REVIEW ARTICLE

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Pole Mutations and MMR in Endometrioid Carcinoma from A Clinical Perspective

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Endometrial carcinoma (EC) is the most prevalent gynecological cancer globally and ranks as the sixth leading cause of cancer-related deaths among women. Polymerase epsilon (POLE) mutations are linked to a high Tumor Mutation Burden (TMB) in endometrioid carcinoma. POLE-mutated tumors typically maintain Microsatellite Stability (MSS), despite their high TMB. This review aims to explore the association between POLE mutations, mismatch repair (MMR) status, and their clinical implications in guiding diagnosis and treatment strategies. Findings indicate that POLE-mutated tumors generally show excellent prognosis and enhanced responsiveness to immunotherapy, such as pembrolizumab, with response rates reported around 36% in MSI-H tumors. In conclusion, molecular classification based on POLE and MMR provides more accurate prognostic stratification and supports personalized treatment approaches in EC.

Keywords: Endometrial Carcinoma (EC), POLE mutations, Tumor Mutation Burden (TMB), Microsatellite Stability (MSS), Mismatch Repair (MMR)

Introduction

Endometrial carcinoma (EC) is the most common gynecological cancer worldwide and is ranked as the sixth leading cause of cancer-related deaths among women, according to the GLOBOCAN 2020 estimates[1]. Endometrial cancer is generally classified into two groups: type I endometrioid tumors are associated with excess estrogen, obesity, hormone receptor positivity, and a good prognosis compared with type II, especially serous, tumors that occur more frequently in older, non-obese women, and have worse results[2].

EC is the most common gynecological cancer worldwide and is ranked as the sixth leading cause of cancer-related deaths among women, according to the GLOBOCAN 2020 estimates[1]. Traditionally, EC has been classified into two main clinicopathological types based on aggressiveness. Type I tumors are usually endometrioid adenocarcinomas, strongly associated with unopposed estrogen exposure, obesity, and hormone receptor positivity. They are more common, accounting for the majority of EC cases, and generally have a favorable prognosis. In contrast, Type II tumors comprise serous, clear cell, and carcinosarcomas. These tumors are less frequent, tend to occur in older, non-obese women, and are characterized by aggressive clinical behavior, poor prognosis, and higher recurrence risk[2-6]. The World Health Organization (WHO) classification further categorizes EC into four histologic types; however, histopathological assessment alone is limited by inter-observer variability and insufficient prognostic accuracy.[3]

The Cancer Genome Atlas (TCGA) proposed a molecular classification that stratifies EC into four subtypes: DNA Polymerase Epsilon (POLE)-ultramutated, microsatellite instability-high (MSI-H), copy-number low

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(CN-low), and copy-number high (CN-high), each with distinct prognostic implications.[7,8,4,6] POLE-mutated tumors show ultrahigh mutation rates and excellent prognosis. MSI-H tumors arise from mismatch repair deficiency (MMRd) and are frequently linked to Lynch syndrome. CN-low tumors often harbor PTEN and CTNNB2 mutations, while CN-high tumors are characterized by TP53 mutations and poor outcomes.[3,7,8] This molecular classification offers improved prognostic stratification and supports personalized treatment strategies in EC.[7,8]

In addition to histopathological classification, The Cancer Genome Atlas (TCGA) has proposed a molecular classification of endometrial carcinoma into four subtyps: POLE ultramutated, microsatellite instability-high (MSI-High), copy-number low (CN-low), and copy-number high (CN-high). These subtypes differ in genomic alterations, clinical behavior, and prognosis, thus providing more accurate stratification for diagnosis and treatment planning. The prognostic relevance of these molecular subtypes is summarized in **Figure 1.**

In endometrial carcinoma, prognosis is largely determined by clinical and pathological characteristics

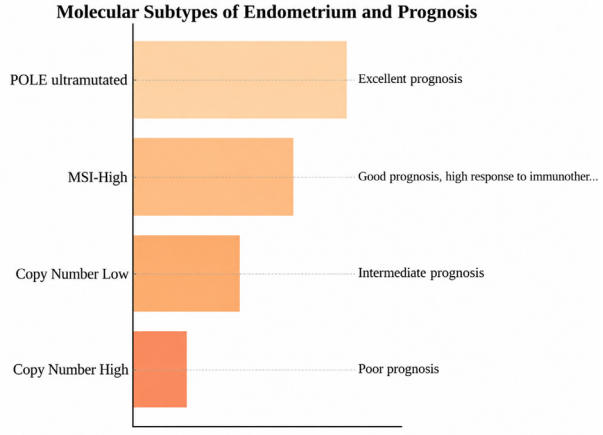


Figure 1. Molecular subtypes of endometrial carcinoma and their prognostic implications.

POLE ultramutated subtype shows excellent prognosis; MSI-High subtype is associated with good prognosis and high response to immunotherapy; Copy Number Low subtype confers intermediate prognosis; while Copy Number High subtype is linked to poor prognosis (TCGA 2013; WHO Classification of Tumors, 2020). such as histopathological type and stage according to the International Federation of Gynecology and Obstetrics (FIGO), but growing evidence suggests that these factors alone have limited predictive value.[3] POLE mutations are genetic mutations that occur in the POLE gene, which can cause deficiencies in DNA reading errors and increase the number of mutations in tumor cells. These mutations can occur in various types of cancer, such as endometrial cancer and colorectal cancer.[8] POLE mutation in endometrial carcinoma refers to alterations in POLE gene, particularly within its exonuclease domain, leading to an ultramutated tumor phenotype characterized by a markedly high mutation rate. These mutations define a distinct molecular subgroup of endometrial cancer—termed POLE/ultramutated—which can be identified through sequencing of the POLE exonuclease domain[4]. POLE mutations contribute to the molecular classification of endometrial cancer and have important implications for prognostication and therapeutic decision-making. Determining POLE mutation status enables a more personalized approach to patient management and may help avoid overtreatment. Emerging evidence suggests that patients harboring POLE mutations may exhibit favorable responses to immune checkpoint inhibitors, such as pembrolizumab.[3,9,10]

Emerging evidence suggests that patients with POLE mutations may exhibit favorable responses to immune checkpoint inhibitors, such as pembrolizumab. In the KEYNOTE-158 trial, pembrolizumab achieved an objective response rate of approximately 36% in patients with MSI-H tumors, including endometrial cancer, supporting its role as an effective therapeutic option in this subgroup.[11]

Although POLE mutations can affect patient prognosis, further research is needed to fully understand the impact of these mutations on various types of cancer.[7] Mutations in the POLE gene (POLEm) and defects in the mismatch repair system (MMRd) lead to a significant number of errors in DNA replication and a high rate of mutations . Tumors with these abnormalities produce abnormal peptides, also known as neoantigens, which have been found to activate an immune response in the host. These neoantigens can be targeted for immunotherapy.[3]

Endometrial carcinoma due to POLE mutations is a fairly significant case. Studies show that POLE mutations

can be found in approximately 7-12% of endometrial carcinoma cases. These tumors have a high rate of mutations and neo-antigens, which causes an increased immune response.[8] In a study of 613 endometrial carcinoma cases, 11.4% had POLE mutations.[7] A study in the US population showed that the proportion of women under 60 years with endometrial cancer who carried the POLE variant increased significantly.[12] In one study, 359 EC cases with POLE mutations were identified, with 294 (82%) having pathogenic mutations.[9] Two studies have reported the incidence of POLE mutations in patients with recurrence after low-risk EC treatment.[5]

POLE mutations are considered driver mutations in endometrial cancer, meaning they play an important role in the development and progression of the disease.[13] POLE mutations have been studied as potential risk predictors for recurrence in low-risk EC.[5] Patients with POLE mutant EC have the best prognosis among the four molecular subgroups.[14] Although POLE mutations and MMR status are increasingly recognized as important prognostic markers in endometrial carcinoma, their routine application in clinical decision-making remains limited. Most studies to date have focused on molecular characterization, but the translation of these findings into daily clinical practice, particularly in resource-limited settings, is still lacking. This review therefore aims to bridge this gap by summarizing current evidence on POLE mutations and MMR status in endometrioid carcinoma, highlighting their clinical implications for diagnosis, prognosis, and therapeutic strategies, with a special emphasis on their role in guiding immunotherapy use. The relationship between POLE mutations, MMR status, and their clinical implications is illustrated in **Figure 2**, providing a conceptual framework for this review.

POLE mutations

POLE mutations are genetic alterations that occur in a gene called POLE, which encodes a DNA polymerase enzyme involved in DNA replication and repair. When mutations occur in the POLE gene, it can lead to a deficiency in the proofreading ability of the DNA polymerase, resulting in an increased mutation rate. This phenomenon is known as the "ultramutated" or "hypermutated" phenotype.[15]

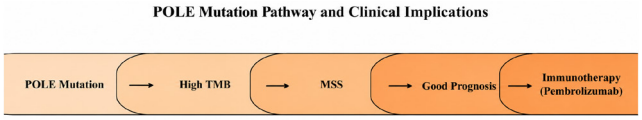


Figure 2. Schematic representation of POLE mutations and MMR status in endometrial carcinoma.
Mutations in the POLE gene lead to ultrahigh tumor mutational burden (TMB) while maintaining microsatellite stability (MSS). This molecular profile is associated with good prognosis, enhanced immunogenicity, and favorable response to immune checkpoint inhibitors such as pembrolizumab, thereby supporting individualized treatment decisions and avoiding overtreatment.[11]

Although tumors with POLE mutations generally show MSS, they still have a high tumor mutational burden (TMB), which increases the neoantigen load and enhances tumor immunogenicity. This unique biology helps explain why some MSS tumors with POLE mutations respond well to immunotherapy, despite lacking MMR deficiency. Patients with endometrial carcinoma harboring POLE mutations have excellent survival outcomes regardless of adjuvant therapy, suggesting intrinsic sensitivity to immune surveillance.[16] Similarly, MSS tumors with POLE mutations have a unique immune microenvironment with increased tumor-infiltrating lymphocytes and checkpoint molecule expression, which may contribute to their responsiveness to immune checkpoint inhibitors.[17]

POLE-mutated endometrial cancer generally exhibits a MSS phenotype, although in some cases, concurrent MMR deficiency has also been observed. The presence of a POLE mutation can have implications for prognosis and potential responsiveness to immunotherapy, but testing for POLE mutations is not routine and is typically reserved for specific clinical scenarios.[18]

The POLE gene mutations possess distinct characteristics that are critical in the field of cancer biology. These mutations are often associated with a significant increase in mutations present in tumor genomes, indicating a higher frequency of genetic alterations compared to tumors lacking POLE mutations. This heightened number of mutations can be attributed to the POLE enzyme's compromised proofreading function, leading to errors during DNA replication.[16] POLE-mutated tumors

typically exhibit MSS, in contrast to microsatellite instability (MSI) commonly observed in other types of cancer. While MSI tumors typically show mutations in DNA mismatch repair genes, errors in POLE-mutated tumors originate from the DNA polymerase itself, resulting in a unique set of mutations.[19] Finally, POLE mutations have a preference for specific cancer types, such as endometrial, colorectal, and sporadically gliomas. By understanding the relationship between POLE mutations and these cancer subtypes, we can improve diagnostic and therapeutic strategies that are tailored to the molecular profiles of individual tumors, ultimately leading to better patient outcomes in clinical practice.[20]

POLE Mutations in Endometrial Cancer

POLE mutations are relatively rare but are more commonly found in certain types of endometrial cancer, particularly in tumors with high tumor grade and MSI-High.[20] They are more frequently observed in endometrioid endometrial carcinomas, which are a type of endometrial cancer that arises from the lining of the uterus. POLE mutations are often associated with high levels of MSI-High, which is a result of deficient DNA mismatch repair. MSI-High tumors have a high mutational load, which can lead to increased neoantigen formation and potential sensitivity to immunotherapy.[18] Some genetic mutations are involved in endometrial cancer prognosis including POLE mutation. Some studies have shown that endometrial cancers with POLE mutations are associated with certain factors. with better prognosis and survival outcomes. This is thought to be related to the high mutation rate, which can create a more immunogenic tumor environment.[21]

Endometrioid cancers with POLE mutations do not represent the entirety of cases. In terms of diversity, endometrioid endometrial cancers encompass a wide array of genetic changes, with POLE mutations being just one possibility among many.[5] Endometrial cancer is classified into four molecular subtypes POLE-mutated, MSI-High, CN-Low, and CN-High.[21] POLE mutations are exclusive to the POLE-mutated subtype, which constitutes only a fraction of endometrioid carcinomas. Additionally, endometrioid endometrial cancers can present with various genetic alterations such as mutations in PTEN, CTNNB2 (beta-catenin), ARID1A, and others. These mutations may have differing implications for prognosis and treatment strategies.[20]

Significance of POLE Mutations in Endometrioid Carcinoma

The importance of POLE mutations in endometrioid carcinoma lies in several key aspects Endometrioid carcinomas with POLE mutations typically exhibit low-grade characteristics, which contrast with the higher grades often seen in cases with p53 mutations.[18] These POLE-mutated carcinomas generally offer a more positive prognosis compared to those with p53 mutations or other molecular subtypes. They often experience better survival rates, lower recurrence rates, and enhanced responses to treatment. POLE-mutated tumors also display a high TMB, indicating a greater number of mutations per megabase of DNA due to the role of the POLE gene in DNA replication. This high TMB makes them more sensitive to immunotherapy, particularly immune checkpoint inhibitors.[22] Furthermore, endometrioid carcinomas with POLE abnormalities are almost always microsatellite stable, translating to an intact DNA mismatch repair system, unlike tumors with frequent MSI which have excellent reactivity to immunotherapies. As a result of this unique molecular pathogenesis mechanism, endometrioid carcinomas with POLE abnormalities harbored in the genome are classified as the “ultra-mutated” ecTMA histotype. Though this molecular category is scarcely indicated, it is viewed as unique, with some certainty of its future in clinical practice.[4] It is essential to know about the importance of POLE mutations in the treatment of EEC patients. Knowing about the POLE mutation status of such tumors may better help in guiding cancer treatment regimens, with the option of using immunotherapy or targeted therapies based on their molecular nature may result in less aggressive treatment plans and surveillance strategies due to endometrial pathology’s better prognosis. POLE mutations and MSI have critical clinical implications as separate molecular pathways in EEC tumors. Overall, EEC tumors have enormous gaps, and there is a massive need to alter treatment plans precisely targeting their molecular pattern for patients’ benefit.[23]

POLE Mutation and MMR Status

POLE mutations are associated with a high TMB in endometrioid carcinoma. These mutations are typically identified in a specific group of endometrial cancers, which is the "ultra-mutated" subtype. Extensive mutations in the POLE gene characterize the subtype. These mutations are associated with low-grade endometrioid carcinomas, a positive prognosis, high TMB, and MSS.[24]

The MMR status of a cell indicates its ability to rectify errors that may occur during DNA replication, specifically those that affect microsatellite sequences. The absence of MMR leads to MSI, where replication errors cause changes in the lengths of microsatellite sequences. One can determine the MMR status through MSI testing. An MSI-High result implies the absence of MMR, while MSI that the MMR is functioning correctly. Lynch syndrome, a hereditary condition associated with MMR deficiency, is linked to several cancers, including endometrial cancer.[3]

The connection between POLE mutations and MSS in endometrioid carcinomas reveals that POLE-mutated tumors usually maintain MSS, despite their high TMB. Unlike MSI-High tumors, which indicate MMR deficiency, POLE-mutated tumors typically arise from defects in DNA polymerase proofreading during replication instead of MMR deficiency.[3] On the other hand, tumors that exhibit MSI-High status are usually associated with MMR gene mutations or Lynch syndrome in endometrioid carcinomas. These MSI-High tumors are linked to an increased risk of endometrial cancer in individuals with Lynch syndrome and often show a favorable prognosis in sporadic MSI-High tumors due to an enhanced immune response, known as immunogenicity.[21]

The POLE mutation pathway found in tumors is unique and has a distinctive molecular signature that results in a higher TMB and MSS status.[23] These tumors typically display low-grade features and are associated with a positive prognosis due to their specific genetic makeup. In contrast, tumors that follow the MMR-deficient pathway frequently show MSI-High status, indicating problems with MMR genes. This pathway is often associated with Lynch syndrome, which increases the risk of various cancers, including endometrial cancer. Interestingly, sporadic cases of MSI-High tumors may surprisingly display a positive prognosis due to increased immunogenicity, leading to improved responses to treatment.[25]

The correlation between POLE mutations and MSS status holds significant clinical relevance. This information aids in categorizing prognoses, where tumors with POLE mutations typically exhibit positive prognostic outcomes, whereas the prognoses for MSI-High tumors differ based on specific contexts. Furthermore, this comprehension assists in determining treatment approaches.[24] Tumors with POLE mutations and elevated TMB and MSS status typically show favorable responses to immunotherapy. Conversely, MSI-High tumors, while potentially benefitting from immunotherapy, do so based on distinct mechanisms related to their immunogenicity rather than TMB or MSS status. This nuanced understanding proves beneficial in creating tailored treatment strategies and optimizing therapeutic outcomes in the management of endometrial carcinoma.[26]

Endometrioid carcinoma displays a correlation between POLE mutations and MMR status, despite each representing distinct molecular pathways. POLE-mutated tumors exhibit a high TMB and MSS status, while MMR-deficient (MSI-High) tumors indicate MMR deficiency and are frequently linked to Lynch syndrome.[18] Understanding these unique pathways is vital for making informed decisions regarding prognosis and treatment strategies for endometrial cancer. MSI is a defect observed in select cancers where the cell's DNA repair mechanism malfunctions, leading to errors in microsatellite replication. Microsatellites are brief, repeated DNA sequences. MSI can be categorized into two types: MSI-High, which denotes substantial instability, and MSI-L. These distinctions in MSI levels are critical for the molecular characterization of tumors, aiding in personalized therapeutic approaches and prognostic evaluations in cancer care.[1]

MSI-High

MSI-High or MSI-H is a term used to describe a significant level of microsatellite instability, indicating numerous errors in the repeated DNA sequences.[1] This type of MSI is commonly linked to Lynch syndrome, an inherited genetic disorder that heightens the chances of developing colorectal cancer and other cancer forms. Tumors with MSI-High status are more receptive to specific immunotherapies, particularly checkpoint inhibitors.[18] This is due to the high number of mutations that result in the production of abnormal proteins which the immune system can identify and eliminate. This underscores the potential efficacy of immunotherapy in treating MSI-High tumors.[25]

MSI-Low

The MSI-Low (MSI-L) status is indicative of a lower occurrence of errors in repeated DNA sequences, in comparison to MSI-High tumors. This results in a decreased level of microsatellite instability, and MSI-Low tumors are relatively rare in clinical settings. It is worth noting that, unlike MSI-High tumors, MSI-Low tumors are less receptive to immunotherapy.[27]

This is a crucial factor to consider in their treatment and management. The assessment of MSI status is a crucial

component in the treatment and management of cancer, as it greatly influences the approach to treatment. Pembrolizumab (Keytruda), an immunotherapy medication, has received FDA approval for tumors with MSI-High status, leading to significant improvements in outcomes for some patients. It's important to note that tumors with MSI-Low status do not necessarily indicate microsatellite stability.[3]

While MSI-L tumors have fewer errors within repeated DNA sequences compared to MSI-High tumors, they still exhibit some degree of microsatellite instability. Microsatellite instability (MSI) can range from MSS to MSI-Low to MSI-High, each representing varying levels of microsatellite instability.[28] MSS tumors have intact DNA repair mechanisms and lack microsatellite instability, indicating minimal to no errors in repeated DNA sequences. In contrast, MSI-Low tumors exhibit a lower level of microsatellite instability compared to MSI-High tumors, with some errors in repeated DNA sequences but at a lower frequency than MSI-High tumors.[1] MSI-High tumors, on the other hand, exhibit a significant level of microsatellite instability, characterized by numerous errors within repeated DNA sequences. These MSI classifications have distinct molecular characteristics that affect cancer diagnostics and treatment considerations.[28]

MSI-Low tumors are characterized by a lower degree of instability, in comparison to MSI-High tumors, but are not classified as MSS tumors. Despite displaying a certain level of microsatellite instability, it is not as pronounced as that observed in MSI-High tumors.[1] The extent of microsatellite instability in MSI-L tumors can have an impact on treatment approaches and prognostic considerations, albeit to a lesser degree than in MSI-High tumors.[21]

The assessment of MSI is an essential procedure for patients diagnosed with endometrioid carcinoma for a variety of reasons. Primarily, it plays a key role in identifying individuals with Lynch syndrome, a genetic condition that elevates the susceptibility to various cancers, such as colorectal and endometrial cancer. By detecting patients with Lynch syndrome through MSI testing, healthcare providers can offer suitable screening and management to both the patient and their family members.[29]

The status of MSI in endometrioid carcinoma holds considerable prognostic significance. Research indicates that tumors exhibiting high levels of MSI generally have a more favorable prognosis compared to MSS or MSI-Low tumors. Individuals with MSI-H tumors often experience improved overall survival rates and a reduced risk of recurrence. These findings underscore the critical role of MSI testing in informing treatment strategies and enhancing patient outcomes.[28] Assessing MSI status is essential for predicting the treatment response in endometrioid carcinoma. Tumors exhibiting high MSI-High are more likely to have a favorable response to immunotherapy, particularly when treated with checkpoint inhibitors such as pembrolizumab (Keytruda). By targeting the immune system, this medication assists in identifying and combating cancer cells. The elevated mutational load present in MSI-High tumors renders them more receptive to immunotherapies. This underscores the significance of MSI testing in tailoring treatment approaches and enhancing therapeutic results for patients.[30] It is essential to comprehend the MSI status of endometrioid carcinoma tumors in order to tailor treatment approaches effectively. Patients with MSI-High tumors could significantly benefit from incorporating immunotherapy into their treatment, whereas individuals with MSI-Low or MSS tumors may require alternative treatment strategies that correspond to their molecular profiles. This underscores the significance of MSI testing in directing precision medicine practices in cancer care.[29]

When overseeing cases of endometrioid carcinoma, it is crucial to conduct MSI testing. This testing is pivotal in identifying patients with Lynch syndrome, aiding in prognosis determination, directing treatment approaches, and facilitating the adoption of personalized therapeutic methods, including immunotherapy, to improve treatment effectiveness.[13] Immunohistochemistry (IHC) is a valuable technique for visualizing and assessing the presence, localization, and abundance of specific proteins within tissue samples when evaluating MSI status in tumors. In the context of MSI testing, IHC plays a key role in evaluating the expression levels of proteins involved in DNA MMR pathways, thereby offering vital information.[23] Immunohistochemistry is a widely used technique to determine the status of specific proteins that are relevant to MSI, including MLH2 (MutL homolog 1), MSH3 (MutS homolog 2), MSH4 (MutS homolog 6), and PMS3 (PMS2 homolog 2).[12] These proteins are essential components of the DNA MMR system, which is responsible for rectifying errors during DNA replication. Failure to express any of these proteins may indicate abnormalities in the MMR system, potentially resulting in MSI.[3]

The tumor analysis process typically commences with tissue sample extraction via biopsy or surgical procedures.

These samples are then processed and embedded in paraffin blocks to create tissue sections, which are subsequently mounted onto slides. Next, the tissue sections are subjected to immunohistochemical staining, wherein specific antibodies are applied to target MLH2, MSH3, MSH4, and PMS3 proteins. The presence or absence of these proteins plays a crucial role as it can signal a deficiency in mismatch repair and the probability of MSI in the tumor.[13] Subsequently, a pathologist meticulously examines the tissue sections under a microscope. This examination is instrumental in determining the presence or absence of MMR proteins, providing invaluable insights into the MSI status of the tumor. The detailed analysis then helps clinicians make informed decisions regarding treatment strategies and prognostic assessments that are customized to the tumor's specific molecular characteristics.[28]

Interpreting the staining outcomes is a crucial part of analyzing the results. If all four proteins exhibit normal staining, it suggests that the DNA MMR system is functioning as it should, and consequently, the tumor is categorized as MSS.[1] Conversely, if there is a loss of staining in one or more of the MMR proteins, it may indicate a possible deficiency in the MMR system. Such a loss of staining is an indication of MSI within the tumor.[9] Immunohistochemistry is an extensively employed and valuable method for MSI testing. Nonetheless, it does not offer the same level of comprehensiveness as PCR-based MSI testing, which directly evaluates the microsatellite repeats in the DNA and is commonly regarded as the gold standard. Despite this, immunohistochemistry is often favored due to its convenience, cost-effectiveness, and capacity to supply valuable insights into MMR protein expression.[31]

Endometrioid cancer cases do not universally exhibit POLE mutations, as these mutations are confined to a subset of endometrial cancers, mainly those displaying endometrioid histology. Nevertheless, it's noteworthy that not all instances of endometrioid carcinoma involve POLE mutations.[27] Concerning implications in cancer improved prognosis studies suggest that tumors with POLE mutations may have a more favorable prognosis compared to those lacking these mutations. This favorable outlook is attributed to the heightened immunogenicity of POLE-mutated tumors, which triggers a more potent immune response against the cancer cells.[25]

Potential Response to Immunotherapy: POLE-mutated tumors, characterized by a high mutational burden, can generate neoantigens recognized by the immune system. This characteristic renders these tumors potentially more receptive to immunotherapy, particularly treatments like immune checkpoint inhibitors.[31] Regarding clinical considerations is testing considerations while POLE mutation testing is not standard practice in routine cancer assessments, it may be warranted in specific cases, especially for endometrial and colorectal cancers exhibiting distinctive features such as high-grade endometrioid histology or early-onset colorectal cancer.[24]

Immunotherapy Decisions is the presence of a POLE mutation can significantly impact treatment strategies, particularly in the context of immunotherapy. Tumors harboring POLE mutations may demonstrate heightened responsiveness to immunotherapy due to their increased immunogenicity, thereby influencing treatment decisions during clinical management.[13]

Conclusion

POLE is a crucial enzyme responsible for maintaining DNA stability. When POLE gene mutations occur, the enzyme's ability to repair base pair errors within DNA can be hindered, which is typically managed by the Mismatch Repair (MMR) system. Endometrioid carcinoma (Ca) is a cancer type that originates in the endometrium, the uterus's inner lining. The correlation between POLE, MMR, and endometrioid cancer stems from the potential disturbance in MMR function caused by POLE gene mutations. Such disruption can result in the accumulation of uncorrected DNA errors that promote uncontrolled cell growth and increase the risk of endometrioid cancer. Therefore, comprehending the association between POLE, MMR, and endometrioid cancer is vital in developing more effective diagnostic and treatment strategies for these conditions.

Future research should focus on integrating routine molecular testing of POLE and MMR into standard diagnostic workflows, particularly in low- and middle-income countries where access remains limited. Development of cost-effective and widely applicable molecular assays is needed to ensure broader clinical implementation. Furthermore, prospective multicenter studies with long-term follow-up are warranted to validate the prognostic and predictive value of POLE mutations and MMR status, and to evaluate the sustained efficacy of immune checkpoint inhibitors, such as pembrolizumab, in this subgroup of endometrial carcinoma.

Authors' Contribution

IQR and APA contributed to the preparation, review, and final approval of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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