2020 WHO Classification of Tumors of the Uterine Corpus International Gynecologic Cancer Society Update

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2020 WHO Classification of Tumors Female Genital Tract

IGCS Update

Corpus

Hyperplasia/Endometrial Intraepithelial Neoplasia

Carcinomas

Endometrial hyperplasia without atypia

WHO 2020 defines *essential* diagnostic criteria

Essential: increased endometrial gland to stroma ratio; tubular, branching and/or cystically dilated glands resembling proliferative endometrium; uniform distribution of nuclear features across submitted tissue

Prognosis and Prediction

Progression to well-differentiated endometrial carcinoma occurs in 1-3% of women with hyperplasia without atypia

Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: crowded glandular architecture and altered epithelial cytology distinct from the surrounding endometrium and/or entrapped non-neoplastic glands

Desirable: loss of immunoreactivity for PTEN, PAX2, or mismatch repair proteins

Prognosis and Prediction

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

Endometrial Carcinoma

Diagnosed on the basis of morphology
Reproducible in most cases but there is interobserver variability in subset of high grade tumors

The Cancer Genome Atlas (TCGA) identified four groups of endometrial carcinomas

Group 1. POLE mutated carcinomas associated with good prognosis
Group 2. Carcinomas with microsatellite instability associated with intermediate prognosis
Group 3. Carcinomas with low copy number alterations associated with intermediate prognosis
Group 4. Carcinomas with high copy number alterations and p53 mutations associated with poor prognosis

Several groups have attempted to introduce the TCGA into clinical practice
Surrogate approach with limited immunohistochemical panel and POLE mutation analysis. Integration of microscopic features and molecular characteristics is the best approach to predict prognosis in regions with the available resources and techniques

Additional novel tumor types are introduced in the current WHO classification
Mesonephric like adenocarcinoma
Gastric type mucinous carcinoma

Carcinosarcoma is recognized an aggressive type of endometrial carcinoma with epithelial-mesenchymal transition

Endometrioid Carcinoma

WHO 2020 defines *essential* and *desirable* diagnostic criteria
- *Essential*: invasive endometrial carcinoma with endometrioid differentiation
- *Desirable*: some degree of squamous, secretory or mucinous differentiation

Grading
- Grades 1, 2, and 3 according to solid non-glandular, non-squamous growth (≤5%, 6-50%, >50%)
  - Severe cytologic atypia in a majority of cells increases grade by one level but serous carcinoma should be excluded.
- Binary grading is recommended
  - FIGO grade 1 and 2: Low Grade
  - FIGO grade 3: High Grade

Immunohistochemistry section is expanded in the current WHO document

- Low grade endometrioid carcinomas show patchy p16 staining and are ER/PR positive (this can be used to differentiate them from endocervical adenocarcinomas)
- High grade endometrioid adenocarcinomas can be hard to differentiate from endometrial serous carcinomas
  - Loss of ARID1A, PTEN or MMR protein immunoreactivity favors high grade endometrioid carcinoma
  - Abnormal p53 expression is reported in 2-5% of low grade and 20% of high grade endometrioid carcinomas

Endometrioid Carcinoma Molecular Classification

	POLE ultramutated	MMR deficient	p53 mutant	No specific molecular profile
Molecular Features	>100 mutations/Mb, SCNA very low, MSS	10-100 mutations/Mb, SCNA low, MSI	<10 mutations/Mb, SCNA high, MSS	<10 mutations/Mb, SCNA low, MSS, 30-40% CTNNB1 mutations
Histological Features	Often high grade and/or ambiguous morphology, prominent TILs	Often high grade, prominent TILs, mucinous, MELF	Mostly high grade	Mostly low grade
Diagnostic Tests	NGS/Sanger/hot spot analysis	MMR IHC MSI, NGS	p53 IHC	MMR proficient Wild type p53 IHC No pathogenetic POLE variant
Clinical Features	Younger age	May have Lynch syndrome	Advanced stage	Higher BMI
Prognosis	Excellent	Intermediate	Poor	Intermediate to excellent

Endometrioid Carcinoma

Staging

According to UICC TNM Classification and FIGO staging system

Prognosis and prediction

FIGO and UICC staging
Focal vs extensive (≥5 vessels) lymphovascular invasion may have prognostic significance
Synchronous endometrioid carcinomas of endometrium and ovaries are mostly clonally related

But indolent behavior supports conservative management if these 4 criteria are met:

1- both tumors are low grade
2- <50% myometrial invasion
3- no involvement of any other site
4- absence of extensive lymphovascular invasion at any location

Efficacy of conservative hormonal treatment of grade 1 endometrioid carcinoma/atypical hyperplasia/EIN may be monitored by histology but this is not yet standard clinical practice

Serous Carcinoma

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: cytologically high grade endometrial carcinoma with complex papillary and/or glandular architecture

Desirable: abnormal p53 and diffuse p16 immunohistochemistry

Immunohistochemistry section is expanded in the current WHO document

p53 shows mutation pattern

Diffuse expression of p16, IMP3 and HMGA2

HER2 may be overexpressed

Aberrant staining for PTEN, β-catenin, ARID1A and MMR is very uncommon

Prognosis and Prediction

Endometrium-limited carcinoma has better prognosis but others have poor outcomes.

HER2 overexpression or gene amplification is seen in >30% of endometrial serous carcinomas

Patients with recurrent or advanced stage HER2-positive endometrial carcinoma benefit from addition of trastuzumab to carboplatin and paclitaxel regimen.

Clear Cell Carcinoma

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: an admixture of tubulocystic, papillary and/or solid patterns; clear to eosinophilic cuboidal, polygonal, hobnail or flat cells

Desirable: confirmation by immunohistochemistry

Immunohistochemistry section is expanded in the current WHO document

HNF1β positive in 67-100%

Napsin A positive in 56-93%

AMACR positive in 77-88%

Mutation pattern p53 staining in 22-72%

ER/PR usually negative or only focally positive

Prognosis and Prediction

5 year survival rate 55-78%

Advanced patient age and tumor stage are accepted poor prognostic factors

Other possible prognostic factors have preliminary or conflicting data

Undifferentiated and Dedifferentiated Carcinomas

WHO 2020 defines *essential* and *desirable* diagnostic criteria

- *Essential*: undifferentiated histology and immunophenotype
- *Desirable*: immunohistochemistry or genetic analysis showing inactivating mutations or loss of expression of SMARCA4 (BRG1), SMARCB1 (INI1), or both ARID1A and ARID1B.

Immunohistochemistry section is expanded in the current WHO document

- Undifferentiated carcinomas:
  - evidence of epithelial differentiation only focally (EMA, CK8/18)
  - ER, PR, E-cadherin negative
  - PAX8 negative or only positive in single cells or small clusters
  - Cromogranin and synaptophysin present in a minority of tumor cells (usually <10%)
  - Loss of SMARCA4 (BRG1) expression in one third of cases

Prognosis and Prediction

- Highly aggressive, recurrence or death from disease in 55-95% of cases.
- Presence of undifferentiated carcinoma component, regardless of the percentage, can portend worse prognosis
- POLE mutation associated with favorable prognosis
- Tumors with SWI/SNF protein deficiency appear to be more aggressive

Mixed Carcinoma

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: two distinct histological types; at least one is serous or clear cell (excludes dedifferentiated and carcinosarcoma.

Desirable: immunohistochemical demonstration of the two distinct carcinoma types

Grading

High grade regardless of relative percentages of serous or clear cell

Prognosis and Prediction

Behavior is dictated by the highest grade component.

Other Endometrial Carcinomas (these are rare)

Mesonephric adenocarcinoma
Squamous cell carcinoma NOS
Mucinous carcinoma, intestinal type
Mesonephric-like adenocarcinoma

The diagnosis of these carcinomas is established by morphology; endometrioid component should be absent and cervical origin/metastasis from gastrointestinal tract should be excluded

Mesonephric-like adenocarcinoma

Variety of histological patterns:

Small glands and tubules with luminal eosinophilic material predominate

Admixture of papillary, ductal, retiform, solid or spindled architecture

Immunohistochemistry: GATA3 positive, may also be positive for TTF1, Calretinin and CD10 (luminal)

Prognosis and Prediction: Newly described entity; limited data suggests aggressive behavior

Mucinous carcinomas of gastric (gastrointestinal) type

Glands form by mucin secreting epithelium, may contain goblet cells

Carcinosarcoma

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: high grade malignant epithelial and mesenchymal components

Desirable: in rare cases immunohistochemistry to confirm specific mesenchymal differentiation

Prognosis and Prediction

FIGO stage I-II	5-year disease specific survival rate is 60%
FIGO stage III	5-year disease specific survival rate is 25%
FIGO stage IV	5-year disease specific survival rate is 10%

Other independent factors associated with poor prognosis

- Size >5cm
- Myometrial invasion >50%
- Lymphovascular invasion
- Sarcoma predominance

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Leiomyoma

Intravenous Leiomyomatosis

Leiomyosarcoma

Leiomyoma

WHO 2020 lists diagnostic criteria for leiomyoma per subtype

Usual type:
interlacing fascicles of spindle cells with eosinophilic fibrillary cytoplasm and cigar shaped nuclei lacking cytological atypia; very low mitotic count

Cellular:
more cellular than surrounding myometrium; thick walled vessels and cleft-like spaces; cells have scant cytoplasm

With bizarre nuclei:
bizarre cells in a background of typical leiomyoma; low mitotic count (<5/10HPF)

Fumarate hydratase deficient:
staghorn vessels; alveolar type edema, may have bizarre nuclei, large nuclei with perinuclear halos, rhabdoid inclusions

Mitotically active:
6-14 mitosis/10HPF; no cytological atypia

Hydropic:
Edematous stroma causing compartmentalization of the smooth muscle cells

Leiomyoma

WHO 2020 lists diagnostic criteria for leiomyoma per subtype

Apoplectic:
stellate zones of hemorrhage, zonation phenomenon, history of progestogen treatment or pregnancy

Lipoleiomyoma:
admixture of mature adipocytes and smooth muscle cells

Epithelioid:
rounded or polygonal cells with eosinophilic granular or clear cytoplasm, no cytological atypia <2 mitoses/10HPF

Myxoid:
circumscribed, hypocellular and myxoid tumor lacking mitoses or cytological atypia

Cotylenoid dissecting:
irregular nodular dissection of bland smooth muscle cells within the myometrium

Diffuse leiomyomatosis:
Innumerable, poorly circumscribed hypercellular tumor nodules with no cytological atypia

Molecular Alterations in Leiomyoma

Frequency	Target(s)	Mechanisms
70%	MED12 (Xq13.1)	Exon 2 mutations
25-29%	HMGA2 (12q15) And HMGA1 (6q21)	Multiple fusion transcripts Commonly HMGA2-RAD51B
4%	COL4A5 and COL4A6 (Xq22)	Somatic or germline X-linked dominant Xq22 deletion (Alport Syndrome/diffuse leiomyomatosis)
1%	FH (1q43)	Somatic (1q43 deletion, mutation and biallelic inactivation) or germline autosomal dominant 1q43 mutation (hereditary leiomyomatosis and renal cell carcinoma)

Leiomyoma

Prognosis and prediction

Usual leiomyomas and subtypes typically have a benign course, although experience with some subtypes is limited

Young women with symptomatic leiomyomas containing fumarate hydratase-deficient morphology should be referred for genetic counselling to exclude HLRCC

Intravenous leiomyomatosis

WHO 2020 defines *essential* diagnostic criteria

Essential: intravascular growth of benign smooth muscle tumor cells in the absence of or outside a leoimyoma

Prognosis and Prediction

Extrauterine extension in about 30% of patients (pelvic veins, inferiuor vena cava, rarely heart/pulmonary vessels

Recurrence ~10% either within veins or rarely as benign metastasizing leiomyoma

Intravenous leiomyomatosis

WHO 2020 defines *essential* diagnostic criteria

Essential: smooth muscle tumor without atypia or necrosis and minimal to absent mitosis, in lungs or lymph nodes in a patient with history of myomectomy or hysterectomy for leiomyoma(s); no history of leiomyosarcoma (gynecological or non-gynecological), no history of intravascular leiomyomatosis.

Prognosis and Prediction

Most cases have indolent course; extensive disease may lead to respiratory failure and death.

Leiomyosarcoma

WHO 2020 defines *essential* diagnostic criteria per type

- Conventional (spindle cell)
  - Two or more of the following
    - Marked cytological atypia
    - Tumor cell necrosis
    - ≥10 mitoses/10HPF
- Epithelioid
  - One or more of the following
    - Moderate to severe cytological atypia
    - Tumor cell necrosis
    - ≥4 mitoses/10 HPF
- Myxoid
  - One or more of the following
    - Moderate to severe cytological atypia
    - Tumor cell necrosis
    - >1 mitosis/10 HPF
    - Infiltrative borders/irregular margins

Leiomyosarcoma

Prognosis and prediction

Poor prognosis even when confined to the uterus. Overall 5 year survical rate (all stages) is 15-25%.
Stage I-II tumors 5 year survival rates

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Endometrial Stromal Nodule

Low Grade Endometrial Stromal Sarcoma

High Grade Endometrial Stromal Sarcoma

Endometrial Stromal Nodule

WHO 2020 defines *essential* diagnostic criteria

Essential: well-demarcated ("at most may have ≤ 3 finger-like projections <3mm from margin"), cells reminiscent of proliferative phase endometrial stroma (except if decidualized), no lymphovascular invasion.

Low Grade Endometrial Stromal Sarcoma

WHO 2020 defines *essential* diagnostic criteria

Essential: proliferative phase endometrial stromal type tumor permeating the myometrium with or without lymphovascular invasion.

Pathogenesis: Two thirds have fusions involving polycomb genes (JAZF-SUZ12, JAZF1-PHF1, EPC1-PHF1, MEAF6-PHF1)

Immunohistochemistry: diffusely and strongly positive for CD10, ER, PR. Cyclin D1 typically focal. Other stains may
Highlight smooth muscle (desmin, h-caldesmon) or sex cord (inhibin, CD99, calretinin, melan-A) differentiation.

Prognosis and prediction: indolent sarcoma; stage is most important prognostic factor.

High Grade Endometrial Stromal Sarcoma

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: monomorphic high grade round and/or spindled cells; brisk mitotic activity; cyclin D1 and BCOR IHC positivity if YWHAE-NUTM2A/B or ZC3H7B-BCOR fusion or BCORITD; a low grade endometrial stromal component if NOS.

Desirable: confirmatory genotype in selected cases.

Pathogenesis: YWHAE-NUTM2A/B or ZC3H7B-BCOR fusions or BCOR internal tandem duplication (ITD).

Histopathology: Permeative, expansile or infiltrative growth; lymphovascular invasion, necrosis, brisk mitotic activity. YWHAE-NUTM2A/B: round cells with eosinophilic cytoplasm and high grade nuclei. There might be low grade endometrial stromal or fibromyxoid components. High grade component is positive for cyclin D1, BCOR, KIT, CD99, CD56. High grade component is negative for CD10, ER, PR, DOG1. ZC3H7B-BCOR: positive for CD10 and cyclin D1, 50% positive for BCOR. Variable ER, PR

Prognosis and prediction: more aggressive than low grade endometrial stromal sarcoma.

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Undifferentiated Uterine Sarcoma

Uterine Tumor Resembling Ovarian Sex Cord Tumor

Perivascular Epithelioid Cell Tumor (PEComa)

Inflammatory Myofibroblastic Tumor

Undifferentiated Uterine Sarcoma

Currently considered a heterogeneous group and a diagnosis of exclusion

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: uniform or pleomorphic high grade mesenchymal cells with brisk mitotic activity; exclusion of other high grade tumors by extensive sampling and immunohistochemistry.

Desirable: exclusion of fusion genes associated with other sarcoma types.

Histopathology: No identifiable differentiation. Destructive pattern of myometrial invasion; necrosis and lymphovascular invasion are common. Often positive for p53 and p16, may be ER/PR positive, variably positive for CD10.

Prognosis and prediction: poor prognosis but hormone receptor positivity and mitotic count may define subset with long term survival.

Uterine Tumor Resembling Ovarian Sex Cord Tumor

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: sex cord patterns without a component of endometrial stromal tumor.

Desirable: immunoreactivity for sex cord stromal markers.

Histopathology: Typically well circumscribed intramural or submucosal. Sheets, insulae, cords, trabeculae, tubules, retiform. Ovoid nuclei, minimal atypia. Malignant exemplars with prominent atypia, brisk mitoses. Variably positive for sex cord markers (inhibin, calretinin, WT1, CD56, CD99, SF1, FOXL2, Melan A), epithelial markers, ER, PR, CD10, smooth muscle markers.

Prognosis and prediction: Benign in most cases; due to potential for recurrence may consider “low malignant potential”.

Perivascular Epithelioid Cell Tumor (PEComa)

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: cells with clear to eosinophilic granular cytoplasm, thin walled vessels surrounding nests of cells; expression of HMB45 or Melan-A and at least one myoid marker.

Desirable: confirmation of TFE3 rearrangement or fusion in TFE3 rearranged tumors.

Pathogenesis: Inactivating mutations of TSC1/TSC2 leading to mTOR signaling activation. Some tumors have TFE3, RAD51B or HTR4-ST3GAL1 fusions.

Histopathology: Epithelioid and/or spindled cells with clear to eosinophilic granular cytoplasm. Epithelioid cells arranged in nests surrounded by delicate thin walled vessels. Spindled cells often in fascicles. Borders may be expansile, permeative or infiltrative. Positive for Cathepsin K, HMB45, Melan A and smooth muscle markers.

Prognosis and prediction per gynecology-specific criteria:

Uncertain malignant potential (fewer than 3) and *malignant* (3 or more) of the following features: ≥5cm, high nuclear grade, >1 mitosis/50mm^2, necrosis, vascular invasion.

Inflammatory Myofibroblastic Tumor

WHO 2020 defines *essential* and *desirable* diagnostic criteria

Essential: bland spindle cells with myxoid fascicular growth; lymphoplasmacytic inflammation; ALK expression.

Desirable: ALK rearrangement.

Pathogenesis: ALK rearrangements by FISH in 75%

Histopathology: well circumscribed or infiltrative margins. Three patterns (may be mixed):

- Myxoid with hypocellular areas, fasciitis-like or tissue culture-like.
- Fascicular/compact
- Hyalinized

Prognosis and prediction: Most are benign and confined to the uterus. Necrosis, >7cm, moderate to severe atypia, high mitotic activity and lymphovascular invasion have been associated with aggressive course.

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Adenomyoma

Atypical Polypoid Adenomyoma

Adenosarcoma

Central Primitive Neuroectodermal Tumor/CNS Embryonal Tumor

Germ Cell Tumors

Adenomyoma

WHO 2020 defines *essential* diagnostic criteria

Essential: nodule or polyp composed of endometrioid-type glands, endometrioid-type stroma and smooth muscle.

Prognosis and prediction: Benign.

Atypical Polypoid Adenomyoma

WHO 2020 defines *essential* diagnostic criteria

Essential: discrete lesion composed of atypical, often complex endometrioid glands with squamous morular metaplasia set in a benign fibromyomatous stroma.

Prognosis and prediction: Risk of progression to endometrial adenocarcinoma is approximately 8.8% (almost all low grade and minimally invasive). Reproductive age women may be treated with curettage and close follow up.

Adenosarcoma

WHO 2020 defines *essential* diagnostic criteria

Essential: proliferation of malignant stroma accompanied by non-neoplastic Mullerian epithelium usually forming broad leaf-like structures projecting into cystic spaces (resembling phylloides tumor of the breast); periglandular cuffing of hypercellular stroma, stromal mitotic activity (can be minimal or absent).

Prognosis and prediction: Favorable unless there is sarcomatous overgrowth, deep myometrial invasion, high grade atypia, extrauterine recurrence.

Note: "*Adenofibroma*" has been removed from the current WHO classification. It is believed that a majority of tumors previously diagnosed as adenofibromas are low grade adenosarcomas or benign endometrial or endocervical polyps with unusual morphology (i.e. focal phylloides like architecture and/or increased stromal cellularity around glands.

Central Primitive Neuroectodermal Tumor/CNS Embryonal Tumor

WHO 2020 defines *essential* diagnostic criteria

Essential: a malignant small cell neoplasm with any degree of neuroglial differentiation; exclusion of Ewing sarcoma.

Histopathology: some may be associated with another tumor type (carcinoma, adenosarcoma, carcinosarcoma). Often positive for synaptophysin, chromogranin, S100. GFAP positive in about 50%. Membranous CD99 and FLI1 expression.

Molecular Pathology: Lack of EWSR1-FLI1 fusion or variants.

Prognosis and prediction: Poor prognosis.

Germ Cell Tumors

WHO 2020 defines *essential* diagnostic criteria

Essential: characteristic microscopic and immunohistochemical features as seen in ovarian counterparts.

Histopathology: yolk sac tumor is more common and has been associated with carcinoma or carcinosarcoma.

Immature/mature teratoma has also been reported in the corpus.

Prognosis and prediction: effect of yolk sac component is unknown (associated carcinoma is usually high-grade).

Immature teratoma of the uterus is associated with aggressive behavior.