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Integrating POLE Mutations and Mismatch Repair Status in Personalized Medicine for Endometrial Cancer

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Abstract

Endometrial cancer represents one of the most common gynecologic malignancies worldwide, with molecular profiling emerging as a transformative approach to its classification and treatment. The traditional histopathological model, based on tumor grade and morphology has evolved with the advent of genomic technologies, leading to the development of The Cancer Genome Atlas (TCGA) molecular subtypes: POLE ultra mutated, microsatellite instability-high (MSI-H) or mismatch repair-deficient (DMMR), copy-number low, and copy-number high. POLE-mutated tumors, characterized by ultrahigh mutational burden and microsatellite stability, generally have excellent prognosis, whereas MSI-H/ DMMR tumors respond favorably to immune checkpoint inhibitors. This review article was intended to underlie the importance of personal treatment of every patient because they exhibit unique molecular characteristics, leading to variations in prognosis and therapeutic response. Therefore, tailoring management to these molecular profiles is essential to achieve optimal outcomes. Integrating immunohistochemistry, PCR, and next-generation sequencing facilitates accurate molecular classification and individualized therapy. The convergence of molecular pathology and genomics represents a paradigm shift in endometrial cancer care, positioning POLE and MMR testing as cornerstone biomarkers for truly personalized medicine.

Keywords: Reproductive Health; Endometrial Cancer; POLE Mutation; DNA Mismatch Repair; Microsatellite Instability

1. Introduction

Endometrial cancer (EC) is the most prevalent gynecologic malignancy in developed nations and represents a significant cause of morbidity and mortality among women worldwide. According to recent epidemiological data, the global incidence of EC continues to rise, particularly in regions with increased life expectancy, obesity prevalence, and metabolic disorders (Colombo et al., 2021). Traditionally, endometrial cancer has been classified based on histopathologic criteria, specifically into type I (endometrioid, estrogen-dependent, and generally low grade) and type II (non-endometrioid, non-estrogen-dependent, and typically high grade). While this dualistic model provides valuable clinical guidance, it fails to capture the underlying molecular heterogeneity of the disease, which directly influences prognosis and therapeutic responsiveness (Talhouk et al., 2017).

Advances in high-troughput sequencing have revolutionized endometrial cancer diagnostics, shifting classification toward molecular-based taxonomy. The Cancer Genome Atlas (TGCA) identified four major molecular subgroups such as POLE-ultramutated, MSI-H/dMMR, copy-number low, and copy-number-high each with distinct prognostic and therapeutic implications (The Cancer Genome Atlas Research Network, 2013). Each category exhibits distinct genomic, correlate with specific prognostic outcomes and therapeutic strategies.

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Among these subtypes, the POLE ultramutated and MMR-deficient subtypes have emerged as crucial molecular signatures due to their prognostic and predictive value. POLE mutations confer ultrahigh tumor mutational burden (TMB) and favorable prognosis, whereas MMR deficiency leads to microsatellite instability (MSI-H) and heightened sensitivity to immune checkpoint inhibitors such as pembrolizumab and s (Le et al., 2017; Oaknin et al., 2022).

Recent guidelines by major oncologic societies, including the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP), have recommended universal MMR immunohistochemistry (IHC) testing for all newly diagnosed endometrial cancers, along with consideration of POLE sequencing and p53 testing to refine risk stratification (Colombo et al., 2021). This integration of molecular biomarkers into clinical practice represents a crucial advancement toward individualized therapy, where treatment is guided by tumor biology rather than morphology.

Although both POLE mutations and MMR deficiency are associated with high mutational loads, they result from distinct mechanism. POLE mutations arise from defective DNA polymerase proofreading, while MMR deficiency reflects impaired mismatch repair (NCCN, 2025). These molecular differences not only affect prognosis but also influence therapeutic decisions, particularly regarding immunotherapy eligibility and adjuvant therapy intensity.

Therefore, this narrative review aims to synthesize and critically analyze current evidence on the diagnostic, prognostic, and therapeutic implications of POLE mutations and MMR deficiency in endometrial cancer. This study motivated by the recognition that each patient echibits distinct molecular characteristics, warranting tailored management strategies. By elucidating the roles of these biomarkers, this review underscores their significance as cornerstones of personalized medicine and highlights emerging trends that will shape the future of endometrial cancer treatment.

2. Review content

2.1. Molecular Classification of Endometrial Cancer

The molecular classification of endometrial carcinoma represents one of the most significant advances in gynecologic oncology in the past decade. Traditionally, tumors were categorized by histopathologic features such tumor grade, cellular differentiation, and architectural patterns. However, this histopathologic system often failed to accurately predict patient outcomes, as tumors with similar morphology could demonstrate vastly different biological behaviors. The Cancer Genome Atlas (TCGA) redefined endometrial cancer into four molecular subtypes such as, POLE ultramutated, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR), copy-number low, and copy number high, each showing distinct genetic and clinical characteristic (The Cancer Genome Atlas Research Network, 2013).

The POLE ultramutated subtype is characterized by mutatios in the exonu lease domain of the POLE gene, resulting in an extremely high tumor muntaional burden (TMB) and generation of the numerour naeoantigens that trigger a string immune respone. Despite thair high-grade morphology, these tumors demonstrate very low recurrence rates and excellent prognosis, often making aggressive adjuvant therapy unnecessary. In contrast, MSI-H/dMMR tumors show defects in DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2), leading to microsatellite instability and frameshift mutation. This subtype has intermediate prognosis but responds remarkanly well to immune checkpoint inhibitor such as pembrolizumab and dostarlimab (Le et al., 2017; Oaknin et al., 2022). MMR deficiency may occur sporadically through epigenetic silencing of MLH1 (via promoter hypermethylation) or as part of the hereditary Lynch syndrome, which confers a heightened lifetime risk of endometrial and colorectal carcinomas.

The copy-number low group, often referred as the no specific molecular profile (NSMP), primarily includes endometrioid carcinomas with satable genomes, low mutation rates, and positive hormone recepetor (ER/PR) expression. These tumors usually have an intermediate outcome and harbor mutations in PTEN, ARID1A, and CTNNB1 (β-catenin). Current research efforts are exploring potential therapeutic strategies targeting the PI3K/AKT/mTOR signaling pathway within this group (Colombo et al., 2021). Conversely, the copy-number high (P53 abnormal) subtype is the most aggressice, defined by TP53 mutations and chromosomal instability. This group includes most serious and high-grade endometrioid carcinomas, which are typically diagnosed at advanced stages and have poor outcomes. Such patients may benefit from intensified chemotherapy and HER-2 targeted therapy when overexpression is present (NCCN, 2025).

While TCGA classification provides valuable molecular insight, its implementation in daily clinical practice initially posed challenges due to the complexity and cost of full genomic sequencing. To overcome this, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) was developed as a more accessible diagnostic model. It combines

POLE exonuclease domain sequencing with IHC for MMR proteins and P53, allowing reliable molecular classification suing formalin-fixed-paraffin-embedded (FFPE) tissue samples (Talhouk et al., 2017).

Integration of molecular subtyping into clinical management has revolutionized risk assessment and treatment planning. Current ESGO/ESTRO/ESP guidelines (2021) and NCCN recommendations (2025) guidelines recommend universal for POLE, MMR, and P53 in all newly diagnosed cases. These molecular markers refine prognostic accuracy and guide therapy intensity, pasients wih POLE-ultramutated tumors may undergo treatment de-escalation, whereas those with dMMR/MSI-H or P53-abnormal tumors may require more aggressive or immune-based approaches. Moreover, molecular classification facilitates identification of hereditary cancer syndromes. For example, MMR-deficient or MSI-H tumors require MLH1 promoter methylation testing to distinguish sporadic from Lynch syndrome related cases and supporting targeted genetic counselling and familial cancer prevention (Hampel et al., 2006).

2.2. The Role of POLE Mutations

2.2.1. The POLE gene encodes the catalytic subunit of DNA polymerase epsilon

Key enzyme responsible for DNA synthesis and proofreading during replication. Mutations within its exonuclease domain, particularly P286R and V411L, impair proofreading activity and result in an "ultramutated" genomic phenotype with extremely high tumor mutational burden (TMB), often exceeding 100 mutations per megabase (Alexandrov et al., 2020). This hypermutated state generates abundant neoantigens, stimulating robust antitumor immune responses. Consequently, POLE-mutated endometrial carcinomas are highly immunogenic despite being microsatellite stable (MSS), distinguishing them from mismatch repair-deficient (MMR-D) tumors that exhibit microsatellite instability (MSI-H) (Rayner et al., 2022).

Clinically, POLE mutations are most often observed in endometrioid histology, representing 7-12% of all EC cases (Colombo et al., 2021). These tumors typically present at early stages, display prominent tumor-infiltrating lymphocytes (TILs), and show high expression of PD-1 and PD-L1, reflecting active immune surveillance (Le et al., 2017). Although some exhibit high-grade morphology, patients with POLE-mutated tumor consistently demonstrate excellent survival and minimal recurrence risk (Talhouk et al., 2017). Their biology supports treatment de-escalation, as prognosis is favorable even in the presence of high-risk histopathologic features (León-Castillo et al., 2020).

Given their strong immunogenicity, POLE-mutated tumors are theoretically sensitive to immune checkpoint inhibitors (ICIs), although most patients achieve excellent outcomes without immunotherapy (Le et al., 2017). Studies suggest that POLE mutations enhance immunce cell infiltration and cytokine signaling within the tumor microenvironment, reinforcing immune-mediated control (León-Castillo et al., 2020).

Routine testing for POLE mutations is now recommended in selected cases, particularly high-grade endometrioid carcinomas, ambiguous morphology, or discordant molecular profiles to guide precise classification and management (Oaknin et al., 2022). Current ESGO/ESTRO/ESP (2021) and NCCN (2025) guidelines endorse a tiered diagnostic approach combining mMR IHC, P53 assessment, and targeted POLE sequencing. Identification of a pathogenic POLE mutation enables clinicians to avoid unnecessary chemotherapy or radiation while maintaining excellent survival outcomes (Colombo et al., 2021).

2.3. Mismatch Repair (MMR) Deficiency and Microsatellite Instability (MSI) Testing

The DNA mismatch repair (MMR) system is a conserved mechanism that maintains genomic stability by correcting replication errors. Core proteins include MLH1, PMS2, MSH2, and MSH6, which form heterodimeric that detect and repair base mismatches and insertion deletion loops (Li, Pearlman, and Hampel, 2023). Dysfunction in any of these proteins leads to microsatellite instability (MSI) a hallmark of genomic hypermutability observed in several malignancies, including endometrial and colorectal carcinomas. MMR deficiency (dMMR) can arise through either from germline mutations, typical of Lynch syndrome, or from somatic MLH1 promoter hypermethylation, which silences gene expression in sporadic cases (Hampel et al., 2006).

Microsatellites instability reflects the functional status of the MMR system and is classified as MSI-high (MSI-H), MSI-Low (MSI-L), or microsatellite stable (MSS). MSI-H tumors exhibit extensive instability and high mutational burden, producing abundant neoantigens that enhance immune recognition and sensitivity to checkpoint inhibitors such as pembrolizumab and dostarlimab (Le et al., 2017).

MSI-L tumors show limited instability and weaker immune activity, while MSS tumors retain intact MMR function. Nonetheless, some MSS tumors, particularly those with POLE mutations, may still display hypermutation and strong immune infiltration (Colombo et al., 2021).

Immunohistochemistry (IHC) remains the standard, cost-effective test for evaluating MMR status by detecting nuclear expression of MLH1, PMS2, MSH2, and MSH6. Loss of nuclear staining for one or more proteins indicates MMR deficiency (dMMR), which correlates with MSI-H status (Colombo et al., 2021). Specific loss patterns guide clical interpretation: concurrent loss of MLH1/PMS2 suggests MLH1 promoter methylation (sporadic cases), whereas combined MSH2/MSH6 loss or isolated loss of MSH6/PMS2 implies a germline mutation and potential Lynch syndrome, warranting confirmatory testing (Hampel et al., 2006). The integration of MMR IHC with MLH1 methylation testing allows distinction between sporadic and hereditary disease, ensuring appropriate genetic counselling and treatment.

From a therapeutic perspective, MMR deficiency and MSI-H status serve as both prognostic and predictive biomarkers. MSI-H tumors generally show intermediate outcomes yet they respond exceptionally well to immune checkpoint inhibitors. The seminal study by Le et al. (2017) demonstrated durable responses to PD-1 blockade in dMMR tumors, leading to tumor-agnostic FDA approval. This was reinforced by the GARNET trial, which confirmed the efficacy of dostarlimab in advanced dMMR endometrial carcinoma (Oaknin et al., 2022).

Current ESGO/ESTRO/ESP and NCCN (2025) guidelines recommend routine molecular testing including MMR IHC, MSI, POLE, and P53 analysis in all newly diagnosed endometrial cancers. Identifying dMMR/MSI-H status informs immunotherapy eligibility and guides treatment intensity, marking MMR testing as a cornerstone of precision oncology in endometrial cancer management.

3. Conclusion

The identification of MMR deficiency and MSI status represents a critical advance in the molecular pathology of endometrial carcinoma. IHC-based detection of MMR protein loss is an effective screening tool that can be complemented by PCR or NGS for comprehensive molecular profiling. Beyond its diagnostic role, MSI-H/dMMR status serves as a robust predictive biomarker for immunotherapy responsiveness, enabling tailored treatment strategies that improve patient outcomes. As precision oncology evolves, universal molecular testing for MMR and MSI is now indispensable in the routine management of endometrial cancer.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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