Histological tumour type (Core and Non-core)

All endometrial carcinomas should be classified according to the World Health Organization (WHO) Classification of Tumours, Female Genital Tumours, 5th edition, 2020 (Table 1).[1] The International Collaboration on Cancer Reporting (ICCR) dataset includes 5th edition Corrigenda, June 2021.[2] It is beyond the scope of this dataset to provide detailed information about the microscopic features of each histologic type. However, some points are highlighted for clarification, particularly regarding the main modifications introduced in the 2020 WHO Classification.[3]

Histological tumour type has consistently been demonstrated as an important biological predictor in endometrial carcinoma. Accurate histological typing is important both in biopsy and resection specimens. Moreover, assessment of histological type determines the extent of the initial surgical procedure, and subsequent use of adjuvant therapy.[4]

Bokhman first described in 1984, two main pathogenetic types based on epidemiological studies and this concept was subsequently further expanded.[5,6] Type I carcinomas are considered low grade, estrogen-related, often clinically indolent and histologically mostly of endometrioid type. In contrast, type II carcinomas are clinically aggressive carcinomas and unrelated to estrogen stimulation and histologically non-endometrioid, particularly of serous and clear cell type. Although the type I versus type II classification is interesting for educational and epidemiological purposes, it is not useful for tumour stratification from the pathologic viewpoint, because there are significant overlapping features at the clinical, pathological, and molecular levels.[7-9]

Low grade (grade 1 and 2) endometrioid carcinomas are the most common tumours and are usually associated with favourable outcome. The prognosis for serous carcinoma is worse with recurrence occurring in about 50% of serous carcinomas compared with 20% recurrence in endometrioid carcinomas. Tumours that show combined or mixed features are rare but do occur. Although there is moderate to excellent (κ=0.62-0.87) reproducibility in histological typing, inter-observer agreement is worse in high grade carcinomas.[10-12]

Low grade endometrioid carcinoma is usually composed of cells arranged in a branching, maze-like glandular or complex papillary pattern of growth, while high grade endometrioid carcinoma has a predominant solid architecture,[13] and serous carcinoma has a complex architectural pattern with papillae and cellular budding.[14] However, serous carcinomas with a prominent glandular pattern can frequently be mistaken as low grade endometrioid carcinoma;[15,16] and endometrioid carcinoma with papillary pattern can sometimes be misinterpreted as serous carcinoma.[17]

Low grade endometrioid carcinoma exhibits some specific types of terminal differentiation such as squamous and mucinous differentiation or specific patterns of growth such as villoglandular, small non-villous papillae, microglandular, sex cord-like formations, corded and hyalinised patterns and sertoliform structures. The 2020 WHO Classification[3] incorporates mucinous carcinoma as a variant of low grade endometrioid carcinoma due to its shared molecular features and natural history. Predominant mucinous features do not significantly affect survival when compared with non-mucinous endometrial carcinomas, although, in some series, the mucinous type has a higher tendency to develop lymph node metastasis,[18] and distinction from proliferative, but not malignant, mucinous lesions may be challenging.[19] The 2020 WHO Classification clearly distinguishes the mucinous variant of endometrioid carcinoma from gastrointestinal-l type mucinous endometrioid carcinoma,[3,20] a rare type of tumour with different features and worse prognosis.

High grade endometrioid carcinoma is characterised by a solid growth pattern associated with mostly moderate nuclear atypia and an increased number of mitoses. Application of the Cancer Genome Atlas (TCGA)-molecular surrogate has demonstrated that this is a heterogeneous group of tumours.[21] This is one of the scenarios that shows the importance of integrating histologic typing with molecular classification.

Serous carcinoma is distinguished from endometrioid carcinoma by its marked nuclear pleomorphism and prominent nucleoli in the background of mostly well differentiated architecture, which is typically papillary, but can also be glandular or even solid. In contrast to the typical round, smooth and regular glandular lumens in endometrioid carcinoma, the luminal surface in serous carcinoma is irregular and the glandular structure often slit-like. Mitoses are prominent. The non-invasive type (formerly called serous endometrial intraepithelial carcinoma) is part of the spectrum of serous carcinoma, which is no longer included as a precursor lesion and can give rise to extrauterine metastasis.[22]

Clear cell carcinoma is infrequent and strict adherence to architectural and cytological diagnostic criteria is necessary, since clear cells are commonly present in endometrioid and serous carcinomas.[23-26] The major architectural patterns are tubulocystic, papillary and solid, and frequently these patterns are admixed. Tumour cells show cuboidal, polygonal, hobnail, or flat appearances, with clear or eosinophilic cytoplasm.

Undifferentiated carcinoma is usually composed of small to intermediate-sized, non-cohesive cells of relatively uniform size arranged in sheets. If a second component of differentiated carcinoma is present, which is most frequently a low grade endometrioid carcinoma occurring in approximately 40% of cases, the term dedifferentiated carcinoma is used.[27,28] The differentiated component can be low or high grade.[29] A significant number of un-/dedifferentiated carcinomas are characterised by an inactivating mutation resulting in loss of SMARCA4 or SMARCB1 protein.[30]

Mixed carcinomas are composed of two or more discrete histological types of endometrial carcinoma, of which at least one component is either serous or clear cell.[31-34] Rigorous criteria should be applied to distinguish them from heterogeneous endometrioid carcinomas (e.g., with a mixture of villoglandular, squamous and mucinous areas), which are frequently associated with MMR deficiency or *POLE* mutations.[35] Any percentage of high grade carcinoma is sufficient to classify the tumour as a mixed endometrial carcinoma. A diagnosis of mixed carcinoma should only be used when both components exhibit a characteristic morphology and immunophenotype.[34]

Carcinosarcoma, formerly included in the group of mixed epithelial and stromal tumours, is now classified as a distinct type of endometrial carcinoma and shows the typical biphasic pattern morphologically.[34] The carcinomatous component shows high grade morphology (serous, endometrioid, mixed or ambiguous), and shows a sharp demarcation from the sarcomatous component. The sarcomatous component can be homologous (no specific mesenchymal differentiation or differentiation towards smooth muscle of endometrial stroma phenotype) or heterologous (mesenchymal differentiation towards mesenchymal lineages not seen primarily in the uterus such as cartilaginous, osseous, skeletal muscle and adipocytic).

Several studies have shown that the presence of heterologous elements in carcinosarcomas is an important adverse prognostic feature particularly in Stage I tumours.[36,37] Reporting of the percentage of epithelial and sarcomatous elements and whether the sarcomatous component is homologous or heterologous is a non-core element. The rare instance of carcinoma arising in an adenosarcoma appears to be a distinct biologic process and should not be diagnosed as carcinosarcoma.[38]

The 2020 WHO Classification[3] includes novel tumour types, such as squamous cell carcinoma, mesonephric and mesonephric-like adenocarcinoma,[39,40] as well as gastrointestinal-type mucinous carcinoma.[20]

Neuroendocrine carcinomas of the endometrium are included in the section on neuroendocrine tumours of the female genital tract in the 2020 WHO Classification.[3,41] Reporting of the neuroendocrine carcinoma subtype is a non-core feature.

Endometrial carcinomas should be adequately sampled. The International Society of Gynecological Pathologists (ISGyP) 2019 guidelines recommend one section per 10 millimetres, considering the largest tumour dimension.[42] An alternative, when dealing with large tumours, is to submit at least four blocks of tumour. However, the entire endometrium and underlying inner myometrium should be submitted for microscopic examination in the setting of a preoperative endometrial specimen demonstrating malignancy, when no gross lesion is seen in the hysterectomy specimen.[42]

Table 1: World Health Organization classification of tumours of the uterine corpus.[1]

Descriptor	ICD-O codes[a]
Endometrial epithelial tumours and precursors	
Endometrial hyperplasia without atypia	
Atypical hyperplasia of the endometrium	8380/2
Endometrioid adenocarcinoma NOS	8380/3
POLE-ultramutated endometrioid carcinoma	
Mismatch repair-deficient endometrioid carcinoma	
P53-mutant endometrioid carcinoma	
No specific molecular profile (NSMP) endometrioid carcinoma	
Serous carcinoma NOS	8441/3
Clear cell adenocarcinoma NOS	8310/3
Carcinoma, undifferentiated, NOS	8020/3
Mixed cell adenocarcinoma	8323/3
Mesonephric adenocarcinoma	9110/3
Squamous cell carcinoma NOS	8070/3
Mucinous carcinoma, gastric (gastrointestinal)-type [b]	8144/3
Mesonephric-like adenocarcinoma	9113/3 [c]
Carcinosarcoma NOS	8980/3
Neuroendocrine tumour NOS	8240/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[43] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented.

[b] Codes marked with an asterisk were approved by the International Agency for Research on Cancer (IARC)/World Health Organization (WHO) Committee for ICD-O at its meeting in June 2020. Incorporates all relevant changes from the 5th edition Corrigenda June 2021.

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