

Arab-British School of Pathology Cairo 2014

## What's New in the 2014 WHO Classification of Tumours of the Female Genital Tract

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### WHO Classification of Tumours of Female Reproductive Organs

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Epithelial ovarian neoplasia  
Cervical and other lower genital tract neoplasia  
Epithelial endometrial neoplasia



## EPITHELIAL OVARIAN TUMOURS

## SEROUS TUMOURS

### Evolution of our understanding of pelvic serous neoplasia

|           |   |
|-----------|---|
| 1961      | FIGO. Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth (low malignant potential)   |
| 1973      | WHO. Tumours of borderline malignancy (carcinomas of low malignant potential) → borderline tumour. Extraovarian lesions designated 'implants' rather than metastasis  |
| 1980s     | Implants divided into non-invasive and invasive as the latter more predictive of an adverse outcome   |
| 1990-2000 | Serous borderline tumour (SBT) with micropapillary architecture identified; associated with a significantly worse outcome. SBT divided into atypical proliferative serous tumour and non-invasive micropapillary (low grade) serous carcinoma |
| 2014      | WHO. SBT/APST and SBT-micropapillary variant/non-invasive low grade serous carcinoma<br>Invasive implants are low grade serous carcinoma  |

### Origins and molecular pathology of epithelial ovarian cancer sub types

|                                   | Precursor  | Molecular features  |
|-----------------------------------|--|---|
| Low-grade serous carcinoma        | Cystadenoma-borderline tumour-carcinoma sequence                 | Mutations in KRAS or BRAF or both   |
| Mucinous carcinoma                | Cystadenoma-borderline tumour-carcinoma sequence                 | Mutations in KRAS; possible TP53 mutation associated with transition from borderline to carcinoma |
| Low-grade endometrioid carcinoma  | Endometriosis and endometrial-like hyperplasia                   | Mutations in CTNNB1 ( $\beta$ -catenin gene) and PTEN with microsatellite instability             |
| Clear cell carcinoma              | Endometriosis in a proportion                                    | PTEN mutation/loss of heterozygosity; PIK3CA mutation   |
| High-grade serous carcinoma       | <i>De novo</i> in epithelial inclusion cysts or tubal epithelium | TP53 mutation and BRCA1/2 dysfunction; PIK3CA amplification (25-40%)                              |
| High-grade endometrioid carcinoma | Epithelial inclusion cysts or glands                             | TP53 mutation and BRCA1/2 dysfunction; PIK3CA mutation  |

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## WHO classification of serous tumours of the ovary 2014

### Benign

- Serous cystadenoma
- Serous cystadenofibroma
- Serous surface papilloma

### Borderline

- Serous borderline tumour/APST
- Serous borderline tumour – micropapillary variant/non-invasive low grade serous carcinoma

### Malignant

- Low grade serous carcinoma
- High grade serous carcinoma

## NON-SEROUS TUMOURS

'As there are no well documented cases of extra-ovarian disease or deaths from adequately sampled mucinous, endometrioid, clear cell and Brenner borderline tumours, there is little justification in calling them borderline. The designation "atypical proliferative tumour" and "borderline tumour" are considered equivalent and can be applied to all these other cell types.'

## WHO classification of mucinous tumours of the ovary 2014

### Benign

- Mucinous cystadenoma
- Mucinous cystadenofibroma

### Borderline

- Mucinous borderline tumour/Atypical proliferative mucinous tumour

### Malignant

- Mucinous carcinoma

## WHO classification of endometrioid tumours of the ovary 2014

### Benign

- Endometriotic cyst
- Endometrioid cystadenoma
- Endometrioid adenofibroma

### Borderline

- Endometrioid borderline tumour/Atypical proliferative endometrioid tumour

### Malignant

- Endometrioid carcinoma

## WHO classification of clear cell tumours of the ovary 2014

### Benign

- Clear cell cystadenoma
- Clear cell adenofibroma

### Borderline

- Clear cell borderline tumour/Atypical proliferative clear cell tumour

### Malignant

- Clear carcinoma

## WHO classification of Brenner tumours of the ovary 2014

- **Benign**
  - Brenner tumour
- **Borderline**
  - Borderline Brenner tumour/Atypical proliferative Brenner tumour
- **Malignant**
  - Malignant Brenner tumour

NB. Transitional cell carcinoma of the ovary is a variant of high grade serous carcinoma or endometrioid carcinoma

Takeuchi et al. Am J Surg Pathol 2013; 37: 1091:

## WHO classification of seromucinous tumours of the ovary 2014

- Benign**
  - Seromucinous cystadenoma
  - Seromucinous adenofibroma
- Borderline**
  - Seromucinous borderline tumour/Atypical proliferative seromucinous tumour
- Malignant**
  - Seromucinous carcinoma

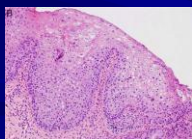
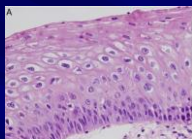
## CERVICAL AND OTHER LOWER GENITAL TRACT NEOPLASIA

### Cervical epithelial neoplasia

- Broad agreement to replace CIN 1, CIN 2 and CIN 3 with LSIL and HSIL
- Two tiered system more biologically and clinically relevant and histologically reproducible

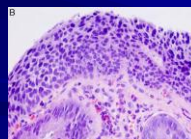
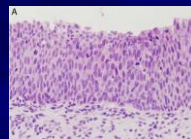
Darragh et al J Low Genit Tract Dis 2012; 16: 205  
Stoler JAMA. 2002; 287: 2140

### LSIL



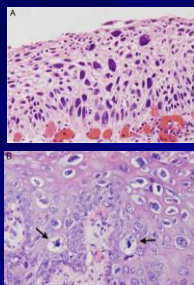
- A proliferation of squamous cells with abnormal nuclear features including increased nuclear size, irregular nuclear membranes, and increased nuclear to cytoplasmic ratios.
  - Minimal cytoplasmic maturation in the lower third of the epithelium, but maturation begins in the middle third and is relatively normal in the upper third.
  - Mitotic figures are limited to the lower one third of the epithelium
- And/or
- The presence of diagnostic cytopathic effect of HPV (koilocytosis)

### HSIL



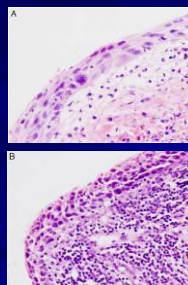
- A proliferation of squamous or metaplastic squamous cells with abnormal nuclear features including increased nuclear size, irregular nuclear membranes, and increased nuclear to cytoplasmic ratios
- Little or no cytoplasmic differentiation in the middle third and superficial thirds of the epithelium.
- Mitotic figures are not confined to the lower third of the epithelium

### Abnormal Mitoses or Significant Nuclear Atypia



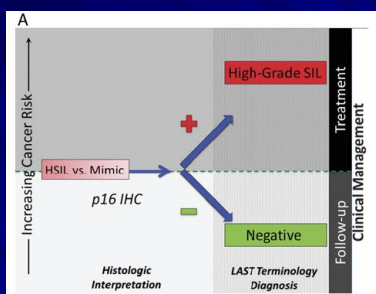
- Abnormal mitoses and marked nuclear atypia more commonly seen in a high-grade lesions.
- Lesions with the overall morphology of LSIL, but either marked nuclear atypia in the lower third of the epithelium or atypical mitoses at any level are considered to be consistent with HSIL
- Positive p16 staining supports the diagnosis of HSIL

### Thin SIL (Thin Dysplasia)

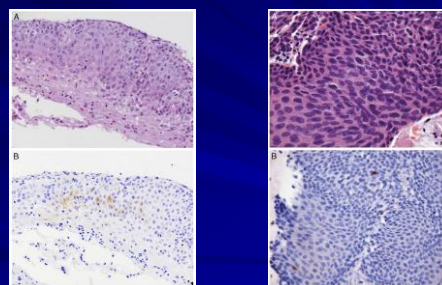


- Immature intraepithelial lesions less than 10 cells thick.
- If a lesion is unequivocal SIL with significant immature abnormal basal proliferation or mitosis above the basal cells, it is designated as HSIL.
- If there is doubt about the nature of the proliferation (i.e. immature metaplasia versus SIL) then p16 staining can be used

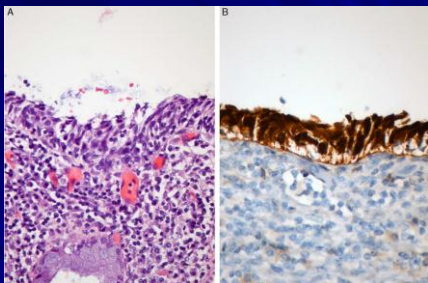
### WG4 Biomarkers in HPV-associated Lower Anogenital Squamous Lesions



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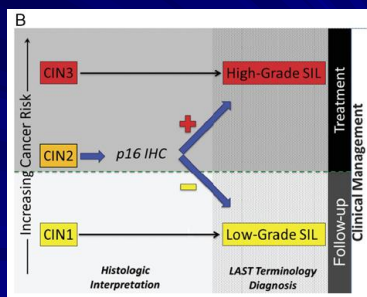
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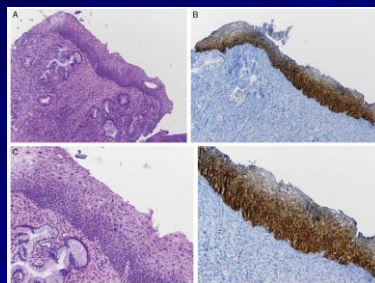
### WG4 Biomarkers in HPV-associated Lower Anogenital Squamous Lesions

- p16 IHC is recommended to help clarify a diagnosis of -IN2
- Strong and diffuse block positive p16 results support a categorisation of precancerous disease
- Negative or non-block positive staining strongly favours an interpretation of low grade disease or a non-HPV associated pathology

## WG4 Biomarkers in HPV-associated Lower Anogenital Squamous Lesions



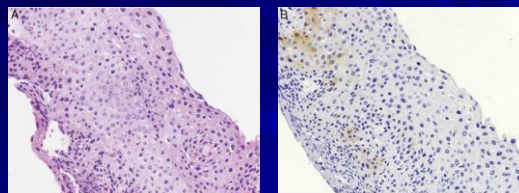
## WG4 Biomarkers in HPV-associated Lower Anogenital Squamous Lesions



## WG4 Biomarkers in HPV-associated Lower Anogenital Squamous Lesions

- p16 is recommended for use as an adjudication tool for cases in which there is a professional disagreement in histology interpretation, with the caveat that the differential diagnosis includes – IN 2 or – IN 3
- p16 IHC should not be used as a routine adjunct to histological assessment of biopsy specimens with morphological interpretations of negative, – IN 1, and – IN 3

## WG4 Biomarkers in HPV-associated Lower Anogenital Squamous Lesions



## Endocervical glandular dysplasia/low grade CGIN

- Poorly reproducible diagnosis for which criteria are not well defined
- Minimal nuclear atypia with hyperchromasia and slightly increased mitoses or apoptotic bodies has been suggested
- Positive p16, high Ki-67 proliferation index and absent hormone receptor staining support diagnosis of AIS/HG-CGIN

## WHO classification of squamous cell tumours and precursors of the cervix 2014

### Squamous cell tumours and precursors

#### Squamous intraepithelial lesions

- Low grade squamous intraepithelial lesion (LSIL)
- High grade squamous intraepithelial lesion (HSIL)

#### Squamous cell carcinoma

- Keratinising, non-keratinising, papillary, basaloid, warty, verrucous, squamotransitional, lymphoepithelioma-like

#### Benign squamous cell lesions

- Squamous metaplasia, condyloma acuminatum, squamous papilloma, transitional metaplasia

## WHO Classification of Glandular Tumours and Precursors 2014

|   |  |
|---|--|
| Adenocarcinoma in situ                  | Villoglandular carcinoma                             |
| Adenocarcinoma                          | Endometrioid carcinoma                               |
| Endocervical adenocarcinoma, usual type | Clear cell carcinoma                                 |
| Mucinous carcinoma                      | Serous carcinoma                                     |
| Gastric type                            | Mesonephric carcinoma                                |
| Intestinal type                         | Adenocarcinoma admixed with neuroendocrine carcinoma |
| Signet ring type                        |  |

## VULVAL EPITHELIAL NEOPLASIA



## WHO Classification of tumours of the vulva

- Squamous cell tumours and precursors
  - Squamous intraepithelial lesion
    - Low grade squamous intraepithelial lesion
    - High grade squamous intraepithelial lesion
    - Differentiated-type vulvar intraepithelial neoplasia
  - Squamous cell carcinoma
  - Basal cell carcinoma
- Glandular tumours
  - Paget's disease
  - Tumours of Bartholin and other anogenital glands
  - Adenocarcinoma of other types

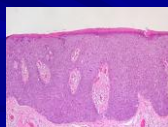
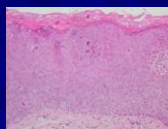
## WHO Classification of VIN 2014

- Low grade SIL (HPV only, VIN 1)
- High grade SIL (usual type VIN 2/3)
- Differentiated type VIN
- Paget's disease

## Two pathways to vulval neoplasia

### HPV-related

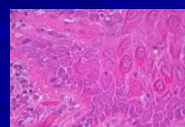
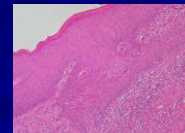
- Young women
- Warty/basaloid (undifferentiated) vulvar intraepithelial neoplasia
- Warty/basaloid carcinoma
- Same HPV types as CIN esp HPV 16
- Mechanisms probably similar
- p16 surrogate marker



## Two pathways to vulval neoplasia

### Non-HPV-related

- Older women
- Associated with lichen sclerosus
- Differentiated (simplex) type VIN
- Often well differentiated squamous cell carcinoma but clinically aggressive
- ?p53 mutation important



## Does this matter?

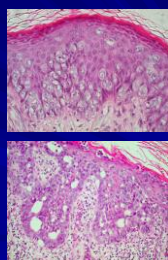
- Potential therapeutic relevance
  - Imiquimod
  - Other agents
- Should we classify on the basis of HPV expression?
- Further molecular investigation of differentiated type VIN required

## Paget's disease



## Paget's disease

- Intraepithelial adenocarcinoma
- 6 – 20% associated with adenocarcinoma skin adnexa or Bartholin's gland
- 5% associated with regional malignant disease, TCC or Cx
- Some associated with distant neoplasm



## Origin of Paget's cells in situ

- Pluripotential germinative cells in epidermal basal layer
- Intraepidermal ectopic cells of Bartholin's or sweat gland origin: vulval equivalent of Toker cells of the nipple
- Apocrine origin or show apocrine differentiation

## Immunohistochemistry of Paget's disease

|               | Primary | 2° Colorectal ca | 2° Bladder ca |
|---------------|---------|------------------|---------------|
| CEA           | +       | +                | -             |
| CK7           | +       | -                | +             |
| CAM 5.2       | +       | +                | +             |
| EMA           | +       | +                | +             |
| GCDP15        | +       | -                | -             |
| CK20          | ±       | +                | +             |
| CDX2          | -       | +                | -             |
| MUC2          | -       | +                | -             |
| Uroplakin III | -       | -                | +             |

## CERVICAL NEUROENDOCRINE TUMOURS

## Terminology (neuro)endocrine tumours of the cervix

- Carcinoid tumour
- Carcinoid tumour with squamous cell carcinoma
- Carcinoid tumour with adenocarcinoma
- Argyrophil cell carcinoma
- Apudoma
- Poorly differentiated small cell carcinoid
- Small cell tumour with neuroepithelial features
- Nonendocrine carcinoid tumour
- Endocrine carcinoma intermediate cell type
- Small cell undifferentiated carcinoma
- Oat cell carcinoma
- Small cell carcinoma
- Small cell neuroendocrine carcinoma
- Neuroendocrine carcinoma, non-small cell type
- Adenocarcinoma with carcinoid features

Alborees-Saavedra. Arch Path Lab Med 1997; 121: 34

## Terminology (neuro)endocrine tumours of the cervix

- Typical (classical) carcinoid tumour
- Atypical carcinoid tumour
- Large cell neuroendocrine carcinoma
- Small cell carcinoma

Alborees-Saavedra. Arch Path Lab Med 1997; 121: 34

## Terminology (neuro)endocrine tumours of the cervix

|                   |                    |                                     |
|-------------------|--------------------|-------------------------------------|
| Typical carcinoid | Atypical carcinoid | Large cell neuroendocrine carcinoma |
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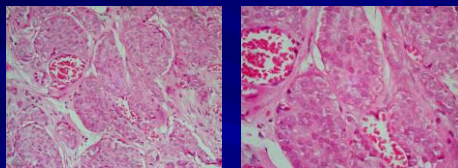
Alborees-Saavedra. Arch Path Lab Med 1997; 121: 34

## Typical (classical) carcinoid tumour of the cervix

- Trabecular, nodular or cordlike growth pattern
- Rosette-like structures common
- Round, small, uniform neoplastic cells with finely granular chromatin and inconspicuous nuclei
- Spindle cells, amyloid and mitotic figures rare
- 70% plus argyrophilic and positive for general neuroendocrine markers
- EM: neurosecretory granules of variable electron density

Alborees-Saavedra. Arch Path Lab Med 1997; 121: 34

## Typical (classical) carcinoid tumour of the cervix

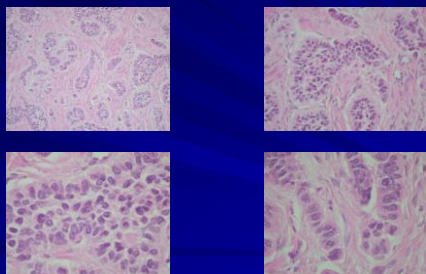


## Atypical carcinoid tumour of the cervix

- Growth pattern, histochemistry, immunohistochemistry and EM features similar to typical carcinoid
- Hypercellular with cytological atypia, increased mitotic activity (5-10 per 10 HPF), and necrosis
- One third express serotonin and smaller proportion other peptide hormones

Alborees-Saavedra. Arch Path Lab Med 1997; 121: 34

### Atypical carcinoid tumour of the cervix

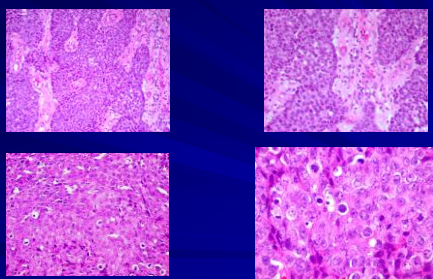


### Large cell neuroendocrine carcinoma of the cervix

- Organoid, trabecular or cordlike growth pattern with peripheral palisading and variable necrosis
- Large neoplastic cells with abundant cytoplasm, vesicular nuclei and prominent nucleoli
- Mitoses more than 10 per 10 HPF
- Arglyophilic and positive for chromogranin or synaptophysin

Albores-Saavedra. Arch Path Lab Med 1997; 121: 34

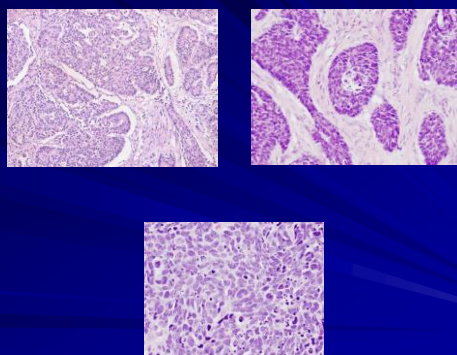
### Large cell neuroendocrine carcinoma of the cervix



### Small (oat) cell carcinoma of the cervix

- Diffuse growth pattern or arranged in nests, trabeculae and cords
- Small round or fusiform cells with scant cytoplasm
- Hyperchromatic nuclei with finely granular chromatin and absent of inconspicuous cytoplasm
- Peripheral palisading and perivascular concentration of cells common
- Immunohistochemistry not required for diagnosis

Albores-Saavedra. Arch Path Lab Med 1997; 121: 34



### WHO classification of neuroendocrine tumours of the cervix 2014

- Low grade neuroendocrine tumour
  - Grade 1 carcinoid tumour
  - Grade 2 atypical carcinoid tumour
- High grade neuroendocrine carcinoma
  - Grade 3 small cell neuroendocrine carcinoma
  - Grade 4 large cell neuroendocrine carcinoma
- Mirrors system used for gastrointestinal and pancreatic tumours

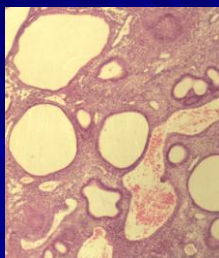
## ENDOMETRIAL TUMOURS

### Endometrioid carcinoma precursors WHO 1994

- Degree of architectural crowding
  - Simple
  - Complex
- Nuclear alteration
  - Non-atypical
  - Atypical

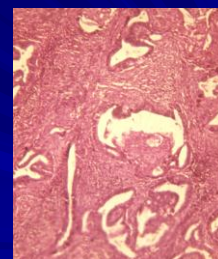
### Simple Non-atypical Hyperplasia

- Variable gland size
- Normal gland/stroma ratio
- No cytological atypia



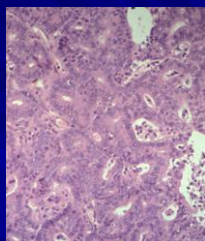
### Complex Non-atypical Hyperplasia

- Architectural irregularity of the glands
- Increased gland/stroma ratio
- No cytological atypia



### Complex Atypical Hyperplasia

- Architectural irregularity and crowding of the glands
- Increased gland/stroma ratio
- Cytological atypia



### Endometrioid carcinoma precursors WHO 2014

- Hyperplasia without atypia
- Atypical hyperplasia/endometrioid intraepithelial neoplasia

## Hyperplasia without atypia

### ■ Definition

- An exaggerated proliferation of glands of irregular size and shape, with an associated increase in the gland to stroma ratio compared with proliferative endometrium

### ■ Synonyms

- Benign endometrial hyperplasia; simple or complex non-atypical endometrial hyperplasia; simple or complex endometrial hyperplasia without atypia;

## Hyperplasia without atypia

### ■ Genetic profile

- Low levels of somatic mutations in scattered histologically unremarkable glands

### ■ Prognosis

- 3-4 fold endometrial carcinoma risk, rising to 10-fold after 10 years
- Progression to endometrial carcinoma in 1-3%

## Atypical hyperplasia/Endometrioid intraepithelial neoplasia

### ■ Definition

- Cytological atypia superimposed on endometrial hyperplasia defines atypical hyperplasia/endometrioid intraepithelial neoplasia (EIN)

### ■ Synonyms

- Simple or complex atypical endometrial hyperplasia; endometrial intraepithelial neoplasia, EIN

## Atypical hyperplasia/Endometrioid intraepithelial neoplasia

### ■ Genetic profile

- Many of the genetic changes seen in endometrioid endometrial carcinoma including microsatellite instability, PAX2 inactivation, and PTEN, KRAS,  $\beta$ -catenin mutation

### ■ Prognosis

- One quarter to one third of women with a biopsy diagnosis of AH/EIN will be diagnosed with cancer at immediate hysterectomy or during the first year of follow-up

## The Cancer Genome Atlas (TCGA) classification of endometrial cancer

1. Ultramutated cancers with DNA polymerase epsilon (POLE) mutations
2. Hypermutated cancers with defective mismatch repair (dMMR) and microsatellite instability (MSI)
3. Cancers with a low frequency of DNA copy number alterations
4. Cancers with a high frequency of DNA copy number alterations but low mutation rate; few DNA methylation changes; low hormone receptor levels; frequent p53 mutation

TCGA, Nature 2013; 497: 67-73

## The Cancer Genome Atlas (TCGA) classification of endometrial cancer

- Group 1 excellent prognosis
- Group 4 poorest prognosis
- Group 2 most common finding (90%) in patients with Lynch syndrome – mutant mismatch repair genes (MLH1 and MLH2)

TCGA, Nature 2013; 497: 67-73

