Review

Medicine

Clinical Characteristics and Detection of Polymerase Epsilon Mutant Endometrial Carcinoma

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Polymerase Epsilon (POLE)-mutant endometrial cancer accounts for 7%-12% of endometrial cancer molecular types, and most of these patients are early-stage endometrioid carcinoma. Although POLE-mutant endometrial cancer has some unfavorable pathological features such as being poorly differentiated, the overall prognosis is good, and postoperative adjuvant treatment may be considered for de-escalation. POLE-mutant endometrial cancer is relatively less sensitive to postoperative adjuvant chemotherapy or radiotherapy, but because of its ultra-high tumor mutation load, recurrent or advanced patients are expected to benefit from programmed cell death receptor 1 (PCDR1) blockade therapy. This review will discuss the clinical features of POLE-mutated endometrial carcinoma and the progress made in the detection of POLE gene mutations.

Keywords: Endometrial Neoplasms; Molecular Classification; POLE Mutation; Prognosis; Outcomes

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ENDOMETRIAL cancer is one of the three major malignant tumors of the female reproductive system (1). Its standard treatment is surgery, and adjuvant radiotherapy and/or chemotherapy are determined after surgery based on pathological factors (2). There are still limitations in precise classification, individualizing treatment, and making prognosis predictions, and the overuse and undertreatment of postoperative adjuvant therapy are still clinical problems. In 2013, the Cancer Genome Atlas Research Network classified endometrial cancer into four types: Polymerase Epsilon (POLE) ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high (3, 4). The latest 2023 edition of the US National Comprehensive Cancer Network (NCCN) (5) and the 2021 European Society of Gynecologic Oncology (ESGO) guidelines both recommend that patients with endometrial cancer undergo molecular typing testing to guide postoperative adjuvant therapy (6). Among the four molecular types, the POLE mutant type has the best prognosis. This paper reviews the clinical features of POLE mutant endometrial carcinoma and POLE gene mutation detection.

Clinical Features of POLE Mutant Endometrial Carcinoma

The POLE gene is located at human 12q24.3, and the full-length cDNA is 63,604 bp, which is the largest catalytic subunit of DNA polymerase (7). It has two main catalytic activities: one is

DNA template-based polymerase activity, and the other is exonuclease correction activity, which plays an essential role in cellular DNA replication and base mismatch repair. Wherein, no matter what type of germline mutation or systematic mutation occurs in the coding gene encoding the POLE exonuclease region, it can lead to loss of correction activity of POLE exonuclease, increased gene instability, and mismatched bases cannot be recognized and excised, resulting in an abnormally high number of mutations in the genome that can cause damage to cells with increasing the risk of cancer.

Studies have found that POLE exonuclease has been detected in a variety of tumors, including endometrial cancer, colorectal cancer (8), non-small cell lung cancer (9), ovarian cancer (10), and high-grade glioma (11). Among them, endometrial cancer is the malignant tumor with the highest incidence of POLE mutation, ranging from 7% to 12% (12). McConechy et al. performed POLE mutation detection on 496 cases of endometrial cancer and found that 9.6% of the patients had POLE mutations, and among these patients, 92% were stage I, and 62% were grade 3, endometrioid histology 82%, and lymphovascular invasion 49% (13).

Although POLE mutant endometrial cancer has some unfavorable pathological features such as poor differentiation, the overall prognosis is good (14). Billingsley et al. found that in poorly differentiated endometrioid carcinoma, compared with POLE wild type, the recurrence rate and mortality rate were all low (15). The subgroup analysis of 245 patients with stage I endometrial cancer who did not receive any adjuvant therapy in the PORTEC-1 study showed that POLE mutations, the 10-year recurrence-free survival rates of wild-type patients were 100% and 80.1% (16). Based on these retrospective studies, the 2021 ESGO guidelines recommend that postoperative adjuvant therapy can be omitted for patients with POLE mutation stage I-II endometrial cancer (17). Among Chinese endometrial carcinoma patients, PROBEAT is the first randomized phase III trial to assess adjuvant therapy based on WHO-endorsed molecular categorization. It is anticipated that customized adjuvant tactics will be improved using molecularly integrated profiles and NCCN standards. And found that if the molecular-directed treatment's control rates are comparable to those of the standard clinicopathological-based treatment, it will show that POLEmut ECs with stage I or stage II can safely forego adjuvant treatment, and HIR (stage IB grade 3 or stage II) ECs with MMRd or NSMP will benefit from less overtreatment, which is anticipated to reduce morbidity and improve quality of life (18). The latest prospective RAINBO BLUE & TAPER study (NCT05640999) also made similar recommendations (19). The final results of this clinical study will provide high-level, evidence-based medical evidence for the postoperative management of POLE-mutant endometrial cancer.

Based on the good prognosis characteristics of POLE mutant endometrial cancer, determine whether this type of young patient can be expanded if they have moderately or poorly differentiated endometrial carcinoma, infiltrate the superficial or even deep myometrium, or combine other medium-to-high-risk pathological factors. There is still a lack of relevant evidence on the indications for fertility-preserving treatment or on whether the treatment-related adverse reactions can be reduced by appropriately prolonging the interval of endometrial pathological assessment or reducing the drug dose during treatment. In addition, POLE gene mutation detection is helpful to identify endometrial cancers with similar morphology, especially poorly differentiated endometrioid carcinoma and serous carcinoma, both of which have high atypia and a solid growth pattern (20, 21). The identification of morphology is usually highly subjective and poor in reproducibility, while POLE detection can objectively divide them into mutant type and wild type, and the prognosis of mutant patients is good, which can effectively avoid overtreatment due to the potential risks of special pathological types.

The sensitivity of POLE mutant endometrial cancer to postoperative adjuvant radiotherapy or chemotherapy has attracted the attention. Bellone et al. found through in vitro experiments that POLE-mutated tumor cells were significantly more resistant to platinum drugs (22), while Van Gool et al. found that POLE-mutated endometrial cancer cell lines were resistant to ionizing radiation, and the sensitivity of common chemotherapeutic drugs (such as cisplatin, paclitaxel, doxorubicin, 5-fluorouracil, methotrexate, and etoposide) was not significantly different from that of the wild type, but the glycosides and fludarabine is enhanced (23). The results suggested that POLE mutant endometrial cancer is relatively less sensitive to postoperative adjuvant chemotherapy or radiotherapy.

In recent years, tumor immunotherapy, especially immune checkpoint inhibitors represented by programmed cell death receptor 1 and its ligand 1 (PD-1/PD-L1) inhibitors, has been widely used in endometrial cancer. A breakthrough has been made in the application of the drug, and tumor mutation load is considered one of the biomarkers for screening patients who benefit from PD-1/PD-L1 blockade therapy (24). POLE-mutant endometrial cancer has an ultra-high tumor mutation load, which leads to somatic mutations that produce a large number of tumors neoantigens that induces a strong immune response, which provides the possibility for PD-1/PD-L1 blockade therapy in patients with advanced or recurrent POLE-mutant endometrial cancer (25). In addition, compared with POLE wild-type endometrial cancer, the number of infiltrating CD4+ and CD8+ T lymphocytes in POLE mutant tumor tissue was significantly increased (26). Tumor-infiltrating T cell gene enrichment, enhanced cytotoxic differentiation, and effect markers were significantly up-regulated, suggesting that there is a more active cytotoxic T cell response in the local tumor microenvironment of POLE mutant endometrial cancer (27, 28). Ma and colleagues used in vitro and in vivo experiments to find that mice carrying POLE/POLD1 functional mutations have enhanced anti-tumor immunity and are sensitive to immune checkpoint inhibitor treatment (29). They established a POLE/POLD1 functional-related feature model to predict patient prognosis and found that characteristic POLE/POLD1 mutations can increase the hydrophobicity of T cell receptor contact residues and change the biochemical characteristics of neoantigens, which is conducive to T cell recognition. On this basis, PD-1/PD-L1 blockade therapy is expected to induce a more effective anti-tumor immune response.

At present, many clinical trials related to the treatment of immune checkpoint inhibitors are in full swing. The phase II

clinical trial (NCT02912572) is aimed at patients with recurrent or persistent POLE mutations and MSI-H endometrial cancer. Study of avelumab monotherapy or combination drugs and found that treatment with avelumab and talazoparib showed a positive toxic effect profile and satisfied the prerequisites to be approved for further research in mismatch repair proficient endometrial cancer suggesting that insights from immunogenomic profiling may be used to guide current and upcoming research on the effects of PD-L1 inhibitor and polyadenosine diphosphate-ribose polymerase combos on endometrial cancer (30). A newly recruited phase I clinical trial (NCT04262089) will investigate pembrolizumab in the neoadjuvant treatment of POLE-mutant and MMRd-type uterine malignancies (31). Preliminary exploratory research and observational clinical research (NCT05103969) will carry out observational research on the clinical biological characteristics and molecular characteristics of 100 multicenter POLE/POLD1 mutation patients with various tumors (32).

POLE Gene Mutation Detection

POLE mutations include systemic mutations and germline mutations, of which the systemic mutation rate is 6%-10% and the germline mutation rate is 0.25%-4% (33). Germline mutations are hereditary, and the mutation types of the POLE gene include nucleotide duplication, deletion, and insertion, and most mutations are aneuploidies. POLE gene mutation detection includes hotspot mutations or pathogenic mutations in the exonuclease domain of POLE genes (34). The exonuclease domain of the POLE gene contains exons 9-14, and more than 80% of the pathogenic variants occur in exons 9 and 13. Pathogenic mutations in the POLE exonuclease domain have the following characteristic genomic alterations: high incidence of C > A variants (more than 20%); low proportion of small insertion and deletion mutations (indels); very high tumor mutations load (>100 mutations/megabase) (35).

Currently, detection methods for POLE gene mutations mainly include Sanger sequencing and next-generation high-throughput sequencing (NGS). The advantages of Sanger sequencing are its low cost and high accuracy. It is very economical and efficient for the detection of known variant sites and can be used as the gold standard for detection. However, the biggest limitation is low coverage and sensitivity, and it cannot detect unknown variant sites. NGS technology has the advantages of high throughput, high accuracy, and rich information, but the high cost and long cycle of detection limit the popularization and application in clinical practice. In addition, in order to reduce detection costs and improve detection sensitivity, targeted sequencing can also be performed after hybridization capture or amplicon enrichment of the target sequence (36).

Clinically, there is still a lack of uniform standards for the detection methods and result interpretation of pathogenic mutation sites in the POLE gene. There are five common hotspot mutations in the POLE gene: P286R, V411L, S297F, A456P, and S459F, covering 95.3% of the known pathogenic mutation sites (37). It was suggested that in clinical practice, these few mutation sites with high mutation frequency and prognostic significance can be detected to reduce the cost of diagnosis, but there is a possibility of a missed diagnosis. It has been reported that the following site mutations also belong to POLE mutations: D275A, D275G, D275V, S279Y, P286H, P286L, P286T, P286S, M295R, F367S, D368Y, V411M, L424I, L424V, L424P, P436R, and M444K. At present, in the absence of whole-exome or whole-genome sequencing (WES or WGS) data, the definition and classification of low-frequency mutation sites, mutations of unknown significance, and newly discovered mutation sites are still very challenging. It is a difficult point in the interpretation of POLE mutation results.

Since de-escalation of postoperative adjuvant therapy is recommended for POLE-mutant early-stage endometrial cancer, an accurate definition of POLE-causing mutations is crucial for the classification of molecular types of endometrial cancer. León-Castillo et al. developed a scoring system using TCGA WES data based on mutation characteristics, tumor mutation burden, DNA microsatellite instability (MSI) status, POLE mutation frequency, and recurrent mutations to evaluate the risk of POLE mutations (38). For pathogenicity, a threshold was set, and a score 4 was defined as a pathogenic POLE mutation, a score of 3 was defined as a variant of unknown significance, and a score of 2 was defined as a non-pathogenic POLE mutation. This scoring method is helpful to assess whether a new variant locus is pathogenic in the absence of WGS data, but this standard has not been widely accepted in clinical practice (39).

Conclusion

POLE-mutant endometrial cancer has a good prognosis, but most of the evidence derived from retrospective studies. Prospective clinical studies with large samples and multiple centers are needed, and its biological characteristics and pathogenesis are still in the exploratory stage. The detection and resulting interpretation of POLE gene mutations still need to be continuously explored. A standardized and easy-to-implement clinical detection method for POLE mutations should be established and promoted to the application of molecular typing of endometrial cancer in clinical practice, which will help effectively assess the prognosis of this type of patient, reasonably guide patients to carry out stratified management, and formulate precise and individualized treatment.■

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