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ORIGINAL RESEARCH

Evaluation of the TCGA-Surrogate (ProMisE) Molecular Classification and Clinical Features of Endometrial Carcinoma: A Study of 97 Cases from China

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Background: Molecular classification of endometrial carcinoma (EC) has gained prominence. This study is a retrospective analysis exploring the value of molecular classification in clinical practice in a Chinese cohort.

Methods: Ninety-seven patients with EC were enrolled in this study. Patient-derived EC samples were used for polymerase-ε exonuclease domain mutation (POLE edm) sequencing. The presence and defects of mismatch repair (MMR) proteins were identified using immunohistochemistry (IHC). Similarly, tumour protein 53 (p53) was identified using IHC. Recurrence-free survival (RFS) was tested between groups using Kaplan–Meier curves with the Log rank test.

Results: Distribution by molecular subtype was as follows: POLE edm (3 patients; 3.1%); MMR deficient (MMRd) (32 patients; 33%); abnormal p53 (p53abn) (49 patients; 50.5%) and wild-type p53 (p53wt) (13 patients; 13.4%). Actual RFS rates for the different molecular subtypes were as follows: POLE edm (100%); MMRd (93.5%); p53abn (77.8%) and p53wt (84.6%). Differences in morphology, myometrial invasion, cervical stromal invasion and lymphovascular space invasion among groups were not significant ($p > 0.05$), but the same was not the case for cervical epithelial invasion. Cervical mucosa invasion in the POLE edm group was significantly different from the other three groups ($p < 0.05$). The results of Kaplan–Meier RFS curves showed that the *p*-value was 0.300 (Log rank test) in molecular subtypes and 0.386 (Log rank test) in the group with/without cervical involvement.

Conclusion: Our results suggest that cervical stromal invasion in EC may have no prognostic significance, the EC ProMisE classifier has no relationship with morphology and routine use of molecular classification is premature. The study was limited by a relatively small sample size and short follow-up duration, and further multicenter studies are warranted to validate these findings.

Keywords: endometrial carcinoma, molecular classification, polymerase-ε, mismatch repair, cervical stromal invasion

Introduction

Endometrial carcinoma (EC) is one of the most common cancers in women, and its incidence is increasing.[1–3] However, the traditional histopathological classification system, which relies primarily on morphological features and histological grading, often fails to capture the complex molecular landscape of EC. This limitation results in suboptimal prognostic assessments and treatment decisions.[4–6]

Traditional histopathological classification of EC relies on morphological features, such as histological subtype and grade. While this method provides a foundation for clinical decision-making, it has limitations in accurately predicting patient outcomes and guiding personalized treatments. For instance, some cases are difficult to classify, and the prognosis for patients with similar histopathological features can vary significantly.[7] In contrast, molecular-based classifications,

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such as The Cancer Genome Atlas (TCGA) classification, offer a more nuanced understanding of EC by categorizing tumors based on genetic and molecular profiles.[8] The TCGA proposed a molecular grading method that classifies ECs into four subtypes: polymerase-ε (POLE) ultramutated, microsatellite instability hypermutated, p53 abnormal, and p53 wild-type. These subtypes have distinct prognoses and therapeutic implications, providing a more precise framework for clinical decision-making.[9] However, the TCGA classification requires extensive genomic sequencing, which can be costly and time-consuming, limiting its widespread clinical application.

To address the limitations of both traditional histopathological classification and the TCGA method, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) was introduced. This classifier categorizes EC into four molecular subtypes using a combination of immunohistochemistry (IHC) and targeted sequencing to assess POLE exonuclease domain mutations, mismatch repair (MMR) protein status, and p53 abnormalities, making it more accessible and cost-effective. Although the ProMisE classifier has been validated in several studies, its application has been predominantly limited to Western populations, with limited data on its performance in non-Western cohorts, particularly in Chinese patients with endometrial carcinoma. Additionally, while molecular classifications offer improved prognostic accuracy, their integration with traditional staging systems remains a challenge.[10]

Several landmark studies have explored molecular classification in EC. For example, a study demonstrated that integrating molecular and clinicopathological factors could improve risk assessment in early-stage EC.[11] However, this study was limited by its focus on early-stage disease and did not fully address the feasibility of molecular classification in a broader clinical context. Another critical challenge is the integration of molecular data with established treatment guidelines. Clinicians often struggle to incorporate molecular findings into clinical decision-making, especially when traditional histopathological features conflict with molecular subtypes. The ProMisE classifier has been shown to change the prognostic risk group classification in a significant number of patients, highlighting the need for a more unified approach. Furthermore, the lack of standardized protocols for molecular testing can lead to inconsistent results and confusion in clinical practice.[12]

Our study aims to bridge the gap between molecular classification and clinical practice by evaluating the ProMisE classifier in a real-world clinical setting, defined here as routine diagnostic practice in a Chinese tertiary hospital, reflecting actual patient populations, treatment decisions, and follow-up patterns. We assess the distribution of molecular subtypes, their association with clinicopathological features, and their prognostic significance in a cohort of 97 patients with EC. By doing so, we aim to demonstrate the feasibility of integrating molecular classifiers into routine practice, ultimately improving patient management and outcomes in EC. Furthermore, molecular classification may help guide clinical decision-making by identifying patients who could benefit from adjuvant therapy or require more intensive follow-up, thereby improving personalized management strategies for endometrial carcinoma. Our study builds on previous research by providing a comprehensive evaluation of the ProMisE classifier and highlighting its potential and limitations in a clinical context.

Materials and Methods

Study Design

This study is a retrospective cohort analysis designed to evaluate the clinical value of molecular classification in EC using the ProMisE algorithm. Ninety-seven patients with pathologically confirmed EC who received treatment at our institution between January 2018 and January 2019 were enrolled. Formalin-fixed, paraffin-embedded (FFPE) tissue samples from these patients were analysed for POLE exonuclease domain mutations (edms), mismatch repair (MMR) protein defects, and p53 abnormalities using sequencing and immunohistochemistry (IHC). Clinicopathological data were collected from medical records, and recurrence-free survival (RFS) was assessed using Kaplan–Meier curves with the Log rank test. Our primary objective was to determine the distribution of molecular subtypes and their association with clinical and pathological features, as well as to evaluate the prognostic significance of these molecular subtypes in a clinical setting.

Participants

Blocks of FFPE tissue from 97 patients with EC who received treatment in our institution from January 2018 to January 2019 were used. Experimental grouping was based on the ProMisE molecular classifier. Medical records of clinicopathological characteristics were obtained in detail. The inclusion criteria were as follows: patients ≥18 y of age with a pathologically proven diagnosis of EC. The exclusion criteria were as follows: prior or concurrent malignant disease or other serious comorbid medical conditions. All patients underwent surgical treatment according to the International Federation of Gynaecology and Obstetrics (FIGO) 2009 staging system and were treated following institutional and international guidelines applicable at the time. The standard surgical procedure included total hysterectomy and bilateral salpingo-oophorectomy, with lymphadenectomy performed when indicated by preoperative or intraoperative assessment. Adjuvant therapy, including radiotherapy and/or chemotherapy, was administered based on individual pathological risk factors. Patients with prior tamoxifen exposure, fertility-sparing management, or metabolic comorbidities (eg, diabetes, hypertension) were not excluded, as these factors were not systematically recorded in all cases; however, their potential impact on prognosis is acknowledged as a limitation.

Morphologic Criteria

All pathological sections were diagnosed by three pathologists according to the World Health Organization's 2020 classification guidelines for EC.[13] The EECs included in this study were graded according to FIGO grading criteria, which is divided into three levels according to the presence of solid, nonglandular, nonsquamous growth. Grade 1 represented ≤5%, G2 represented 6%–50% and G3 represented >50% of all cases.

POLE Sequencing

Genomic DNA was extracted from FFPE tissue samples. Tumour-rich areas were identified using haematoxylin and eosin-stained slides, and corresponding regions were isolated using whole-slide microdissection. The Sanger sequencing method was used to extract DNA from EC samples using kits. Polymerase chain reaction (PCR) products were obtained by amplification, as well as gel recovery. The PCR products were sequenced using a 3730XL sequencer (ABI, Foster City, CA, USA). Mutation analysis was performed by sequence comparison with wild-type. The sequencing data were analysed using SeqScape Software (Applied Biosystems, USA). DNA extraction quality was assessed by spectrophotometric analysis using NanoDrop (Thermo Fisher Scientific, USA), and only samples with A260/A280 ratios between 1.8 and 2.0 were included for sequencing. The minimum DNA input for PCR amplification was 50 ng, and Sanger sequencing sensitivity was approximately 15% for detecting mutant alleles. Sequences were compared to a reference POLE gene sequence (GenBank accession number NM_006231) to identify mutations. Variants were classified based on their presence in known pathogenic mutation databases (eg ClinVar) and in the literature. Only mutations located in the exonuclease domain (exons 9–14) that are known to affect POLE function were considered relevant for classification.

Immunohistochemistry

Immunostaining of protein MMR and p53 were performed in this study. Protein MMR and p53 antibodies and related kits for IHC staining were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd (Fuzhou, China). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections using standard protocols. Sections were cut at 3–4 μm thickness, deparaffinized, rehydrated, and subjected to antigen retrieval using citrate buffer (pH 6.0). The slides were then incubated with primary antibodies against MMR proteins (MLH1, PMS2, MSH2, and MSH6) and p53. Immunoreactivity was visualized using the Roche Benchmark automated IHC system with diaminobenzidine (DAB) as the chromogen, followed by hematoxylin counterstaining.

Mismatch repair deficiency was defined by the complete absence of nuclear staining in tumour cells for any one of the MMR proteins (MLH1, PMS2, MSH2 or MSH6). A case was considered MMR deficient (MMRd) if there was a loss of staining for either PMS2 or MSH6 or if there was an isolated loss of MLH1 or MSH2.[13–16] Tumour protein 53 status was determined by immunohistochemistry according to established criteria.[17] p53 was classified as abnormal in cases showing any of the following patterns: strong nuclear expression in ≥75% of tumour cells (overexpression), complete

absence of nuclear staining with preserved internal positive control (null pattern), or unequivocal cytoplasmic staining, as shown in Figure S1. Cases with wild-type staining pattern, defined as nuclear expression in 1–74% of tumour cells with variable intensity and without cytoplasmic staining, were classified as p53wt. Subclonal p53 staining, characterized by distinct populations of p53-positive and p53-negative tumour cells, was carefully evaluated; in such cases, final p53 status was determined by the predominant staining pattern. Notably, no cases were excluded due to intermediate or heterogeneous staining, as all could be assigned to either wild-type or abnormal category based on the predominant pattern.

For MMR proteins, nuclear staining was evaluated by two independent pathologists blinded to the clinical data. The staining was scored as positive (retained expression) or negative (complete loss of expression) based on the presence or absence of nuclear staining in tumour cells. The threshold for positivity was set at ≥10% of tumour cells showing nuclear staining for each MMR protein, which aligns with widely adopted algorithms in endometrial cancer and gastrointestinal cancer studies.[18]

ProMisE Classification Algorithm

The ProMisE classification was applied using a sequential hierarchical algorithm as follows: First, all cases were tested for POLE exonuclease domain mutations by Sanger sequencing. Cases with pathogenic POLE mutations were classified as POLEmut, regardless of subsequent MMR or p53 status. Second, POLE-wildtype cases were evaluated for MMR protein expression by immunohistochemistry. Cases with loss of any MMR protein (MLH1, PMS2, MSH2, or MSH6) were classified as MMRd. Third, POLE-wildtype and MMR-proficient cases were assessed for p53 expression by immunohistochemistry. Cases with aberrant p53 expression (overexpression, null pattern, or cytoplasmic staining) were classified as p53abn, while those with wild-type staining pattern were classified as p53wt, corresponding to the no specific molecular profile (NSMP) subgroup.

Outcomes and Endpoints

The primary outcome of this study was the distribution of molecular subtypes according to the ProMisE classifier and their association with clinicopathological features of EC. Related endpoints included the frequency of each molecular subtype (POLE edm, MMRd, p53abn and p53wt) and the comparison of clinicopathological characteristics (eg, histological grade, myometrial invasion, cervical invasion, lymph node status and lymphovascular space invasion [LVSI]) between these subtypes.

The secondary outcome was the prognostic significance of these molecular subtypes, as assessed by RFS. The related endpoint was the RFS rate, which was analysed using Kaplan–Meier survival curves and the Log rank test to compare survival outcomes among different molecular subtypes and between groups with and without cervical involvement.

Statistics

Statistical analysis was performed using SPSS version 17.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using one-way analysis of variance (ANOVA), and categorical variables using the chi-squared test or Fisher's exact test as appropriate. Recurrence-free survival was analyzed using the Kaplan–Meier method and Log rank test. A two-tailed p value < 0.05 was considered statistically significant.

Results

Clinicopathological Data

The pathological diagnosis of all patients was as follows: 90 cases of type I EC (EEC), 5 cases of type II EC and 2 cases of mixed carcinoma. As shown in Table 1, the symptoms with which patients sought medical treatment were as follows: abnormal uterine bleeding in 91 patients (93.8%), uterine enlargement in 2 patients, endometrial thickening in 2 patients, vaginal discharge in 1 patient, and 1 patient was diagnosed during evaluation for secondary infertility. The maximum age of patients in this study was 80 y, and the minimum age was 22 y, with a mean of 54.7 y. The mean age of the cohort was

Table 1 The Clinicopathological Characteristicsof EC Subtypes

Variable	POLE edm (n=3)	MMRd (n=32)	p53abn (n=49)	p53wt (n=13)	*P* value
Age (years), mean±SD	55.0±0.5	54.8±1.4	54.8±1.5	53.7±1.9	0.981
BMI (kg/m^2), mean±SD	26.6±1.7	23.7±0.48	24.5±0.41	24.6±0.94	0.678
FIGO stage, n (%)					
I	3 (100)	28 (87.5)	40 (81.6)	10 (76.9)	0.682
II	0 (0)	2 (6.3)	5 (10.2)	2 (15.4)	
III–IV	0 (0)	2 (6.3)	4 (8.2)	1 (7.7)	
Histological type, n (%)					
Endometrioid	3 (100)	30 (93.8)	43 (87.8)	12 (92.3)	0.715
Non-endometrioid	0 (0)	2 (6.3)	6 (12.2)	1 (7.7)	
Histological grade, n (%)					0.405
Low-grade (G1–G2)	2 (66.7)	29 (90.6)	41 (83.7)	10 (76.9)	
High-grade (G3/type II)	1 (33.3)	3 (9.4)	8 (16.3)	3 (23.1)	
Myometrial invasion, n (%)					0.828
<50%	2 (66.7)	26 (81.3)	38 (77.6)	10 (76.9)	
≥50%	1 (33.3)	6 (18.8)	11 (22.4)	3 (23.1)	
Cervical invasion, n (%)	2 (66.7)	4 (12.5)	9 (18.4)	4 (30.8)	0.099
Epithelial only	2 (66.7)	1 (3.1)	4 (8.2)	1 (7.7)	**0.022**
Stromal	0 (0)	3 (9.4)	5 (10.2)	3 (23.1)	0.565
Lymph node status, n (%)					0.294
Positive	0 (0)	3 (9.4)	3 (6.1)	2 (15.4)	
Negative	1 (33.3)	16 (50.0)	31 (63.3)	6 (46.2)	
Not assessed	2 (66.7)	13 (40.6)	15 (30.6)	5 (38.5)	
Lymph node assessment method, n (%)					0.453
Lymphadenectomy	1 (33.3)	16 (50.0)	31 (63.3)	6 (46.2)	
Sentinel node biopsy only	0 (0)	3 (9.4)	3 (6.1)	2 (15.4)	
None	2 (66.7)	13 (40.6)	15 (30.6)	5 (38.5)	
LVSI, n (%)	0 (0)	4 (12.5)	3 (6.1)	4 (30.8)	0.093
Adjuvant therapy, n (%)					0.356
None	2 (66.7)	18 (56.3)	22 (44.9)	6 (46.2)	
Radiotherapy only	1 (33.3)	8 (25.0)	12 (24.5)	4 (30.8)	
Chemotherapy ± RT	0 (0)	6 (18.8)	15 (30.6)	3 (23.1)	
Type of operation, n (%)					0.091
Hysterectomy + BSO	1 (33.3)	22 (68.8)	20 (40.8)	7 (53.8)	
Hysterectomy + BSO + LND	2 (66.7)	10 (31.2)	29 (59.2)	6 (46.2)	

Notes: Values are presented as mean ± SD or n (%). P values were calculated using ANOVA for continuous variables and chi-square or Fisher's exact test for categorical variables. Bold indicates statistical significance ($p < 0.05$).

Abbreviations: LVSI, lymphovascular space invasion; BSO, bilateral salpingo-oophorectomy; LND, lymph node dissection; RT, radiotherapy; CT, chemotherapy.

54.7 ± 10.2 years. The mean BMI was 24.5 ± 2.8 kg/m^2. There was no significant difference in age, BMI or operation type among experimental groups.

Distribution by molecular subtype was as follows: POLE edm (3 patients; 3.1%), MMRd (32 patients; 33%), p53abn (49 patients; 50.5%) and p53wt (13 patients; 13.4%). The hierarchical classification process yielded the following stepwise results: Of 97 cases, 3 (3.1%) were identified as POLEmut at the first step. Among the remaining 94 POLE-wildtype cases, 32 (34.0%) showed MMR deficiency and were classified as MMRd. Of the 62 POLE-wildtype and MMR-proficient cases, 49 (79.0%) exhibited aberrant p53 expression and were classified as p53abn, while the remaining 13 (21.0%) with wild-type p53 pattern were classified as p53wt/NSMP (Figure S1). The detailed information of POLE mutations identified in this study is presented in Table S1. There were 82 cases with low-grade EEC (G1 or G2) and 15 cases with high-grade (G3 or type II). Presentation of representative pathology results are shown in Figure 1. There were no significant differences in histological grade, myometrial invasion, cervical stromal invasion, lymph node metastasis or LVSI among groups, but this was not the case for cervical epithelial invasion. Cervical mucosa invasion in the POLE

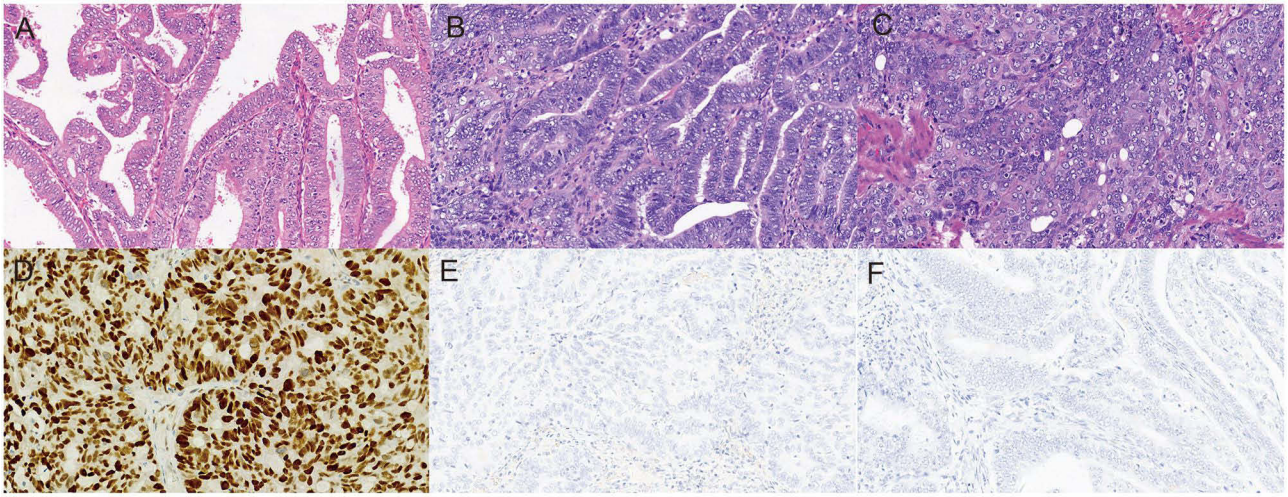

Figure 1 (**A**) is low-grade (G1), (**B**) is low-grade (G2) and (**C**) is high-grade (G3), (**D**) p53 abnormality (p53 abn), (**E**) PMS2-negative, (**F**) MSH6- negative.

edm group was different compared with other groups ($p < 0.05$) (Table 1). Cervical involvement was observed in 19 cases (19.5%), of which 8 cases showed only epithelial invasion and 11 cases exhibited stromal invasion.

Survival Analysis

Primary endpoints included the distribution of molecular subtypes and their association with clinicopathological features, such as histological grade, myometrial invasion, cervical invasion, lymph node status and LVSI. The secondary endpoint was the prognostic significance of each molecular subtype, as assessed by RFS rates.

All patients underwent surgery and adjuvant therapy according to FIGO 2009 guidelines.[19] The median follow-up duration was 23 months (range 3–35 months), calculated using the reverse Kaplan–Meier method. Patients who were lost to follow-up were treated as censored cases in survival analysis, as handled by the Kaplan–Meier method. Recurrence-free survival rate was used for final survival analysis. At the time of data collection, the RFS rate was 100% in the POLE edm group, 93.5% in the MMRd group, 77.8% in the p53abn group and 84.6% in the p53wt group ($p = 0.300$; Log rank test). There was no significant difference in survival between participants with cervical involvement (77.8%) and those without cervical involvement (86.5%) ($p = 0.386$) (Figure 2). Key results and endpoints are summarised in Table 2.

Discussion

In this study, we applied the ProMisE molecular classification system to a cohort of 97 Chinese patients with endometrial carcinoma and correlated the molecular subtypes with clinicopathological features and recurrence-free survival. The distribution of molecular subtypes in our cohort showed a lower frequency of POLE-mutated tumors (3.1%) and a higher proportion of p53-abnormal cases (50.5%) compared to previously published Western cohorts, suggesting potential ethnic or regional differences in the molecular landscape of EC. While most conventional histopathological parameters did not differ significantly across subtypes, cervical epithelial invasion was significantly more frequent in the POLE-mutated group. Recurrence-free survival varied among subtypes, with POLE-mutated cases having the most favorable outcome and p53-abnormal cases the poorest, although these differences did not reach statistical significance, likely attributable to the limited sample size and short follow-up period. Our findings highlight the feasibility of implementing ProMisE classification in a Chinese clinical setting and underscore the need for larger, multicenter studies to further validate its prognostic utility across diverse populations.

The molecular subtype distribution observed in our cohort deviates from patterns reported in Western populations, where POLEmut tumors are typically associated with high-grade endometrioid histology and p53abn cases predominantly with non-endometrioid subtypes.[20] Notably, the high frequency of p53abn cases in our series despite the

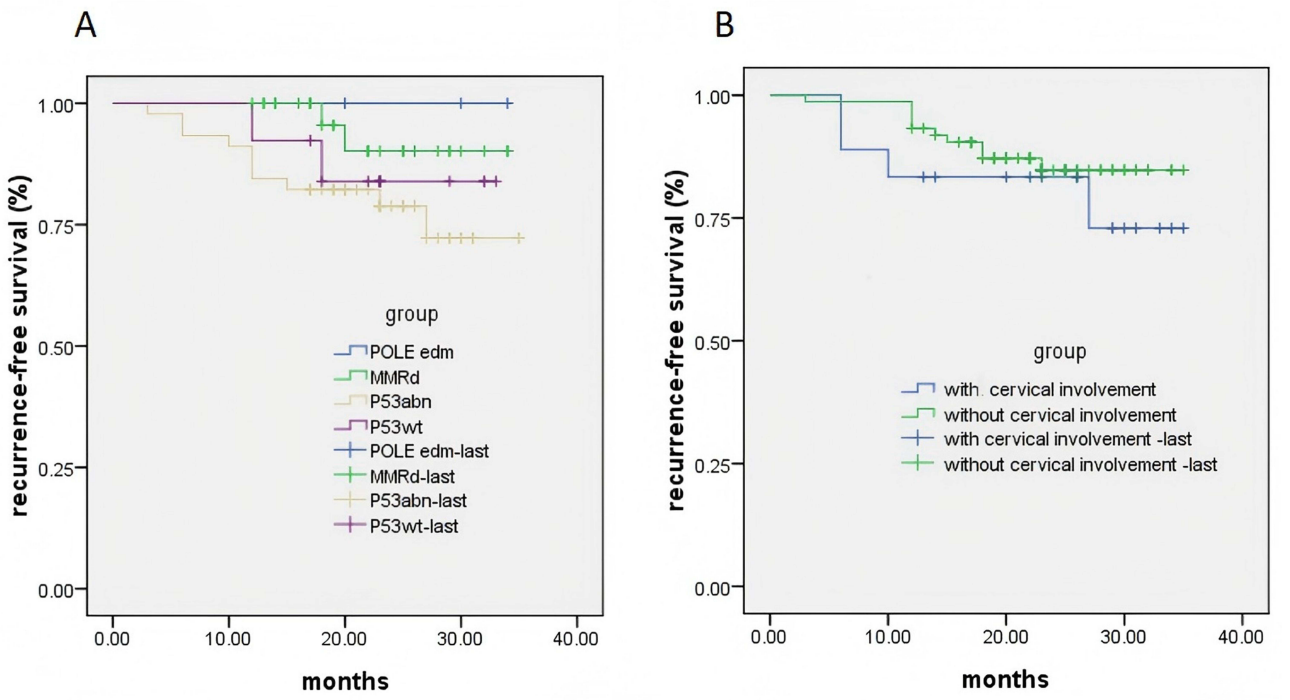

Figure 2 Kaplan–Meier survival analysis of endometrial carcinoma (EC). (**A**) Recurrence-free survival (RFS) by molecular subtype (p = 0.300, Log rank test). (**B**) RFS by cervical involvement (p = 0.386, Log rank test).

predominance of low-grade endometrioid histology suggests potential ethnic or regional variations in endometrial carcinogenesis. However, with only 7 non-endometrioid cases, our ability to fully capture classic p53abn-associated patterns typically seen in serous and clear cell carcinomas was limited. The underrepresentation of non-endometrioid histologies precludes definitive conclusions regarding p53abn patterns across the full EC spectrum and warrants validation in larger, more histologically diverse cohorts. All POLE mutations identified were pathogenic, which may partly account for the higher rate of cervical epithelial invasion observed in this small subset. However, given that the POLEmut group comprised only 3 patients, any comparisons involving this subgroup must be interpreted with extreme caution. The overall POLE mutation rate in our cohort was 3.1%, lower than the approximately 6% reported in Western series.[21] This discrepancy may reflect technical limitations of Sanger sequencing, which has a mutant allele detection threshold of approximately 15% and may undercall mutations in samples with low tumor cellularity or subclonal

Table 2 Summary of Key Results and Endpoints

Outcome/Endpoint	POLE edm	MMRd	P53abn	P53wt	*P* value
	n=3	n=32	n=49	n=13	
Primary Endpoints					
Distribution of Subtypes (%)	3.1%	33.0%	50.5%	13.4%	
Cervical Epithelial Invasion (%)	66.7%	3.1%	8.2%	7.7%	0.022
Secondary Endpoint					
RFS Rate (%)	100%	93.5%	77.8%	84.6%	0.300
Median follow-up duration (months)	23	23	23	23	
Other Findings					
Myometrial Invasion >50% (%)	33.3%	18.8%	22.4%	23.1%	0.828
Lymph node positive (%)	0%	9.4%	6.1%	15.4%	0.294
LSVI (%)	0%	12.5%	6.1%	30.8%	0.093

Note: Values are presented as percentages or as indicated.
Abbreviations: RFS, Recurrence-Free Survival; LVSI, Lymphovascular Space Invasion.

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patterns. Targeted next-generation sequencing, with greater sensitivity for low-frequency variants, might identify additional POLEmut cases and yield a higher mutation rate. Nevertheless, the absence of lymphovascular space invasion in all three POLEmut cases may indicate a lower risk of recurrence in this small subset, although this observation requires validation in larger cohorts. Given the retrospective use of archival FFPE samples, Sanger sequencing was the most feasible method available, and future studies employing more sensitive technologies are needed to determine whether the true POLE mutation frequency in Chinese endometrial cancer patients differs from our observations.

Emerging evidence from Chinese and Indian populations has challenged the favorable prognosis traditionally attributed to POLEmut EC, with some studies reporting poorer outcomes, particularly in patients receiving chemoradiation or those exhibiting microcystic, elongated, and fragmented (MELF) invasion patterns.[22–24] In our cohort, the POLEmut group exhibited a high rate of cervical epithelial invasion yet demonstrated 100% RFS, a seemingly paradoxical finding. Several mechanisms may explain this observation: the ultramutated phenotype of POLEmut tumors elicits robust antitumor immune responses that may control micrometastatic disease despite local invasion;[25] the absence of lymphovascular space invasion in all three POLEmut cases suggests limited systemic dissemination potential; and the complex interplay between molecular subtype and invasion patterns, where MELF invasion may paradoxically increase recurrence risk in POLEmut tumors,[20,26,27] highlights the need for integrated histopathological and molecular assessment. These findings raise the possibility that the prognostic implications of POLE mutations may be modified by genetic background or other population-specific factors, warranting further investigation.

The distinct biological behavior across molecular subtypes can be attributed to underlying genomic characteristics. POLEmut tumors harbor an ultramutated phenotype with high neoantigen load, typically eliciting robust antitumor immune responses that confer excellent prognosis. MMRd tumors also exhibit high mutation burden and immunogenicity, though to a lesser degree. Conversely, p53abn tumors are characterized by genomic instability and apoptosis resistance, underpinning their aggressive clinical course, while p53wt tumors generally maintain genomic stability. The preferential cervical epithelial involvement in POLEmut cases may reflect biologically aggressive local growth patterns driven by extreme mutational burden, though this observation requires validation. Elucidating these mechanistic differences is essential for refining prognostic stratification and therapeutic targeting in EC.

Since the 2019 International Society of Gynecological Pathologists (ISGyP) recommendations, molecular classification has been integrated into the FIGO 2023 and ESGO/ESTRO/ESP 2021 guidelines.[28] However, the relationship between molecular subtypes and conventional histomorphological parameters remains incompletely understood.[29]

Notably, cervical epithelial invasion differed significantly across subtypes, with the highest frequency in POLEmut cases. While this finding requires validation in larger cohorts, it raises the possibility that specific molecular alterations may influence patterns of local tumor spread. According to FIGO 2009 staging, cervical stromal invasion defines stage II disease, whereas epithelial involvement alone remains stage I.[30] Our observation that cervical involvement—whether epithelial or stromal—did not significantly impact RFS aligns with prior studies questioning the prognostic relevance of cervical invasion.[31,32] These results lend support to ongoing debates regarding whether cervical involvement should continue to inform stage II designation.

The short follow-up period and limited sample size in this study preclude definitive prognostic conclusions. Although RFS differences across molecular subtypes did not reach statistical significance, the observed trends—favorable outcomes in POLEmut and MMRd cases and poorer outcomes in p53abn cases—are consistent with established biological principles. Recurrence-free survival was selected as the primary endpoint given the short follow-up, during which recurrences are more likely captured than deaths, and to align with published ProMisE validation studies[33–35] and recent large-scale trials.[3,6] Importantly, the prognostic performance of the ProMisE classifier has been extensively validated in Western populations, but its applicability in non-Western cohorts, including Chinese patients, remains underexplored.[33,34] A recent study by Dahiya et al[35] even reported worse outcomes for POLEmut cases in an Indian cohort, contrasting with the favorable prognosis typically described, suggesting that ethnic or environmental factors may modulate the prognostic impact of molecular subtypes. This underscores the necessity of population-specific validation before widespread clinical implementation.

The predominance of p53abn cases and paucity of POLEmut tumors in our cohort suggests an overrepresentation of aggressive disease biology, warranting cautious interpretation and validation in larger, more diverse populations. Despite

these imbalances, this study provides preliminary real-world evidence for ProMisE implementation in a Chinese clinical setting, contributing valuable reference data for individualized management.

Our findings align with established literature demonstrating the prognostic value of ProMisE classification.[36,37] However, unlike previous studies that reported significant RFS differences across subtypes, we observed only non-significant trends, likely attributable to limited sample size and short follow-up. Notably, we identified a higher rate of cervical epithelial invasion in POLEmut cases, a finding not previously emphasized, which merits further investigation.

The integration of immunohistochemical classifiers, such as the ICEC system, offers a complementary approach to molecular profiling.[38,39] While ICEC provides a cost-effective alternative by assessing MMR proteins, combining it with ProMisE may enhance prognostic accuracy, particularly in resource-constrained settings. However, the present study did not perform a direct cross-tabulation between ProMisE and ICEC classifications, as the ICEC system has not yet been routinely implemented in our institutional practice and was beyond the scope of this study, which focused primarily on validating the ProMisE classifier in a Chinese cohort. Therefore, the optimal strategy for integrating multiple classification systems, including the concordance and complementary value of ProMisE and ICEC, requires prospective evaluation in future studies.

This study has several limitations, including its retrospective design, modest sample size, short follow-up, and single-institution setting, which may limit generalizability and statistical power. Additionally, the use of Sanger sequencing for POLE mutation detection may have underestimated the true mutation rate due to its limited sensitivity for low-abundance variants, particularly in samples with low tumor cellularity or subclonal mutations. Importantly, data on potential confounders such as metabolic comorbidities, prior tamoxifen exposure, and fertility-sparing management were not systematically collected, precluding adjustment for these factors in survival analyses. Additionally, the heterogeneity in lymph node assessment methods (lymphadenectomy vs. sentinel node biopsy vs. none) and adjuvant therapy regimens may have influenced RFS outcomes across subgroups. The low POLE mutation rate also precludes robust subgroup analysis. These constraints underscore the need for larger, multicenter prospective studies with extended follow-up to validate our observations and refine prognostic algorithms.

Future research should prioritize several key directions. First, prospective validation of the ProMisE classifier in larger, more diverse populations is essential to confirm its prognostic utility across different ethnic and geographic groups. Second, efforts should focus on integrating molecular classification with immunohistochemical classifiers to develop more comprehensive and accessible prognostic tools. Third, investigating the underlying biological mechanisms driving subtype-specific tumor behaviors may reveal novel therapeutic targets. Fourth, cost-effectiveness analyses are needed to guide the practical implementation of molecular classification in routine clinical settings. Fifth, exploration of emerging biomarkers and advanced genomic technologies could further refine risk stratification and personalize treatment strategies. Ultimately, combining molecular classification with traditional clinicopathological parameters may optimize therapeutic decision-making, although the prognostic relevance of cervical invasion called into question by our findings warrants re-evaluation in future staging systems.

Conclusion

In summary, our study provides novel insights into the molecular classification of endometrial carcinoma in a Chinese cohort. The distribution of ProMisE molecular subtypes in this population differs from that reported in Western cohorts, suggesting potential ethnic variation in the molecular and prognostic landscape of EC. These findings highlight the importance of incorporating molecular data into risk stratification and individualized management. However, given that the POLEmut group comprised only 3 patients, any comparisons involving this subgroup must be interpreted with extreme caution. Additionally, the absence of lymphovascular space invasion in all three POLEmut cases may indicate a lower risk of recurrence in this small subset, although this observation requires validation in larger cohorts. In particular, the observed differences in cervical mucosal invasion among molecular subtypes highlight potential biological diversity that warrants further clinical investigation. Moreover, the ProMisE classifier should be regarded as a complementary tool to assist, rather than replace, conventional clinicopathological assessment in clinical decision-making.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Fujian Maternity and Child Health Hospital (NO. 2018038). Written informed consent was obtained from the participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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