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# Molecular insights into the classification of high-grade endometrial carcinoma

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**Summary**

Endometrial carcinoma, which is associated with a mortality rate of approximately 20%, is the most common gynecological malignancy in the Western world. It is a heterogeneous disease, with multiple histotypes, each constituting a different disease entity. However, interobserver diagnostic agreement is suboptimal, particularly among the most lethal histotypes. Most recent data also indicate that histotype assignment is not independently associated with survival, while in contrast, clinicopathological risk stratification and genomic classification are significantly prognostic. Recent work has shown that there are four molecular subgroups of endometrioid carcinomas instead of the two types proposed by Bokhman in the 1970s. Carcinomas with *polymerase E (POLE)* exonuclease domain hotspot mutations are highly prognostically favourable; those with copy-number alterations and *TP53* mutations are highly aggressive; and microsatellite unstable and 'copy-number low' endometrioid carcinomas are associated with intermediate prognoses. This review summarises the genetic foundations of the various histotypes of endometrial carcinoma and synthesises this information in the form of algorithms, or classifiers, that recapitulate genomic classification that is not only prognostic, but also potentially diagnostic and therapeutically predictive. A review of Lynch syndrome and Lynch-like syndrome is also provided.

*Key words:* Endometrial carcinoma; high-grade carcinoma; TCGA; molecular classification; *POLE*; microsatellite instability.

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## INTRODUCTION

Endometrial carcinoma is the most common gynecological malignancy in the Western world and accounts for approximately 74,000 deaths per year worldwide.[1,2] Although the majority of endometrial carcinomas are generally low grade and low stage, with favourable prognoses, the high-grade group accounts for a disproportionate number of endometrial cancer deaths.[3,4]

From the pathogenetic point of view, Bokhman proposed that endometrial cancer can be classified into two types (type I and II) based on epidemiological, clinical, and endocrine characteristics.[5] Type I tumours are low-grade and oestrogen-related endometrioid carcinomas, and are associated with obesity, endometrial hyperplasia, and favourable outcomes. Type II tumours are oestrogen-independent, of non-endometrioid histology (mainly serous and clear cell carcinoma), are seen in post-menopausal women, and are associated with atrophic endometrium, and poor outcomes. While this dualistic model is useful and provided the framework for many studies that contributed to our current understanding of endometrial carcinomas, including their molecular alterations, it is imperfect and difficult to apply in clinical practice due to the significant overlap between type I and II tumours and substantial heterogeneity within each type. Many high-grade endometrial carcinomas, particularly International Federation of Gynecology and Obstetrics (FIGO) grade 3 endometrioid carcinomas and clear cell carcinomas, cannot be placed into either group.

Histologically, endometrial carcinomas are classified into the following subtypes based on the 2014 World Health Organization (WHO) classification system of gynecologic tumours: endometrioid carcinoma (FIGO grade 1, 2, and 3), serous carcinoma, clear cell carcinoma, undifferentiated/dedifferentiated carcinoma, carcinosarcoma (formerly malignant mixed Müllerian tumour), neuroendocrine tumours, and mixed type.[6] The traditional stratification of endometrial carcinoma by patient age, tumour grade, and clinical stage has been important in assessing prognosis and guiding surgical treatment and subsequent use of adjuvant therapy.[7] Early-stage endometrioid cancers are generally treated by surgery, with or without adjuvant brachytherapy. Advanced-stage carcinomas are treated with upfront surgery followed by chemotherapy, with or without radiation therapy. Histotyping, however, only has a profound influence on therapy when the carcinoma is low stage, as patients with serous carcinomas and carcinosarcomas typically undergo chemotherapy almost regardless of stage. Some data suggest that histotype may not be independently associated with clinical outcomes,[8–10] as some histotypes, particularly serous carcinomas and carcinosarcomas, are intrinsically high grade, occur in older patients, and tend to present at an advanced stage. Other histotypes are highly heterogeneous from a morphological and genomic perspective, complicating efforts to link endometrioid or clear cell histotypes to specific clinical outcomes.

High-grade endometrial carcinoma constitutes a biologically, morphologically, genetically, and clinically heterogeneous group of tumours. Histologically, high-grade endometrial carcinomas are diagnostically recognisable in prototypic examples on review of haematoxylin and eosin (H&E) slides, with or without immunohistochemistry;

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however, as many as 30% of high-grade endometrial carcinomas are not prototypic.[9] Several studies have shown suboptimal interobserver reproducibility in the pathological diagnosis of high-grade endometrial carcinoma, even with the use of immunohistochemistry,[9–11] limiting the ability to develop individualised treatments and calling for the need to improve and refine the current classification schemes. Over the past decade, many studies have assessed genetic alterations in endometrial carcinoma associated with each histological type. The recent application of next-generation sequencing technologies has led to a rapid and substantial shift toward understanding the molecular alterations in endometrial carcinoma. In 2013, The Cancer Genome Atlas Research (TCGA) network performed a comprehensive genomic and transcriptomic analysis of endometrioid and serous carcinomas and classified them into four molecular subgroups, including *polymerase E (POLE)*-ultramutated, microsatellite unstable/hypermutated, copy-number low/microsatellite stable, and copy-number high (serous and serous-like) tumours.[12] The TCGA genomic classification system provided significant prognostic and potential therapeutic information; *POLE*-ultramutated tumours were associated with the best disease-free survival (DFS), copy-number high tumours were associated with the worst DFS, and the other two groups were associated with intermediate DFS. Subsequently, several investigators developed more practical methods to identify distinct subgroups with a prognostic signature, consistent with the molecular subgroups identified by TCGA,[13,14] and attempted to apply this construct to other high-grade endometrial carcinomas, such as clear cell carcinoma[15] and undifferentiated and dedifferentiated carcinomas.[16]

In this review, we discuss the various histological types of high-grade endometrial carcinoma and the molecular aberrations and immunophenotype of each type. We also discuss the TCGA molecular classification of endometrial carcinomas, including the characteristics of each subgroup. Finally, we highlight the role of integrating molecular pathology into the current pathological classification scheme.

## HISTOLOGICAL CLASSIFICATION OF HIGH-GRADE ENDOMETRIAL CARCINOMA, IMMUNOPHENOTYPE AND GENOTYPE

### FIGO grade 3 endometrioid carcinoma

FIGO grade 3 endometrioid carcinoma demonstrates solid, trabecular or nested growth and may resemble poorly differentiated, non-keratinising squamous cell carcinoma (Fig. 1). Endometrioid glandular differentiation is usually focally present with or without other features that support endometrioid differentiation, including squamous and mucinous differentiation.[6,17] At the molecular level, *PTEN* (a tumour suppressor gene), *PIK3CA*, and *ARID1A* (a chromatin remodelling gene) are mutated in >60% of FIGO grade 3 endometrioid carcinomas.[12,18,19] *KRAS* and *CTNNB1* (β-catenin) are mutated in 40%,[12,18–20] while high somatic copy-number alterations and abnormal DNA ploidy are seen in 24% and 37% of such tumours, respectively.[12,21] Overall, approximately 20–30% of endometrioid carcinomas are microsatellite instability-high (MSI-H),[12,18–20,22,23] in most cases due to *MLH1* promoter methylation. *TP53* mutations have been reported in 20–30% of FIGO grade 3 endometrioid carcinomas.[12,19,24] Immunohistochemically, a large percentage of FIGO grade 3 endometrioid carcinomas show loss of PTEN, ARID1A (BAF250a), and/or DNA mismatch repair protein expression, and at least focal expression of oestrogen and progesterone receptors (ER and PR, respectively).[25,26] However, PTEN staining can be difficult to interpret, as the antibody can be technically challenging to work with.[26] Aberrant p53 and p16 expression is seen in a subset of FIGO grade 3 endometrioid carcinomas.[25] Aberrant p53 is usually in the form of overexpression (>60–75% strong uniform staining) corresponding to a missense mutation, or in a minority of cases, there will be complete loss of p53 staining in tumour cells in the presence of positive (wild-type positivity) internal control. This 'null-pattern' staining corresponds to a nonsense mutation, leading to the formation of a truncated protein that is not detected by commercially available p53 antibodies.[27,28] A recent report on *TP53*-mutated ovarian carcinomas described two additional very uncommon staining patterns that result from *TP53* mutation: diffuse cytoplasmic staining and patchy, low-level expression that cannot be distinguished from the 'wild-type' staining pattern seen in tumours lacking *TP53* mutation.[29] To our knowledge, this has not yet been studied in the endometrium.

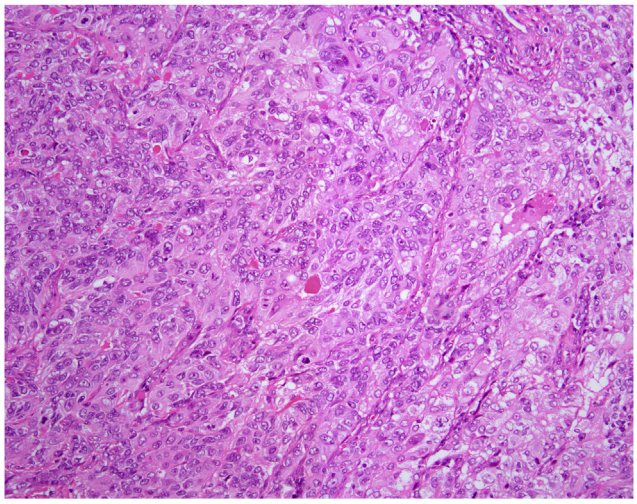

**Fig. 1** International Federation of Gynecology and Obstetrics (FIGO) grade 3 endometrioid carcinoma with a solid growth pattern and nuclear atypia.

### Serous carcinoma

Serous carcinoma typically shows irregular papillae with micropapillae and irregular luminal borders, slit-like spaces and tufted dyshesive cells exhibiting marked nuclear atypia and pleomorphism with smudgy chromatin or macronucleoli (Fig. 2). Occasionally, serous carcinoma shows predominantly glandular and/or solid architecture, which can mimic FIGO grade 3 endometrioid carcinoma. Cytoplasmic clearing might mimic clear cell carcinoma. Atrophic endometrium and/or an atrophic polyp is usually seen in the background.[6,17] At the genetic level, serous carcinoma is characterised by frequent mutations in *TP53* (>90%), *PPP2R1A*, *FBXW7*, *Her2* amplification and high copy-number alterations, whereas mutations involving *PTEN*, *ARID1A*, DNA mismatch repair genes, and *KRAS* are rare.[12,18–20,30] Abnormal DNA ploidy is seen in the majority of serous

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