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Review Article

Molecular approaches for classifying endometrial carcinoma☆

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HIGHLIGHTS

- Histological classification of EC has some issues that can be subjected to debate.
- Molecular classification separates EC into 4 categories with different prognosis.
- EC is a heterogeneous disease even at a molecular level.
- POLE-mutated and MSI might be more sensitive to immunotherapy with anti-PD1/PDL1 antibodies.
- CN-low and -high might be less sensitive to anti-PD1/PDL1 antibodies and combinations could be more promising.

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ABSTRACT

Endometrial carcinoma is the most common cancer of the female genital tract. This review article discusses the usefulness of molecular techniques to classify endometrial carcinoma. Any proposal for molecular classification of neoplasms should integrate morphological features of the tumors. For that reason, we start with the current histological classification of endometrial carcinoma, by discussing the correlation between genotype and phenotype, and the most significant recent improvements. Then, we comment on some of the possible flaws of this classification, by discussing also the value of molecular pathology in improving them, including interobserver variation in pathologic interpretation of high grade tumors. Third, we discuss the importance of applying TCGA molecular approach to clinical practice. We also comment on the impact of intratumor heterogeneity in classification, and finally, we will discuss briefly, the usefulness of TCGA classification in tailoring immunotherapy in endometrial cancer patients. We suggest combining pathologic classification and the surrogate TCGA molecular classification for high-grade endometrial carcinomas, as an option to improve assessment of prognosis.

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In western countries, endometrial carcinoma (EC) is the most common malignant tumor of the female genital tract, accounting for 10–20 per 100,000 person-years. Bockman first described the 2 main clinicopathological types of EC, by emphasizing the concept that the complex of endocrine and metabolic disturbances arising long before the development of EC determines the biological peculiarities of the tumor, its clinical course, and the prognosis of the disease [1]. From the pathogenetic point of view, EC falls into two different types, so-called types I and II. Type I tumors are low-grade and estrogen-related endometrioid carcinomas (EEC) while type II are non-endometrioid (NEEC) (mainly serous and clear cell) carcinomas. Type I versus Type II classification is interesting from the pathogenetic viewpoint, but sometimes difficult to be applied to clinical practice, because there are difficulties is placing some endometrial carcinoma subtypes in one of these two groups. Histological classification is nowadays gold standard for patient stratification. However, molecular studies have obtained promising results, to provide important information for prognosis and for predicting response to novel therapies. Integration of pathology and molecular biology seems crucial for an optimal diagnostic and prognostic classification [2,3].

1. Pathologic classification of endometrial carcinoma

EC is heterogeneous from the pathologic viewpoint. There are different histological types, with different microscopical features, pathogenesis, behaviour and prognosis. WHO has recently updated the pathologic classification of EC [4]. Nine different subtypes are recognized (Table 1), but EEC and serous carcinoma (SC) account for the vast majority of them.

EECs are estrogen-related carcinomas, which occur in perimenopausal patients, and are preceded by precursor lesions (endometrial hyperplasia/endometrioid intraepithelial neoplasia). Microscopically, low-grade EEC (EEC 1–2) contains tubular glands, somewhat resembling the proliferative endometrium, with architectural complexity with fusion of the glands and cribriform pattern. High-grade EEC shows solid pattern of growth. In contrast, SC occurs in postmenopausal patients in absence of hyperestrogenism. At the microscope, SC shows thick, fibrotic or edematous papillae with prominent stratification of tumor cells, cellular budding, and anaplastic cells with large, eosinophilic cytoplasms. The vast majority of EEC are low grade tumors (grades 1 and 2), and are associated with good prognosis when they are restricted to the uterus. Grade 3 EEC (EEC3) is an aggressive tumor, with increased frequency of lymph node metastasis. SCs are very aggressive, unrelated to estrogen stimulation, mainly occurring in older women. EEC 3 and SC are considered high-grade tumors. SC and EEC3 have been compared using the surveillance, epidemiology and End Results (SEER) program data from 1988 to 2001. They represented 10% and 15% of EC respectively, but accounted for 39% and 27% of cancer death respectively [5].

Table 1
Pathological classification of endometrial carcinoma, WHO 2014.

Endometrioid carcinoma
Mucinous carcinoma
Serous endometrial intraepithelial carcinoma
Serous carcinoma
Clear cell carcinoma
Neuroendocrine Tumors
Mixed cell adenocarcinoma
Undifferentiated carcinoma
Dedifferentiated carcinoma

Histological type, according to traditional microscopic parameters has consistently been proved to be an important predictor of survival, but also a determinant for the extent of the initial surgical procedure and subsequent use of adjuvant therapy. Histological typing correlates not only with prognosis, but also with the molecular alterations of each tumor type. For example, EEC and SC, the two most common types, show different molecular alterations, expression and methylation profiles. EEC shows microsatellite instability (MI), and mutations in the PTEN, K-RAS, PIK3CA, and beta-catenin genes, whereas SC exhibits alterations of TP53, loss of heterozygosity (LOH) on several chromosomes, as well as other molecular alterations (STK15, p16, E-cadherin and C-erb B2) [2,3]. Exome sequencing analyses show that the genes most frequently mutated in EEC are PTEN (77%), PIK3CA (53%), PIK3R1 (37%), CTNNB1 (36%), ARID1A (35%), K-RAS (24%), CTCF (20%), RPL22 (12%), TP53 (11%), FGFR2 (11%), and ARID5B (11%). In contrast, the genes most frequently mutated in SC are TP53 (90.7%), PIK3CA (41.9%), PPP2R1A (36,6%), FBXW7 (30.2%), CHD4 (16.3%), CSMD3 (11.6%), and COLA 11 (11.6%) [6]. It is important to notice that TP53 is mutated in >90% of SC, but also in 11% of EEC (grades 1, 2 and 3). TP53 mutations are seen in 20–30% of grade 3 EEC. That means that TP53 mutations, by themselves are not exclusive of type II EC.

The most recent WHO classification scheme has introduced interesting improvements:

1) The category of serous endometrial intraepithelial carcinoma has been included. It is characterized by replacement of the surface endometrial epithelium by highly atypical cells with extension to endometrial glands, with identical cytological features to invasive SC, but without stromal invasion. Formerly considered a precursor of SC, it is now recognized it may be associated with high-stage disease and a fatal outcome, since cells may spread to the peritoneal surface via transtubal spread of tumor cells from the uterine cavity.
2) The categories of squamous cell and transitional cell carcinomas have been deleted. Although controversial, they are unusual tumors, closely related to EEC.
3) Neuroendocrine carcinomas have been incorporated, also by including the vast majority of tumors formerly classified as small cell carcinomas.
4) The category of undifferentiated carcinoma has been better defined by including also Dedifferentiated carcinoma, which are those undifferentiated tumors that presumably arise from preexisting EEC 1–2.

2. Flaws of the pathologic classification of endometrial carcinoma

Although the current histological classification is good for tumor stratification, in our opinion, there are some issues that can be subjected to debate, which can lead to possible future improvements. Some of these areas of improvement may benefit from advances in understanding of the molecular alterations involved in the different types of tumor. Some of these points are:

1. Better definition of mucinous carcinoma, with possible inclusion as a variant of EEC. This is an unusual type of tumor. Vast majority of cases show EEC features with extensive amounts of mucin-producing cells, with microscopic and molecular features very similar to conventional low-grade EEC.
2. Better definition of low-grade EEC that will recur, with validation of promising prognostic markers.

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