Endometrial carcinoma is the most common gynecologic malignancy in the United States. The current 2020 World Health Organization (WHO) classification of endometrial carcinomas is primarily based on morphology. These tumors have been traditionally divided into 2 pathogenetic groups: type I and type II endometrial cancers. Type I cancer is mostly of endometrioid type, representing up to 80% of endometrial carcinomas, and generally comprises low-grade, early-stage neoplasms associated with estrogen excess and favorable prognosis. Type II endometrial cancers represent up to 10% of the cases, and are nonendometrioid, high-grade carcinomas, generally including serous carcinoma, clear cell carcinoma (CCC), and carcinosarcoma, as well as dedifferentiated carcinoma (DC) and undifferentiated carcinoma (UC). Type II cancers overall carry a high risk of recurrence and poor prognosis. About 10% of endometrial carcinomas exhibit more than one histologic subtype and do not fit within this dualistic model, and are therefore classified as mixed carcinomas. Moreover, it is well known that a subset of high-grade endometrial carcinomas cannot be reliably classified by histopathology alone, particularly grade 3 EECs, ESC, and CCCs; therefore, ancillary immunohistochemistry is routinely applied to assist in their recognition.

It is worth noting that even each distinct histologic subtype may not consistently predict a similar clinical outcome within the subtype. Recent molecular studies have provided novel insights into the reclassification of endometrial carcinomas for clinical management and prognostication. It has been reported that most endometrioid tumors harbor frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A, KRAS, and ARID5B. Polymerase epsilon (POLE) mutation is described in approximately 5% to 6% of endometrioid tumors. Remarkably up to 25% of high-grade endometrioid tumors and endometrial serous tumors share similar biomarker profiles: extensive copy number alterations, few DNA methylation changes, low estrogen receptor (ER)/progesterone receptor (PR) expression, and frequent TP53 mutations. More recently, a new stratification of endometrial carcinoma into 4 molecular categories has been proposed by The Cancer Genome Atlas (TCGA) based on the genomic alterations: POLE ultramutated, microsatellite instability hypermutated, copy number low (microsatellite stable or no specific molecular profile), and copy number high (serouslike, p53 mutant). This molecular classification has been poised to gain further prominence in guiding the prognostic evaluation for tailored treatment strategies in the near future.

Conclusions.—The current practice of classifying endometrial cancers is predominantly based on morphology. The use of ancillary testing, including immunohistochemistry, is helpful in the identification, differential diagnosis, and classification of these cancers. New developments such as molecular subtyping have provided insightful prognostic values for endometrial carcinomas. The proposed The Cancer Genome Atlas classification is poised to be the gold standard for the diagnosis and management of these tumors.

Data Sources.—Literature review and authors' personal practice experience.

Objective.—To discuss the utilities of commonly used immunohistochemical markers for the classification of endometrial carcinomas and to review the recent advancements of The Cancer Genome Atlas molecular reclassification and their potential impact on treatment strategies.

Context.—Endometrial carcinoma is the most common gynecologic malignancy in the United States and has been traditionally classified based on histology. However, the distinction of certain histologic subtypes based on morphology is not uncommonly problematic, and as such, immunohistochemical study is often needed. Advances in comprehensive tumor sequencing have provided novel molecular profiles of endometrial carcinomas. Four distinct molecular subtypes with different prognostic values have been proposed by The Cancer Genome Atlas program: polymerase epsilon ultramutated, microsatellite instability hypermutated, copy number low (microsatellite stable or no specific molecular profile), and copy number high (serouslike, p53 mutant).

Objective.—To discuss the utilities of commonly used immunohistochemical markers for the classification of endometrial carcinomas and to review the recent advancements of The Cancer Genome Atlas molecular reclassification and their potential impact on treatment strategies.
### Immunohistochemical Features and Molecular Profiling of Endometrial Carcinomas

| Marker | Endometrioid | Serous | Clear Cell |
|--------|--------------|--------|------------|
| P53    | --/abnormal (20%–45% in FIGO 3) | Abnormal (90%–100%) | --/abnormal (33%) |
| P16    | --/+       | +++ (90%) | --/+ (33%) |
| PR     | +          | +/-    | --         |
| ER     | +          | +      | --         |
| HNF-1β | +/++       | -      | +/++++     |
| Napsin A | -    | -      | +/+++      |
| AMACR  | -          | Present | Loss (13%–22%) |
| PTEN   | Loss       | Present | Present    |
| MMR    | Loss       | Normal  | Usually normal |

Abbreviations: AMACR, α-methylacyl-CoA racemase; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; MMR, mismatch repair protein; PR, progesterone receptor; --, negative; +, focal positivity; ++, patchy positivity; ++++, strong diffuse positivity.

### ENDOMETRIOID CARCINOMA

Endometrial endometrioid carcinoma (EEC) is the most common histologic type among endometrial carcinomas. It typically consists of glandular, cribriform, papillary, and microglandular growth patterns, with pseudostratified nuclei and variable nuclear pleomorphism (Figure 1, A through H). Low-grade EECs display diffuse strong positivity for ER/PR, negativity to patchy positivity for p16, and usually wild-type p53 staining pattern (Figure 1, C through F). High-grade (International Federation of Gynecology and Obstetrics [FIGO] 3) EECs may have different immunohistochemical and mutation profiles compared with low-grade EECs. The ER/PR staining pattern of high-grade EECs can be variable. Aberrant p53 expression is reported in 2% to 5% of low-grade EECs in contrast to 20% to 45% of high-grade EECs. More than 60% of FIGO 3 EECs also show loss of PTEN or ARID1A expression. Interestingly, ARID1A loss is associated with MMR deficiency and wild-type p53 expression.

### CLEAR CELL CARCINOMA

Endometrial clear cell carcinoma (CCC) is a rare type of endometrial cancer, accounting for less than 5% of all endometrial carcinomas. Clear cell carcinomas consist of proliferation of varying combinations of papillary, tubulocystic, and solid growth patterns (Figure 5, A through H).
Figure 1. Histology and immunohistochemistry of endometrial endometrioid carcinoma. Endometrial endometrioid carcinoma shows a glandular growth pattern (A and B), a wild-type p53 expression (C), patchy p16 staining (D), diffuse nuclear staining for estrogen receptor (E) and progesterone receptor (F), focal nuclear positivity for HNF-1β (G), and negativity for napsin A (H) (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]; original magnification ×100 [C through H]).
These tumors are characterized by immunoreactivity for hepatocyte nuclear factor 1β (HNF-1β), napsin A, and α-methylacyl CoA racemase (AMACR), and negative staining for ER and PR (Figure 5, E through H). Notably, aberrant p53 expression is seen in one-third of CCCs. Patients with p53 mutated CCCs suffer from more aggressive clinical outcome compared with those without the mutation. MMR deficiency has been identified in 0% to 19% of CCCs. Loss of ARID1A is present in 13% to 22% of the tumors. Normal expressions of PTEN and CTNNB1 are usually seen, and rare cases with POLE mutation have been identified. Overall, the genetic findings suggest that the mutation profile of endometrial CCC is more serous-like than endometrioid-like.

**MIXED CARCINOMA OF THE ENDOMETRIUM AND CARCINOSARCOMA**

Endometrial mixed carcinoma is composed of 2 or more histologic subtypes of carcinomas with at least one falling in the type 2 category (serous or clear cell carcinoma). This mixed-type group represents up to 10% of endometrial cancers. Although the 2014 WHO classification requires each component to comprise at least 5% of the entire tumor, the presence of any percentage of a type 2 carcinoma component satisfies the diagnostic criterion for mixed carcinoma per the 2020 WHO classification. Recognition of mixed carcinoma is clinically relevant, and complete surgical staging should follow.

Carcinosarcoma/malignant mixed Müllerian tumor is a biphasic tumor composed of high-grade carcinomatous and sarcomatous components, accounting for up to 5% of endometrial carcinomas. Similar genetic mutations are shared between the 2 components, supporting that the sarcoma is derived from the carcinoma through epithelial-mesenchymal transition. For carcinosarcomas, 80% to 90% of cases carry TP53 mutation and about 67% carry PI3K pathway mutations.

**UC AND DC OF THE ENDOMETRIUM**

Undifferentiated carcinoma of endometrium is an aggressive subtype that represents about 2% of endometrial carcinomas. Histologically, UC consists of a sheetlike growth of discohesive cells that are monotonous and round or polygonal with scant cytoplasm, large vesicular nuclei, prominent nucleoli, and dense chromatin. No evidence of
Figure 3. Immunohistochemical markers for endometrial serous carcinoma. Endometrial serous carcinoma shows papillary and glandular patterns (A) with the tumor cells displaying high nuclear grade and prominent macronucleoli (B). It exhibits overexpression of p53 (C) with strong and diffuse p16 staining (D), variable positivity for estrogen receptor (E), negativity for progesterone receptor (F) and HNF-1β (G), and focal positivity for napsin A (H) (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]; original magnification ×100 [C through H]).
lineage differentiation (solid growth without any pattern or glandular formation) should be found. Commonly seen in these tumors are prominent stromal infiltrating lymphocytes and brisk mitotic activity. Tumor necrosis may also be abundant.

Dedifferentiated carcinoma of endometrium is defined by the presence of 2 distinct carcinoma components: well-differentiated (FIGO 1 or 2) endometrioid adenocarcinoma and UC. The former is usually a mucosal lesion, whereas the latter is often deeply myoinvasive. The 2 components can vary in proportions, and the interface between the 2 can be abrupt or admixed. Irrespective of the amount of the undifferentiated component, DCs are far more aggressive than FIGO 2 endometrioid carcinomas. The undifferentiated component generally does not stain for epithelial markers (eg, cytokeratin [CK] AE1/AE3, CAM 5.1), E-cadherin, and gynecologic markers (eg, PAX8, ER, PR), in stark contrast to diffuse positivity of these markers in the endometrioid component. EMA and CK8/18 can be focally positive in the undifferentiated tumor cells. Neuroendocrine markers may stain scattered tumor cells (generally less than 10% of tumor cells). Interestingly, although morphologic and immunohistochemical features are significantly different, molecular analysis indicates that the undifferentiated component shares similar molecular alterations with the corresponding endometrioid component, suggesting a clonal evolution. About half of UC/DC cases show MMR deficiency and about 20% to 50% show aberrant expression of p53 in both components. Half to two-thirds of UC/DCs show switch/sucrose nonfermentable (SW1/SNF) complex inactivation, which may result in loss of expression SMARCA4/BRG1, SMARCB1/INI1, ARID1A and ARID1B in the UC component.

OTHER TYPES OF ENDOMETRIAL CARCINOMA

Neuroendocrine neoplasms (NENs) are rare in the endometrium and often occur in association with other histologic types of endometrial carcinoma, mostly the endometrioid type. In the 2020 WHO classification, NENs in the female genital tract are classified as well-differentiated neuroendocrine tumors, that is, carcinoid tumor, and poorly differentiated neuroendocrine carcinomas (NECs), including small cell and large cell NEC. Endometrial NENs have similar histologic appearance to their counterparts in other organs. Poorly differentiated NECs are more prevalent than well differentiated neuroendocrine tumors in the uterine corpus. Most endometrial NENs are large cell NECs consisting of large polygonal cells having vesicular or

Figure 4. Expression patterns of p53 immunostaining. A, Normal wild-type pattern of p53 expression in an endometrioid carcinoma, showing variable intensities of tumor cell nuclei. B through D, Three abnormal p53 patterns in endometrial serous carcinomas. B, Overexpression of p53 in more than 75% of tumor cells. C, Null pattern with complete absence of p53 staining; note the wild-type internal control. D, Cytoplasmic pattern in tumor cells; note the p53 wild-type pattern in benign stromal cells (original magnification ×100).
Figure 5. Histology and immunohistochemical markers for endometrial clear cell carcinoma. Clear cell carcinoma displays a solid pattern with clear cytoplasm (A and B), a wild-type p53 pattern (C), strong and diffuse p16 staining (D), negativity for estrogen receptor (E) and progesterone receptor (F), positivity for HNF-1β (G), and focal positivity for napsin A (H) (hematoxylin-eosin, original magnifications ×100 [A and ×200 [B]; original magnification ×100 [C through H]).
hyperchromatic nuclei and growing in organoid fashion (nests, trabeculae, or cords) with peripheral palisading. Mitotic figures in NECs are numerous, and geographic necrosis and hemorrhage are common. The 2014 WHO diagnostic criteria require more than 10% of the tumor cell to express one or more neuroendocrine markers (synaptophysin, chromogranin, and CD56), whereas the 2020 WHO version does not provide a clear cutoff. Some authors have proposed a 20% positivity cutoff to establish a diagnosis of NEN. Recent studies show that INSM1 seems to be a highly sensitive and specific neuroendocrine marker for the gynecologic tract. Rare tumor cells may stain positive for CD117 and TTF-1. Positive PAX8 immunostain is present in only a subset of the cases (33%).

Mesonephric-like adenocarcinoma is a rare type of endometrial carcinoma, representing about 1% of endometrial carcinomas. It is histologically similar to mesonephric carcinoma in cervix, but not associated with mesonephric remnants. Mesonephric-like adenocarcinoma is characterized by a variety of histologic architectures, including tubular, glandular, ductal, papillary, and solid growth patterns, but lacks squamous and mucinous differentiation. The classic pattern is tubules lined by cuboidal cells with eosinophilic colloidlike material within lumen. Most cases show variable positivity for GATA3, TTF-1, CD10 (apical/luminal staining), and PAX8, negativity for ER and PR, and a wild-type p53 pattern. Notably, GATA3 and TTF-1 can display an inverse staining pattern, which is a useful feature in limited biopsy specimens. The tumor cells also frequently show mutations of KRAS and PIK3CA and gain of 1q, and may show ARID1A mutation in a subset of tumors.

**GENERAL APPROACHES IN USING IMMUNOHISTOCHEMISTRY IN SUBCLASSIFICATION OF ENDOMETRIAL CARCINOMAS**

The diagnosis of low-grade endometrial carcinoma (FIGO 1 and 2 EECs) is usually not problematic. High-grade endometrial carcinomas, notably FIGO 3 endometrioid carcinoma, serous carcinoma, and clear cell carcinoma, may have overlapping histologic and immunohistochemical features that may impose significant diagnostic challenges (Figure 6).

A frequently encountered problem is the distinction of FIGO 3 EEC from ESC, for which an immunohistochemical panel of p53, p16, ER, and PR is generally helpful (Table; Figures 1, C through F, and 3, C through H). Briefly, combined aberrant p53 and strong/diffuse p16 staining along with patchy variable expression of ER and/or PR supports a diagnosis of serous carcinoma. Wild-type p53 and patchy p16 staining along with strong ER/PR expression favors a diagnosis of endometrioid carcinoma. In this basic panel, p16 is an essential marker for identifying p53 mutated EECs, as most EECs show variable patchy staining, with negative areas scattered throughout the tumor. For more difficult cases, for example tumors with aberrant p53 expression, patchy p16 staining, and ER and/or PR positivity, additional MMR, PTEN, and ARID1A immunostains may be pursued. Loss of expression of at least one MMR protein and negative PTEN or ARID1A expression favors a diagnosis of FIGO 3 EEC. Caution is needed in the interpretation of p16 in a small biopsy, as in limited tissue sampling, patchy p16 staining may be misread as diffuse/strong staining. If p53 staining is wild type, ESC should not be diagnosed unless the histomorphology is unequivocal for serous differentiation. Indeed, a small subset (approximately 5%) of ESCs harbor TP53 mutation but show a wild-type p53 immunostaining pattern. These tumors must be evaluated with a combination of morphologic assessment and extended immunohistochemical panel including MMR expression, PTEN, and ARID1A. Unfortunately, PTEN and ARID1A are not available in most pathology laboratories.

Although immunohistochemical studies play a limited role in the differential diagnosis of FIGO 3 EEC and CCC, a panel of HNF-1β, napsin A, AMACR, ER, and PR may be used to help with the distinction (Table; Figures 1, E through H, and 5, C through H). AMACR is highly specific for CCC but not very sensitive. Napsin A is intermediate in terms of sensitivity and specificity between HNF-1β and AMACR. A combined positivity of these 3 markers may improve the distinction between CCCs and EECs.

For the distinction between serous and clear cell carcinomas, a panel of p53, p16, ER, PR, HNF-1β, napsin A, and AMACR can be used (Table; Figures 3, C through H). The diagnostic values of p53 and p16 are limited, as about 30% of clear cell carcinomas have aberrant p53 expression and strong p16 reactivity, although a wild-type p53 pattern has a high negative predictive value against the diagnosis of serous carcinoma. ER and PR are variably positive in ESC, in contrast to generally negative staining of the 2 markers in CCC. Either HNF-1β or napsin A seems to have significant performance in distinguishing CCC from ESC. For this purpose, both markers are comparable, and both are superior to AMACR. From a practical perspective, any 2 of the 3 markers may improve the identification of the CCC histotype. Lastly, loss of ARID1A suggests a diagnosis of CCC.

The differential diagnosis of DC includes carcinosarcoma/malignant mixed Müllerian tumor and FIGO 2 or 3 EEC. Unlike the latter entities, the undifferentiated component in DC shows focal positivity for EMA and CK8/18 and negativity for keratin AE1/AE3, E-cadherin, PAX8, ER and PR. Comparatively, with carcinosarcoma, which usually contains high-grade carcinoma and pleomorphic spindle cell proliferation, DC has a low-grade gland-forming endometrioid carcinoma and an undifferentiated component of dyscohesive epithelioid cells that are negative for smooth muscle markers and epithelial markers.

The main considerations in the differential diagnosis of NEN include high-grade endometrioid adenocarcinoma, UC/DC, carcinosarcoma, and Ewing sarcoma/primitive neuroectodermal tumor. The histologic features on hematoxylin–eosin–stained sections are crucial for establishing the NEN diagnosis. Most NENs have a strong and diffuse positivity for one or more neuroendocrine markers, as opposed to focal staining in nonneuroendocrine tumors. It is worth noting that the diagnosis of NEN should rely largely on morphology rather than the cutoff value of neuroendocrine markers. For small cell carcinoma, neuroendocrine immunohistochemical stains are supportive, but not required. Notably, expression of one neuroendocrine marker in endometrial carcinomas is relatively frequent.
The loose terminology neuroendocrine differentiation is sometimes used in a pathology report to describe tumors that show neuroendocrine immunohistochemical expression. This terminology is to be avoided as it might cause confusion to clinicians. It is also recommended that in limited biopsy sample, neuroendocrine markers should be avoided unless there is clear evidence of neuroendocrine features, considering that the staining pattern may not represent the true nature of the whole lesion.

**TCGA CLASSIFICATION AND POTENTIAL INFLUENCE ON CLINICAL CARE**

The current system of risk assessment for endometrial carcinomas is based on clinicopathologic features, such as age, histologic subtype, tumor grade, and presence of lymphovascular space invasion. Survival has been found to correlate with the stage and histologic subtype of the diagnosis. Serous tumors or advanced-stage endometrial carcinomas...
cancers usually warrant adjuvant treatment. Patients with stage I or II disease usually have a more favorable prognosis than those with stage III or IV disease. However, the TCGA molecular classification identifies the patients who may have a different risk of recurrence from what is projected by traditional clinical risk-group assessment.

According to the TCGA molecular classification, FIGO 3 EECs can be stratified into 4 distinct subgroups with different prognostic implications: POLE-ultramutated, MMR-deficient/hypermutated, p53 mutant/copy number high, or no specific molecular profile/copy number low. Patients with POLE-ultramutated EECs have the most favorable outcomes, which seems to supersede other prognostic factors such as high-grade disease. MMR-deficient EECs have an intermediate prognosis, whereas no specific molecular profile type carries an intermediate to excellent prognosis. The p53 mutated FIGO 3 EECs have a similar unfavorable survival to ESC, compared with their p53 wild-type counterparts.

Interestingly, FIGO 3 EECs with p53 mutation can be further stratified by MMR status into MMR-deficient EEC p53 mutated cases that behave like EEC3 p53 wild-type tumor and MMR-proficient p53 mutated cases that behave like ESC. Similarly, recent studies have found that CCCs can also be divided into the 4 TCGA classifications. Clear cell carcinomas with POLE-ultramutated or MMR-deficient tumors typically have an excellent prognosis; in contrast, copy number–low (endometrioid-like)/p53 wild-type and copy number–high (serous-like)/p53 aberrant CCCs are usually associated with a poor prognosis.

It is noteworthy that TCGA molecular groups are also represented in UC/DC, with the MMR-deficient group appearing as the most common, followed by the copy number–low/p53 wild-type group, the p53 mutant group, and the POLE-ultramutated group. Further studies are needed to establish the prognostic significance of the TCGA classification in endometrial UC/DC. For carcinomas, 60% to 78% are classified as POLE-ultramutated or MMR-deficient groups. According to the TCGA classification of endometrial cancers, moreover, about 15% of patients with early-stage disease may benefit from additional adjuvant treatment if the tumor carries p53 mutation. In contrast, some patients with advanced disease may have tumors with favorable molecular features, such as being POLE ultramutant or MMR deficient, and they may potentially be spared from adjuvant treatment. Overall, the incorporation of TCGA molecular subgrouping with clinicopathologic factors seems to be able to achieve a superior risk assessment for subsequent clinical decision-making regarding adjuvant treatment.

In summary, the use of ancillary testing, including immunohistochemistry, is helpful in the identification, differential diagnosis, and classification of endometrial cancers. Molecular classification adds valuable prognostic and predictive information and can improve risk stratification for subsets of endometrial carcinomas. Independently or in combination with clinicopathologic features, such a molecular approach is poised to gain further prominence in guiding the prognostic evaluation and achieving tailored individual treatment strategies for patients with endometrial cancers.
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