2020 WHO UPDATE: UTERINE CERVIX

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Background

• Most cervical carcinomas are related to human papillomavirus (HPV) infection:
  ➢ >99% of squamous cell carcinomas
  ➢ 85-90% of adenocarcinomas

• In the vulva and oropharynx, HPV-independent carcinomas are generally more aggressive than those associated with HPV

• The 2014 WHO classification of epithelial tumors of the uterine cervix is morphology based and does not take etiology (association with HPV) into consideration
2020 WHO Classification of Epithelial Tumors of the Uterine Cervix

• Squamous cell carcinomas have been reclassified based on association with HPV infection

• Invasive and in situ endocervical adenocarcinomas have been reclassified based on association with HPV infection

• The staging has been updated to FIGO 2018
2014 WHO Classification of Epithelial Tumors of the Uterine Cervix

**Squamous cell tumours and precursors**
- Squamous intraepithelial lesions
  - Low-grade squamous intraepithelial lesion
  - High-grade squamous intraepithelial lesion
- Squamous cell carcinoma, NOS
  - Keratinizing
  - Non-keratinizing
- Papillary
- Basaloid
- Warty
- Verrucous
- Squamotransitional
- Lymphoepithelioma-like

**Glandular tumours and precursors**
- Adenocarcinoma in situ
- Adenocarcinoma
  - Endocervical adenocarcinoma, usual type
  - Mucinous carcinoma, NOS
    - Gastric type
    - Intestinal type
    - Signet-ring cell type
  - Villoglandular carcinoma
  - Endometrioid carcinoma
  - Clear cell carcinoma
  - Serous carcinoma
  - Mesonephric carcinoma
  - Adenocarcinoma admixed with neuroendocrine carcinoma
SQUAMOUS LESIONS

• Squamous cell carcinoma
  o Two categories:
    ➢ HPV-associated (common, >99%)
    ➢ HPV-independent (rare, ~1%)
  o Currently no difference in treatment
  o Distinction not possible based on morphology and requires ancillary testing (p16 immunohistochemistry, HPV testing)
  o The type of carcinoma should be reported if possible
Squamous Cell Carcinoma

Well-differentiated, keratinizing

Poorly differentiated, non-keratinizing
2020 WHO Classification of Epithelial Tumors of the Uterine Cervix

SQUAMOUS LESIONS

• Squamous intraepithelial lesions
  o A single HPV-associated category:
    ➢ HSIL / CIN 2-3 (high-grade squamous intraepithelial lesion)
    ➢ LSIL / CIN 1 (low-grade squamous intraepithelial lesion)
  o No evidence that HPV-independent precursor lesions exist
GLANDULAR LESIONS

• Invasive endocervical adenocarcinoma
  o Two categories:
    ➢ HPV-associated (85-90%)
    ➢ HPV-independent (10-15%)
  o Distinction possible based on morphology
  o Ancillary testing (p16 immunohistochemistry, HPV testing) is helpful
2020 WHO Classification: Invasive endocervical adenocarcinoma

- HPV-associated (85-90%)
  - Usual type (~75%), mucin in 0-50% of tumor
  - Villoglandular variant
  - Mucinous type (~10%), mucin in ≥50% of tumor
  - Mucinous NOS adenocarcinoma
  - Intestinal adenocarcinoma
  - Signet-ring cell adenocarcinoma
  - Stratified mucin-producing carcinoma

- HPV-independent (10-15%):
  - Gastric-type adenocarcinoma
  - Clear cell carcinoma
  - Mesonephric adenocarcinoma
  - Endometrioid adenocarcinoma
An international study of 409 cases (USA, Romania, Japan, Mexico, Italy, Israel):

- Evaluating tumor morphology AND diagnostic techniques including immunohistochemistry and HPV testing
- Establishing a morphologic classification system linked to ETIOLOGY
NHPVA (non HPV-associated) tumors were LARGER and affected OLDER patients than HPVA (HPV-associated) tumors (p<0.001).

Almost half of NHPVA patients presented at ≥stage II.
HPV Associated

Apical mitoses and apoptotic bodies

Non-HPV Associated

No easily identifiable mitoses and apoptotic bodies
Apical mitoses
HPV-associated types:
Diffuse “block-like” expression of p16
Usual type: Pseudostratified, hyperchromatic nuclei, apical mitoses and apoptotic bodies, 0-50% mucin
Usual type, villoglandular variant: Long slender papillae lined by columnar epithelium of usual type with mild atypia
Mucinous type, mucinous NOS adenocarcinoma: Mucinous cytoplasm resembling normal endocervix with pale-purple staining on H&E
Mucinous type, intestinal adenocarcinoma: Goblet cell and/or enteroendocrine cell differentiation representing ≥50% of tumor
Mucinous type, signet-ring cell adenocarcinoma:
Loose non-cohesive round cells with mucinous vacuoles displacing nuclei, representing ≥50% of tumor
Mucinous type, stratified mucin-producing carcinoma: Invasive nests of stratified epithelium with intracytoplasmic mucin, often associated with adjacent stratified mucin-producing intraepithelial lesion (SMILE)
HPV-independent, gastric type adenocarcinoma: Abundant clear, foamy or eosinophilic cytoplasm and distinct cell borders, variable cytologic atypia
Clinical features of gastric type adenocarcinoma

- Advanced stage at presentation (stage II and higher)
  - 66% vs 12%

- High incidence of disease recurrence
  - 34% vs 4%

- High incidence of distant metastases including abdominal
  - 19% vs 3%

- High mortality rate
  - 39% vs 8%

- Well differentiated variant (minimal deviation adenocarcinoma, adenoma malignum) may be associated with germline STK11 mutations (Peutz-Jegher syndrome)
HPV-independent, clear cell carcinoma: Papillary, tubulocystic and/or solid architecture, uniformly atypical clear, eosinophilic, flat or cuboidal cells
HPV-independent, mesonephric carcinoma: Mixed patterns (tubular, ductal, papillary etc), optically clear bland nuclei with grooves, positive GATA3 and TTF1, negative ER/PR
HPV-independent, endometrioid adenocarcinoma: Confirmatory endometrioid features, may resemble usual type adenocarcinoma
2020 WHO Classification of Epithelial Tumors of the Uterine Cervix

• *Endometrioid adenocarcinoma:*
  
  o Most ‘endometrioid’ endocervical adenocarcinomas represent HPV-associated usual-type adenocarcinomas with mucin depletion
  
  o Careful search for morphologic features of HPV-associated adenocarcinoma (apical mitoses, apoptotic bodies) and diffuse p16 staining should allow for an accurate classification of these tumors
  
  o True endometrioid adenocarcinomas are HPV-negative, thought to arise in endometriosis, and should only be diagnosed after exclusion of mimics such as HPV-associated usual-type adenocarcinoma and extension from an endometrial endometrioid carcinoma
2020 WHO Classification of Epithelial Tumors of the Uterine Cervix

• **Serous carcinoma:**
  – Omitted as there is no definitive evidence that it can occur as a primary tumor in the uterine cervix

• **Adenocarcinoma, not otherwise specified:**
  – Omitted to encourage pathologists to categorize all cervical adenocarcinomas as either the HPV-associated or one of the HPV-independent subtypes
Endocervical Adenocarcinoma In Situ

- **Two categories:**
  - HPV-associated
  - HPV-independent
- Precursor for invasive endocervical adenocarcinoma
- Replacement of normal surface epithelium and endocervical glands with preservation of the normal architecture
- Common partial gland involvement or surface epithelial involvement
- No desmoplastic stromal reaction and minimal inflammatory response
Gastric type adenocarcinoma in situ: Glandular epithelium with distinct cell borders and eosinophilic to pale mucinous cytoplasm, variable nuclear atypia, intraglandular complexity may be seen.
FIGO 2018 Staging of Cervical Carcinoma

• Major changes

  o **Stage I:**
    📢 Assessment of stage IA disease using only depth of stromal invasion, while horizontal extent is omitted
    📢 Subdivision of stage IB into 3 categories

  o **Stage III:**
    📢 Inclusion of lymph node metastasis, identified by imaging or pathologic examination
Staging of Cervical Carcinoma: Stage I

**2015 (AJCC 8th Ed)**

- **pT1a**: Microscopic carcinoma
  - 1a1: Depth $\leq$ 3 mm, horizontal extent $\leq$ 7 mm
  - 1a2: Depth $>$ 3 mm but $\leq$ 5 mm, horizontal extent $\leq$ 7 mm
- **pT1b**: Clinically visible lesion confined to cervix or microscopic lesion $>$ IA
  - pT1b1: Size $\leq$ 4 cm
  - pT1b2: Size $>$ 4 cm

**2018 (FIGO)**

- **IA**: Microscopic carcinoma
  - IA1: Depth $\leq$ 3 mm
  - IA2: Depth $>$ 3 mm but $\leq$ 5 mm
- **IB**: Macroscopic carcinoma or size $>$ stage IA
  - IB1: Depth $>$ 5 mm and size $\leq$ 2 cm
  - IB2: Size $>$ 2 cm but $\leq$ 4 cm
  - IB3: Size $>$ 4 cm

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Staging of Cervical Carcinoma: Stage III

2015 (AJCC 8th Ed)
- pT3: Tumor involving pelvic sidewall and/or lower third of vagina and/or causing hydronephrosis or non-functioning kidney
  - pT3a: Tumor involving lower third of vagina but not pelvic wall
  - pT3b: Tumor involving pelvic wall and/or causing hydronephrosis or non-functioning kidney

2018 (FIGO)
- III: Tumor involving pelvic sidewall and/or lower third of vagina and/or causing hydronephrosis or non-functioning kidney and/or involving pelvic and/or para-aortic lymph nodes
  - IIIA: Tumor involving lower third of vagina but not pelvic wall
  - IIIB: Tumor involving pelvic wall and/or causing hydronephrosis or non-functioning kidney
  - IIIC: Pelvic and/or para-aortic lymph node metastasis
    - IIIC1: Pelvic lymph node metastasis
    - IIIC2: Para-aortic lymph node metastasis

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2020 WHO Classification of Tumors of the Uterine Cervix: Clinical Significance

• **The new etiology based classification of epithelial tumors and precursor lesions:**
  - Allows more accurate assessment of the role of:
    - HPV testing in screening programs
    - HPV vaccination
  - Harmonizes the classification across female lower genital tract sites
  - Linked to clinical outcomes

• **The updated FIGO 2018 staging:**
  - Incorporates imaging and pathologic findings rather than clinical findings alone
Summary of Major Changes

**Epithelial invasive tumors and glandular precursor lesions:**

- Classification based on their association with human papillomavirus (HPV) infection
- Omission of serous carcinoma and adenocarcinoma, not otherwise specified
- The FIGO 2018 staging system

**Mesenchymal and biphasic tumors:**

- See *Uterine Corpus*