<th>Comparison of classification systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exophytic condyloma</td>
<td>Low risk</td>
<td>Two-tiered CIN</td>
</tr>
<tr>
<td>Exophytic condyloma</td>
<td>High risk</td>
<td>Dysplasia/CIS</td>
</tr>
<tr>
<td>Flat condyloma</td>
<td>Low and high risk</td>
<td>SIL (Squamous intraepithelial lesion)</td>
</tr>
<tr>
<td>CIN 1</td>
<td>Low and high risk</td>
<td>Low-grade CIN</td>
</tr>
<tr>
<td>CIN 2</td>
<td>High risk</td>
<td>High-grade CIN</td>
</tr>
<tr>
<td>CIN 3</td>
<td>High risk</td>
<td>Carcinoma in situ</td>
</tr>
</tbody>
</table>

“CIN”

- Nuclear atypia in all layers
- Low-grade CIN, LSIL
  CIN 1: Maturation in upper 2/3
- High-grade CIN, HSIL
  CIN 2: Maturation in upper 1/2
  CIN 3: Maturation in upper 1/3 or absent

Histopathologic spectrum

- Negative for SIL (Benign / Reactive / Metaplastic process)
- Metaplasia with atypia, atypical immature metaplasia
- Squamous intraepithelial lesion (SIL)
  - Low-grade SIL:
    - Exophytic condyloma / Papillary immature metaplasia
    - Flat condyloma / Cervical intraepithelial neoplasia (CIN) 1
  - High-grade SIL:
    - CIN 2, 3, “Carcinoma in situ (CIS)”
    - “Papillary squamous cell carcinoma in situ”
    - “Keratinizing SIL”, “Eosinophilic dysplasia”

LSIL spectrum

- Koilocytosis (koilocytic atypia),
- Flat condyloma, Exophytic condyloma,
- Papillary immature metaplasia, CIN 1

Low-risk HPV (type 6 / 11) or high-risk HPV

- More likely low-risk HPV:
  - Exophytic condyloma, PIM
- Low-risk or high-risk HPV:
  - Flat condyloma, CIN 1
What is “koilocytes”?

Abnormal nuclear features:
- Enlarged nuclei with variation in and shape, irregular nuclear border, hyperchromasia (including smudged or pyknotic nuclei), binucleation / multinucleation

Abnormal cytoplasmic features:
- Enlarged cell size with variation in size, irregular-shaped perinuclear cytoplasmic cavitation / halo, perihalo cytoplasmic condensation

LSIL criteria

Low-power: alteration of epithelial organization
High-power:

Major histologic criteria – Nuclear atypia
- [intermediate & superficial cells: density, size, staining]
- > 3 fold difference in size + variable staining

Minor histologic criteria (Nuclear atypia < major)
- Binucleation (≥2 cells in 1 HPF)
- Irregular shaped cytoplasmic halos (rim of dense cytoplasm, inconspicuous intercellular bridges)

Crum CF, Rose PG. In: Diagnostic Gynecologic & Obstetric Pathology. 2006

Differential diagnoses of LSIL

- Non-specific reactive epithelial changes
- Inflammatory changes
- Postmenopausal squamous atypia
- Cautery artifacts: nuclear enlargement

- HSIL
- SCC: Warty (condylomatous), Papillary

“LSIL” diagnosis

- Consensus review to improve agreement?
- Pathologists trained and working together may be subject to the same diagnostic bias (Pirog EC 2002)
- Moderate agreement for “normal” and “LSIL”, excellent for “HSIL”, even between gynecologic pathologists (Parker MF 2002)
- Objective tests for HPV?
  - Expensive / Not widely available

Comparison between LSIL & HSIL

<table>
<thead>
<tr>
<th></th>
<th>LSIL</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maturation</td>
<td>Mature</td>
<td>Less mature / immature</td>
</tr>
<tr>
<td>Increased nuclear density (crowding/overlapping)</td>
<td>Mild</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Location of prominent atypia</td>
<td>Upper layer</td>
<td>Upper and lower layers</td>
</tr>
<tr>
<td>Nuclear chromatin [Hyperchromasia]</td>
<td>Dense / uniformly</td>
<td>Coarsely / unevenly</td>
</tr>
<tr>
<td>Chromocenters in nuclei</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal mitoses</td>
<td>- (rare)</td>
<td>+ or -</td>
</tr>
<tr>
<td>Overlapping &amp; atypia of parabasal cells</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mitotic index in upper layers</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ki-67 index</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Differential diagnoses of HSIL

- Reactive/reparative epithelial changes
- Immature squamous metaplasia
- Atrophy (with nuclear enlargement)
- Transitional cell metaplasia
- SCC

Differential diagnoses of HSIL

- Reactive/reparative epithelial changes
- Immature squamous metaplasia
- Atrophy (with nuclear enlargement)
- Transitional cell metaplasia
- SCC
Important factors in interpretation

Quality of sections
• Well-preserved tissue?, Presence of artifacts?
  - Quality of tissue preservation/fixation
• Good enough to interpret?
  - Quality of processing/sectioning
• Tangential section plane?
  - Plane of tissue embedding
• Partial epithelial thickness?
  - Diagnostic criteria based on complete thickness

Interpretation
• Follow available criteria as much as possible (Sensitivity VS Specificity)
• Overdiagnosis = patients’ psychological stress, unnecessary treatment & medical costs

Reporting
• Uniform or accepted diagnostic terms for communication with clinicians
• Suggestion for further management for uncommon lesions that clinicians may be unfamiliar with

Pitfalls in “LSIL” diagnoses

• LSIL VS Non-HPV-related changes
• LSIL VS HSIL

Pitfalls in diagnoses of papillary squamous lesions (“LSIL”)

• Exophytic condyloma VS Warty (condylomatous) SCC
• Papillary immature metaplasia VS Papillary SCC

DDx of papillary cervical neoplasia

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Differentiation</th>
<th>Koilocytosis</th>
<th>Basal atypia</th>
<th>Infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condyloma</td>
<td>Mature</td>
<td>Yes</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Immature condyloma (papillary immature metaplasia)</td>
<td>Immature squamous</td>
<td>Minimal</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Squamotransitional</td>
<td>Immature squamous</td>
<td>No</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Condylomatous</td>
<td>Mature</td>
<td>Variable</td>
<td>Yes</td>
<td>Present</td>
</tr>
<tr>
<td>Verrucous</td>
<td>Mature</td>
<td>No</td>
<td>Minimal</td>
<td>Blunt</td>
</tr>
<tr>
<td>Papillary</td>
<td>None (modif)</td>
<td>No</td>
<td>Yes</td>
<td>Present</td>
</tr>
</tbody>
</table>

Pitfalls in diagnoses of “immature-appearing” squamous epithelium

• HSIL vs HSIL mimics
  – Atrophy
  – immature metaplasia
  – Transitional cell metaplasia
Reactive HSIL

<table>
<thead>
<tr>
<th>Maturation</th>
<th>Reactive</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of superficial cells</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Intraepithelial inflammatory infiltrate / Spongiosis</td>
<td>More likely</td>
<td>Less likely</td>
</tr>
<tr>
<td>Nuclear spacing</td>
<td>Uniform, evenly spaced</td>
<td>Disorganized (loss of polarity)</td>
</tr>
<tr>
<td>Nuclear crowding</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>N/C ratio</td>
<td>Variable</td>
<td>Variable / high</td>
</tr>
<tr>
<td>Variation in nuclear size &amp; shape</td>
<td>Absent or mild</td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear outlines</td>
<td>Smooth, slightly irregular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Variable, vesicular nuclei</td>
<td>Hyperchromatic (coarse)</td>
</tr>
<tr>
<td>Nucleolus</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Mitotic figures and distribution</td>
<td>Infrequent, lower third</td>
<td>Variable</td>
</tr>
<tr>
<td>Atypical mitosis</td>
<td>Absent</td>
<td>Variable</td>
</tr>
<tr>
<td>Ki-67 index / positivity</td>
<td>Variable / no clustering</td>
<td>High / clustering</td>
</tr>
</tbody>
</table>

**Atypical immature metaplasia (AIM)**
- Definitive diagnosis of HSIL could not be made
- AIM shares some but not all morphologic features of HSIL
- Metaplastic epithelium with lack of maturation
- Enlarged or multiple nuclei confined to suprabasal areas
- Variable hyperchromasia and mild chromatin irregularity
- Lack of coarsely clumped chromatin and nuclear membrane irregularities
- Lack of mitotic figures

**Pitfalls in interpretation of cellular strips**
- Immature epithelium vs HSIL
- HSIL vs SCC (frequently impossible)
- Endometrial tissue vs HSIL (in curettage specimen)

**Spectrum of diagnosis in our routine reports**
- Low-grade squamous intraepithelial lesion
- High-grade squamous intraepithelial lesion
- SIL of uncertain grade (LSIL vs HSIL: HSIL cannot be definitely excluded)
- Squamous cell carcinoma, exophytic (papillary) portion only, stromal invasion cannot be evaluated
- Squamous cell carcinoma, depth and width of invasion less than 1 mm, no lymphovascular space invasion
  (Note: larger area of stromal invasion cannot be excluded if the entire lesion is not excised for evaluation)

**Spectrum of diagnosis in our routine reports**

- Confirmed CIN 1 (LSIL):
  - Follow-up (Cytology±HPV test or Colposcopy) or Treat
- CIN 2/3 (HSIL):
  - Treat: Cone biopsy
Summary

Reactive atypia VS SIL
- No significant surface atypia ~ Reactive
- High nuclear density (crowding) ~ SIL

LSIL VS HSIL
- Immature + Coarse chromatin ~ HSIL
- Conspicuous parabasal atypia ~ HSIL
- Mitoses in upper layers ~ HSIL
- Abnormal mitoses ~ HSIL

“in some instances the diagnosis may be made on instinct alone, but instinctive diagnosis may not be reproducible if rendered frequently”

Crum CP, Rose PG. In: Diagnostic Gynecologic & Obstetric Pathology. 2006

Glandular tumors and precursors
- Adenocarcinoma (ACA)
- Early Invasive Adenocarcinoma (EIA)
- Adenocarcinoma In Situ (AIS)
- Glandular dysplasia
- Benign glandular lesions
  - Mullerian pilloma
  - Endocervical polyp

ADENOCARCINOMA
- MUCINOUS ACA.(50%)
- ENDOMETROID ACA.
- CLEAR CELL ACA.
- SEROUS ADA.
- MESONEPHRIC ACA.

MUCINOUS ADENOCARCINOMA
- Endocervical type
- Intestinal type
- Signet ring type
- Minimal deviation type
- Villoglandular type

The possibility of early invasion
- Atypical glands deeper than normal
- Small, irregularly shaped glands
- Individual glands
- Inflammatory or desmoplastic stroma
- Exuberant glandular budding
- Confluent foci of back-to-back glands
- Complex papillary pattern
AIS vs EIA (MIA): Zaino

Two Unequivocal Features for Invasion
1. Individual cells or fragmented or incomplete glands lined by cytologically malignant-appearing cells at stromal interface
2. Malignant-appearing glands surrounded by desmoplastic stroma

AIS vs EIA (MIA): Zaino

It is critical to ascertain that the glands are lined by cytologically appearing malignant cells b/c endocervicitis, microglandular hyperplasia, and rupture of mucin-filled glands may have incomplete glands associated with dense inflammation and edema or fibrosis.

AIS vs EIA (MIA): Zaino

Three additional features
1. Architecturally complex, branching, irregular, or small glands which grow confluently
2. Cribriform growth pattern of malignant-appearing epithelium devoid of stroma within a single gland profile
3. Presence of glands below deep margin of normal glands

AIS vs EIA (MIA): Ostor

• Pathognomonic features: LVSI and Solid pattern
• Dense inflammatory reaction around AIS is not uncommon and may not be seen in MIA
• Glands may be irregular in AIS
• Cribriform and papillary patterns are common in AIS

AIS vs EIA (MIA): Ostor

• No anatomical planes in the cervix
• In about 20% of cases, it is impossible to distinguish AIS from EIA
• In doubtful cases, it is recommended that tumor thickness be measured

AIS vs EIA (MIA): Ostor

• Definitive Dx. of MIA needs CKC or TAH
• Adequate sampling of cone Bx. (2 mm intervals, 3 levels cut from each block)
• Invasive adenocarcinoma following loop excision of AIS (1995)
• LEEP is contraindicated for Dx. & Rx. of cervical glandular lesions
Any New Techniques???

- Int J Gynecol Pathol 2002 (Michael Wells)
- Investigative approaches to endocervical pathology (Dx. / prognosis / pathogenesis)
- Histochem., immunohisto., molecular markers
- There remains no substitute for meticulous examination of the H&E section

Reporting for EIA

- Biopsy: Greatest dimension
- Cone Bx.: Depth / thickness (mm.) (best guess)
- Horizontal dimension or width (mm.)
- Multiple foci or single
- LVSI ( + / - , number if + as 1-9 or ≥10)
- Margins esp. endocervical margin
- Dialogue between pathologist & clinician
- Reviewed by 2 or more pathologists

AIS as Precursor Lesion

- Reasonable evidence supports AIS as precursor lesion of adenocarcinoma
- Coexistence of SIL or SCC with AIS (up to 70%)
- Seems to begin at TZ and extended along endocervical canal (up to 3 cm.)
- Accessible to Dx. By brush or broom cyto. Sampling & superficial Biopsy
- Definitive Rx. = Hysterectomy (cone biopsy in selected cases)

Evidence

- The mean age at diagnosis for AIS (38 years) is approximately 10 years prior to the mean age at diagnosis for ACA
- AIS is morphologically similar to ACA
- AIS is frequently found in association with ACA
- Similar HPV types (types 16 and 18) are found in AIS and ACA

Diagnostic features of AIS

- Preservation of normal glandular architecture
- Crowded, enlarged, hyperchromatic, stratified nuclei
- Mitotic figures essential to diagnosis ("suspended" appearance)
- Apoptotic bodies are present in most cases
- Abrupt transition to normal endocervical epithelium is characteristic

Benign Mimics of Endocervical AIS

- Tuboendometrioid Metaplasia
- Endometriosis
- Endocervicitis
- Radiation Therapy
- Arias-Stella Reaction
Immunohistochemistry and AIS
- Often CEA positive (intracytoplasmic)
- High Ki-67 proliferative index
- P53 negative
- Altered (increased) cell cycle-related molecule expression (cyclin E, p16, p21, p27)
- Decreased ER/PR expression
- p16 positive

Endocervical Glandular Dysplasia (EGD)
- Glandular lesion characterised by significant nuclear abnormalities that more than those encountered in glandular atypia but not fulfil the criteria for AIS
- Severe atypical glandular cells involved only one gland
- Appropriate Rx.?? CKC / D&C / TAH

Glandular Atypia / Dysplasia / AIS / Adenocarcinoma
- Biological continuum ???? (no proof/Ostor)
- Glandular atypia and dysplasia are ill-defined lesions and extremely rare
- No studies of biological potential
- No evidence of progression to AIS
- No reproducible diagnostic criteria

Not reporting glandular dysplasia in clinical practice
- Zaino RJ: Mod Pathol 2000
  : Int J Gynecol Pathol 2002
  : Dx. & Rx. as AIS
- Silverberg SG: Int J Gynecol Pathol 2002
  : EGD = reactive / benign
  : Lower threshold for AIS (H&E)

Counterpoint
- Int J Gynecol Pathol 2004 : Apoptosis, Proliferation (Mitois, MIB1), P53, Bcl2  EGD closely related to AIS than EGA
- Hum Pathol 2004 : p16 & pRb
- Gynecol Oncol 2004 : LEEP as Rx. For AIS-EGD
- Five papers from Europian countries : biomarkers & CGIN (cyclin, p16, CEA, MIB-1, PTEN)

Epithelial Tumors (malignant)
- Squamous cell carcinoma (75-80% / 80%)
- Adenocarcinoma (20-25% / 15%)
- Other epithelial tumors
  adenosquamous (2%)
  adenoid cystic
  adenoid basal
  neuroendocrine tumors (2%)
  undifferentiated
Neuroendocrine tumors (carcinoma)

- Carcinoid Tumor: rare (1)
- Atypical Carcinoid Tumor*: rare (13)
- Large Cell NECA*: rare (2)
- Small Cell CA: 1-2% (120/136)

DDx of Neuroendocrine tumors

<table>
<thead>
<tr>
<th>Mitoses</th>
<th>Nuclear atypia</th>
<th>Necrosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid tumor</td>
<td>rare</td>
<td>absent</td>
</tr>
<tr>
<td>Atypical carcinoid tumor</td>
<td>≤10/10hpf</td>
<td>moderate</td>
</tr>
<tr>
<td>Large cell NECA</td>
<td>&gt;10/10hpf</td>
<td>marked</td>
</tr>
</tbody>
</table>

*Desmoplasia is usually not a feature of neuroendocrine tumors

Small cell carcinoma: histopathology

- Dense cellularity
- Small round or spindle cells
- Scant cytoplasm
- Hyperchromatic, molded nuclei with finely dispersed chromatin, indistinct nucleoli
- Obscured nuclear details

Small cell carcinoma: Histopathology

- Arranged in nest, trabeculae,
- Peripheral palisading, prominent perivascular concentration
- Numerous mitoses
- Confluent necrosis
- LVSI – prominent
- SCC or AdenoCA in ~ 50%

Small cell carcinoma: IHC

- Chromogranin, Synaptophysin, CD56
- 60% NO reactivity for chromogranin, synaptophysin
- one third NO reactivity for neuron-specific enolase
- IHC – NOT required to make this diagnosis

Small cell carcinoma: DDx

- Other endocrine tumor of the cervix
- Poorly differentiated squamous cell CA
- Lymphoepithelioma-like carcinoma
- Adenoid basal carcinoma
- Lymphoma & leukemia
- Endometrial stromal sarcoma
- Metastatic small cell carcinoma
**Small cell carcinoma : DDx**

- Features favor small cell CA over poorly differentiated SCC
  - Younger age / Absence of CIN
  - Positive for neuroendocrine markers
  - Hyperchromatic, molded nuclei with finely dispersed chromatin, indistinct nucleoli
  - Arranged in nest, trabeculae, cords
  - If overlap → based primarily on histologic features

**Small cell carcinoma : behaviour**

- Clinical/biological evidence of hormonal production – rare
- Early metastasis by lymphatic & hematogenous routes → LN, lung, bone, brain, liver
- Rx: RH, chemotherapy and radiation
- Dz free interval usually < 2 years
- 5-year survival ~ 14 -39%

**Comparison of HPV subtypes between different regions in Thailand, IRAC study, and Taiwan.**

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</thead>
<tbody>
<tr>
<td>16</td>
<td>North</td>
<td>56(58.3)</td>
<td>56(58.3)</td>
<td>15(16.1)</td>
<td>15(16.1)</td>
<td>17(22.67%)</td>
<td>5(15.6)</td>
<td>4(4.4)</td>
<td>6(5.3)</td>
</tr>
<tr>
<td>18</td>
<td>Northeast</td>
<td>6(6.3)</td>
<td>6(6.3)</td>
<td>57(61.27)</td>
<td>57(61.27)</td>
<td>54(70.59%)</td>
<td>26(81.3)</td>
<td>11(11.1)</td>
<td>26(47.1)</td>
</tr>
<tr>
<td>16, 18</td>
<td>South</td>
<td>0(0)</td>
<td>0(0)</td>
<td>11(11.71)</td>
<td>11(11.71)</td>
<td>1(1.33%)</td>
<td>1(1.1)</td>
<td>1(1.1)</td>
<td>1(1.1)</td>
</tr>
<tr>
<td>16 or 18</td>
<td>Central</td>
<td>62(64.4)</td>
<td>62(64.4)</td>
<td>83(90.27)</td>
<td>83(90.27)</td>
<td>58(77.33%)</td>
<td>32(100)</td>
<td>5(5.5)</td>
<td>14(82.4)</td>
</tr>
</tbody>
</table>

**Will HPV vaccine effectively protect our girls?**

1. Detect 13 oncogenic HPVs :
   - HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
   - > 99% of HPV- causing cervical cancer

2. **Commercial HPV detection kits**
   1. Hybrid Capture 2 (HC2): analytical sensitivity ~ 5000 copies/specimen
   2. AMPLICOR HPV Test: analytical sensitivity ~ 100 copies/ml

*Commercial HPV Kits in Clinical Use*

1. **No HPV** → **No CIN/Cancer**
2. **Screening**
3. **Role of HPV test**
4. **Triage equivocal Pap**
5. **Follow-up post treatment**

1. Detect 13 oncogenic HPVs :
   - HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
   - > 99% of HPV- causing cervical cancer

2. **Commercial HPV detection kits**
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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%

What Is Essential for Surgical Pathology to Fulfill Our Patient Care responsibilities?

- Clinician (Non – pathologist)
  1. Provides an essential clinical data and surgical findings
  2. Proper initial handling of specimens
- Pathologist
  Generation of an accurate and timely diagnostic report

Request Form

- Must be completely filled
- Must have relevant clinical history & surgical findings
- Must state clearly what had been done to the specimen
- Must specify clearly (with diagram) about the interested area

Proper initial dissection of specimens

- Each specimen is unique and requires variation in the dissection
- Need proper instruments
- One section with largest and smooth cut surface
- Serial sections are needed for large tumor
- Avoid manipulation of the surface epithelium, serosal lesion and ruptured area on cystic tumor

Cone biopsy

- 12 นาฬิกา เช่น 12 นาฬิกา : ไม่ต้อง切割 และเขียนระบุตำแหน่งนาร์คิสท์ที่เกิด
- ควรเปิดทุกราย : ถ้า มีรูปแบบเปิด เปิดแล้วตรงไว้ cervical wall ด้านนอก จากกัน ถึงกัน
- ขั้นที่สำคัญ : เบื้องต้นบางแห่ง lesion
  - เบื้องต้นอยู่ตรงแนว และ ลงไว้ตรงนโยบายการจะเปิด

Cone biopsy

- เปิด 12 นาฬิกา ทุกราย : ไม่จำเป็น ซึ่งอยู่กับตำแหน่ง lesion
  - เขียนระบุว่าเปิดที่ตำแหน่งใด
- ถ้ามีอาการใด ๆ หรือ steenosis จนเปิดไม่ได้ ทำอย่างไร?
  - ไม่ต้องเปิด ผู้ตัดเนื้ออาจเปลี่ยนวิธีตัด (sagittal sectioning)
- ตัดชิ้นเนื้อโดยLEEP เป็น 2 ชิ้น ซึ่งตัดอักษร LEEP บนชิ้น 2 ชิ้น