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ORIGINAL RESEARCH

Analysis of the Clinicopathological Characteristics of Different Molecular Subtypes in Endometrial Cancer: A Retrospective Single Center Study

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Background: There is significant heterogeneity in the proportion of molecular subtypes of endometrial cancer and its relationship with clinicopathological characteristics among different races and regions. It aims to analyze the differences in the clinicopathological characteristics of different molecular subtypes of endometrial cancer in Eastern Guangdong Province, China.

Methods: Five hundred and sixty-three endometrial cancer patients in Meizhou People's Hospital from January 2018 to August 2024 were collected. The relationship of molecular subtypes (DNA polymerase epsilon (POLE) mutant, mismatch repair deficiency (dMMR), p53 abnormal, and non-specific molecular profile (NSMP)) and clinicopathological characteristics (age, reproductive history, menopausal status, and pathological data covered histological type, tumor differentiation, muscular infiltration, lymphovascular invasion, perineural invasion) were analyzed.

Results: The molecular subtypes dMMR, p53 abnormal, POLE mutant, and NSMP were detected in 197 (35.0%), 155 (27.5%), 52 (9.2%), and 159 (28.2%) patients, respectively. There were statistically significant differences in distributions of histological types ($p = 0.012$, $\chi^2 = 14.073$), tumor differentiation ($p < 0.001$, $\chi^2 = 16.457$), and disease stage ($p = 0.019$, $\chi^2 = 9.796$) in NSMP and non-NSMP cases. The proportion of POLE mutant in endometrioid carcinoma was higher than those of other histological types, while the proportion of p53 abnormal was relatively high in high-grade and highly invasive histological types. The proportion of p53 abnormal subtype was relatively high among patients with mixed carcinoma. In addition, the proportions of poor tumor differentiation in the dMMR and p53 abnormal groups were higher than that in the NSMP group.

Conclusion: The distribution of molecular subtypes among patients with different histopathological types shows significant differences. The proportion of POLE mutant type in endometrioid carcinoma is higher than that of other histological types, while the proportion of p53 abnormal type is relatively high in high-grade and highly invasive histological types such as serous carcinoma and clear cell carcinoma. It provides valuable reference for guiding the diagnosis and treatment of endometrial cancer by integrating molecular subtypes with clinicopathological characteristics.

Keywords: endometrial cancer, molecular subtype, clinicopathological characteristics, POLE, NSMP

Introduction

Endometrial cancer is a malignant tumor that originates from the epithelial cells of the endometrium.[1] It mainly includes various pathological types such as endometrioid adenocarcinoma, serous carcinoma, and clear cell carcinoma, among which endometrioid adenocarcinoma is the most common.[2] In the early stage of endometrial cancer, it is often manifested as abnormal uterine bleeding, vaginal discharge and other symptoms.[3] If not diagnosed and treated in time, cancer cells can spread to the myometrium, pelvic lymph nodes, and distant organs, seriously threatening the life and health of patients.[4] In recent years, the prevalence of endometrial cancer worldwide has shown a continuous upward trend.[5,6] According to the latest global cancer statistics, endometrial cancer ranks sixth among new cancer cases in women.[7]

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In terms of the pathogenesis of endometrial cancer, the occurrence of estrogen-dependent endometrial cancer is closely related to long-term and continuous estrogen stimulation.[8,9] Under normal circumstances, the endometrium shows periodic proliferation, secretion, and shedding under the synergistic effect of estrogen and progesterone.[10] When the level of estrogen is too high and there is a lack of progesterone antagonism, the endometrium will remain in a state of excessive proliferation continuously, and atypical hyperplasia may occur, which may eventually develop into cancer.[11,12] Estrogen-independent endometrial cancer mainly includes pathological types such as high-grade serous carcinoma and clear cell carcinoma.[13,14] The cancer cells of this type of endometrial cancer have a poor degree of differentiation, and the cell morphology and tissue structure show a high degree of atypia. Estrogen-independent endometrial cancer is mainly related to mutations in the *TP53* gene, overexpression of the human epidermal growth factor 2 (HER2), and changes in DNA methylation patterns.[15–18]

The traditional classification method based on histological features has certain limitations in guiding the clinical treatment and predicting prognosis of endometrial cancer.[19] With the rapid development of molecular biology techniques, the molecular typing of endometrial cancer has gradually become a research hotspot.[20,21] The endometrial cancer molecular typing was incorporated into the guidelines of the National Comprehensive Cancer Network (NCCN)[22] and the World Health Organization (WHO).[23] In 2021, the risk assessment rules based on molecular typing were incorporated into the guidelines of the European Society of Gynaecological Oncology (ESGO).[24] According to the WHO classification, endometrial cancer is classified into four types: DNA polymerase epsilon (POLE) mutant, mismatch repair deficiency (dMMR), p53 abnormal, and non-specific molecular profile (NSMP) types.[20,25] Some studies suggested that the choice of treatment strategies for endometrial cancer should be based on a comprehensive consideration that includes the molecular subtypes of endometrial cancer.[20,26] Molecular typing can facilitate individualized treatment management for endometrial cancer and improve patient prognosis.[27,28]

The molecular classification of endometrial cancer is closely related to the clinicopathological characteristics (including age, histological type, degree of differentiation, degree of myometrial invasion, and clinical stage), but there are also some inconsistent research results.[29–31] The relationship between them requires more researches to reveal. At present, the application of molecular typing in the clinical diagnosis and treatment of endometrial cancer still faces many problems that need to be solved urgently.[32–34] Furthermore, due to the cognitive differences among the diagnostic physicians, the assessment of the molecular classification of endometrial cancer based on the Cancer Genome Atlas (TCGA) sub-classes may lead to non-standardized and inconsistent results.[35] Compared with the randomized Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial data, the characteristics of molecular subtypes of endometrial cancer in different regions and among different populations may vary.[36] The characteristics of molecular subtypes of endometrial cancer vary among different regions and populations.[37,38] This study aims to analyze the differences in the clinicopathological characteristics of different molecular subtypes of endometrial cancer in this region (Eastern Guangdong Province, China) and provide a reference for individualized diagnosis and treatment of patients with endometrial cancer.

Materials and Methods

Participants

This study adopted a retrospective cohort study design. Patients diagnosed with endometrial cancer in Meizhou People's Hospital from January 2018 to August 2024 were selected as the research subjects. Inclusion criteria: (1) confirmed as endometrial cancer by histopathological diagnosis; (2) have complete clinicopathological data; (3) there are molecular typing results; and (4) no neoadjuvant chemotherapy, radiotherapy or endocrine therapy was received before the operation. Exclusion criteria: (1) combined with other primary malignant tumors; (2) lack of clinicopathological data; (3) insufficient tumor tissue samples cannot be obtained for molecular typing detection; and (4) endometrial cancer with multiple molecular subtypes. Ultimately, 563 patients with endometrial cancer were included.

Data Collection

The clinicopathological data of patients were collected in detail through the hospital's electronic medical record system. Clinical data include the patient's age, reproductive history, menopausal status, and pathological data covered histological type (such as endometrioid carcinoma, serous carcinoma, clear cell carcinoma, squamous cell carcinoma, and mixed

carcinoma), tumor differentiation, muscular infiltration, lymphovascular invasion, perineural invasion, and molecular subtypes, and disease stage. All pathological diagnosis results were independently reviewed by two senior pathologists.

The diagnostic criteria for tumor differentiation in endometrial cancer are centered on the histopathological morphology. Mainly based on the WHO Classification of Tumors of the Female Reproductive Organs, the degree of differentiation is classified into high differentiation, moderate differentiation, and low differentiation according to the similarity of tumor cells to the normal endometrial glandular epithelium.

Immunohistochemical Detection of Mismatch Repair (MMR) Proteins and p53

MMR proteins include mismatch repair protein 1 (MutL homolog 1, MLH1), mismatch repair protein 2 (MutS homolog 2, MSH2), mismatch repair protein 6 (MutS homolog 6, MSH6), and postmeiotic segregation increased 2 (PMS2). The staining of MLH1, MSH2, MSH6, PMS2, and p53 were all located in the nucleus. If brownish staining appears in the nuclei of all four MMR proteins, it is determined that MMR expression is complete (MMR-perfect, pMMR). If one or more MMR proteins do not show nuclear staining, it is determined that MMR is defective (MMR-defective, dMMR). p53 is positively expressed when brownish granules appear in the cell nucleus. If p53 shows diffuse positive (positive rate $\geq$ 70%) or complete negative (positive rate < 10%), it is determined as p53 abnormal.

Detection of Pathogenic Mutations in the Exonuclease Domain of the POLE Gene

Tissue samples preserved in formalin and embedded in paraffin (FFPE) were sectioned into 5μm-thick slices. Ten of these slices were then placed into EP tubes to facilitate DNA extraction. DNA was extracted using Qiagen QLAamp DNA FFPE Tissue KIT. A Nanodrop 2000 (Thermo Scientific) served to measure DNA concentration. DNA samples were to be diluted to 2 ng/μL, and the corresponding OD260/OD280 ratio needed to fall within 1.8–2.0. The *POLE* gene mutation detection was carried out amplification refractory mutation system polymerase chain reaction (ARMS-PCR) technology. Select the commercial detection kit (Hangzhou Detong Biotechnology Co., Ltd.) targeting the hotspot mutation regions of the *POLE* gene (high-frequency mutation sites in exons 3–14) for detection. Follow the instructions to add samples and use the real-time fluorescence quantitative PCR instrument (Roche LightCycler 480) for detection. Positive control, negative control, and blank control were set to control the detection process. Recorded the threshold cycle number (Ct value) of all samples and determine the positivity or negativity of the mutation according to the kit instructions.

Statistical Analysis

The data were analyzed using the SPSS 26.0 and GraphPad Prism softwares. The patients' clinicopathological features were summarized with descriptive statistics. χ^2 test and Fisher's exact test were used to explore the correlation between molecular subtypes and clinicopathological characteristics. $p < 0.05$.

Results

Clinicopathological Features of Patients with Endometrial Cancer

Among 563 patients with endometrial cancer included in this study, 223 (39.6%) patients were aged <55 years old and 340 (60.4%) with aged ≥55 years old. There were 547 (97.2%), and 385 (68.4%) patients with reproductive history, and menopause, respectively. In terms of the types of tumor histopathology, 483 cases were patients with endometrioid carcinoma, accounting for 85.8%, followed by serous carcinoma (n = 33, 5.9%), clear cell carcinoma (n = 11, 2.0%), and squamous cell carcinoma (n = 2, 0.4%). There were 12 (2.1%) patients with mixed carcinoma. There were 118 (21.0%), 313 (55.6%), and 79 (14.0%) patients with well-differentiated, moderately differentiated, and poorly differentiated tumors, respectively. There were 84 (14.9%), 312 (55.4%), and 92 (16.3%) patients with tumor cells infiltrating the endometrium only, muscular layer infiltration <1/2, and muscular layer infiltration ≥1/2, respectively. Lymphovascular invasion and perineural invasion were identified in 74 cases (13.1%) and 3 cases (0.5%), respectively. For disease staging, stage I, II, III, and IV were observed in 417 (74.1%), 27 (4.8%), 69 (12.3%), and 20 (3.6%) patients, respectively. The molecular subtypes dMMR, p53 abnormal, POLE mutant, and NSMP were detected in 197 (35.0%), 155 (27.5%), 52 (9.2%), and 159 (28.2%) patients, respectively (Table 1).

Table 1 The Clinicopathological Features of Patients with Endometrial Cancer

Clinicopathological Features	Total (n = 563)
Age (years)	
<55, n (%)	223(39.6%)
≥55, n (%)	340(60.4%)
Reproductive history	
No, n (%)	16(2.8%)
Yes, n (%)	547(97.2%)
Menopause	
No, n (%)	174(30.9%)
Yes, n (%)	385(68.4%)
Unknown, n (%)	4(0.7%)
Histological type	
Endometrioid carcinoma, n (%)	483(85.8%)
Serous carcinoma, n (%)	33(5.9%)
Clear cell carcinoma, n (%)	11(2.0%)
Squamous cell carcinoma, n (%)	2(0.4%)
Mixed carcinoma, n (%)	12(2.1%)
Others, n (%)	7(1.2%)
Unknown, n (%)	15(2.7%)
Tumor differentiation	
Well, n (%)	118(21.0%)
Moderate, n (%)	313(55.6%)
Poor, n (%)	79(14.0%)
Unknown, n (%)	53(9.4%)
Muscular infiltration	
Endometrium, n (%)	84(14.9%)
<1/2 muscular layer, n (%)	312(55.4%)
≥1/2 muscular layer, n (%)	92(16.3%)
Unknown, n (%)	75(13.3%)
Lymphovascular invasion	
Absent, n (%)	405(71.9%)
Present, n (%)	74(13.1%)
Unknown, n (%)	84(14.9%)
Perineural invasion	
Absent, n (%)	469(83.3%)
Present, n (%)	3(0.5%)
Unknown, n (%)	91(16.2%)
Disease stage	
I, n (%)	417(74.1%)
II, n (%)	27(4.8%)
III, n (%)	69(12.3%)
IV, n (%)	20(3.6%)
Unknown, n (%)	30(5.3%)
Molecular subtypes	
dMMR	197(35.0%)
p53 abnormal	155(27.5%)
POLE mutant	52(9.2%)
NSMP	159(28.2%)

Comparison of Clinicopathological Features of NSMP and Non-NSMP Endometrial Cancer

In this study, 159 (28.2%) patients with NSMP molecular subtype and 404 (71.8%) with non-NSMP. There was statistically significant difference in distributions of histological type (p = 0.012, χ^2= 14.073), tumor differentiation

Table 2 Comparison of Clinicopathological Features of NSMP and Non-NSMP Endometrial Cancer

Clinicopathological Features	NSMP (n = 159)	Non-NSMP (n = 404)	*P* Values
Age (years)			
<55, n (%)	65(40.9%)	158(39.1%)	0.703 (χ^2= 0.150)
≥55, n (%)	94(59.1%)	246(60.9%)	
Reproductive history			
No, n (%)	8(5.0%)	8(2.0%)	0.085 (χ^2= 3.847)
Yes, n (%)	151(95.0%)	396(98.0%)	
Menopause			
No, n (%)	55(34.6%)	119(29.5%)	0.267 (χ^2= 1.244)
Yes, n (%)	104(65.4%)	281(69.6%)	
Histological type			
Endometrioid carcinoma, n (%)	151(95.0%)	332(82.3%)	0.012 (χ^2= 14.073)
Serous carcinoma, n (%)	1(0.6%)	32(7.9%)	
Clear cell carcinoma, n (%)	3(1.9%)	8(2.0%)	
Squamous cell carcinoma, n (%)	1(0.6%)	1(0.2%)	
Mixed carcinoma, n (%)	2(1.3%)	10(2.5%)	
Others, n (%)	1(0.6%)	6(1.5%)	
Tumor differentiation			
Well, n (%)	43(27.0%)	75(18.6%)	<0.001 (χ^2= 16.457)
Moderate, n (%)	103(64.8%)	210(52.0%)	
Poor, n (%)	9(5.7%)	70(17.3%)	
Muscular infiltration			
Endometrium, n (%)	25(15.7%)	59(14.6%)	0.969 (χ^2= 0.072)
<1/2 muscular layer, n (%)	97(61.0%)	215(53.2%)	
≥1/2 muscular layer, n (%)	29(18.2%)	63(15.6%)	
Lymphovascular invasion			
Absent, n (%)	125(78.6%)	280(69.3%)	0.583 (χ^2= 0.436)
Present, n (%)	20(12.6%)	54(13.4%)	
Perineural invasion			
Absent, n (%)	143(89.9%)	326(80.7%)	0.557 (χ^2= 1.312)
Present, n (%)	0(0)	3(0.7%)	
Disease stage			
I, n (%)	138(86.8%)	279(69.1%)	0.019 (χ^2= 9.796)
II, n (%)	5(3.1%)	22(5.4%)	
III, n (%)	12(7.5%)	57(14.1%)	
IV, n (%)	4(2.5%)	16(4.0%)	

Abbreviations: dMMR, mismatch repair-deficient; POLE, DNA polymerase epsilon; NSMP, no specific molecular profile.

($p < 0.001$, χ^2= 16.457), and disease stage ($p = 0.019$, χ^2= 9.796) in NSMP and non-NSMP cases. There was no statistically significant difference in distributions of age ($p = 0.703$), reproductive history ($p = 0.085$), menopause ($p = 0.267$), muscular infiltration ($p = 0.969$), lymphovascular invasion ($p = 0.583$), and perineural invasion ($p = 0.557$) in NSMP and non-NSMP groups (Table 2).

The Proportion of Various Molecular Subtypes of Different Histopathological Types

There were 483 (85.8%), 33 (5.9%), 11 (2.0%), 2 (0.4%), and 12 (2.1%) cases were endometrioid carcinoma, serous carcinoma, clear cell carcinoma, squamous cell carcinoma, and mixed carcinoma. In endometrioid carcinoma, the dMMR molecular subtype has the highest proportion (37.3%), followed by NSMP (31.3%), p53 abnormal (22.2%), and POLE mutant (9.3%). In serous carcinoma, The proportion of p53 abnormal molecular subtype accounts for the vast majority (84.8%), followed by dMMR (6.1%), POLE mutant (6.1%), and NSMP mutant (3.0%). In clear cell

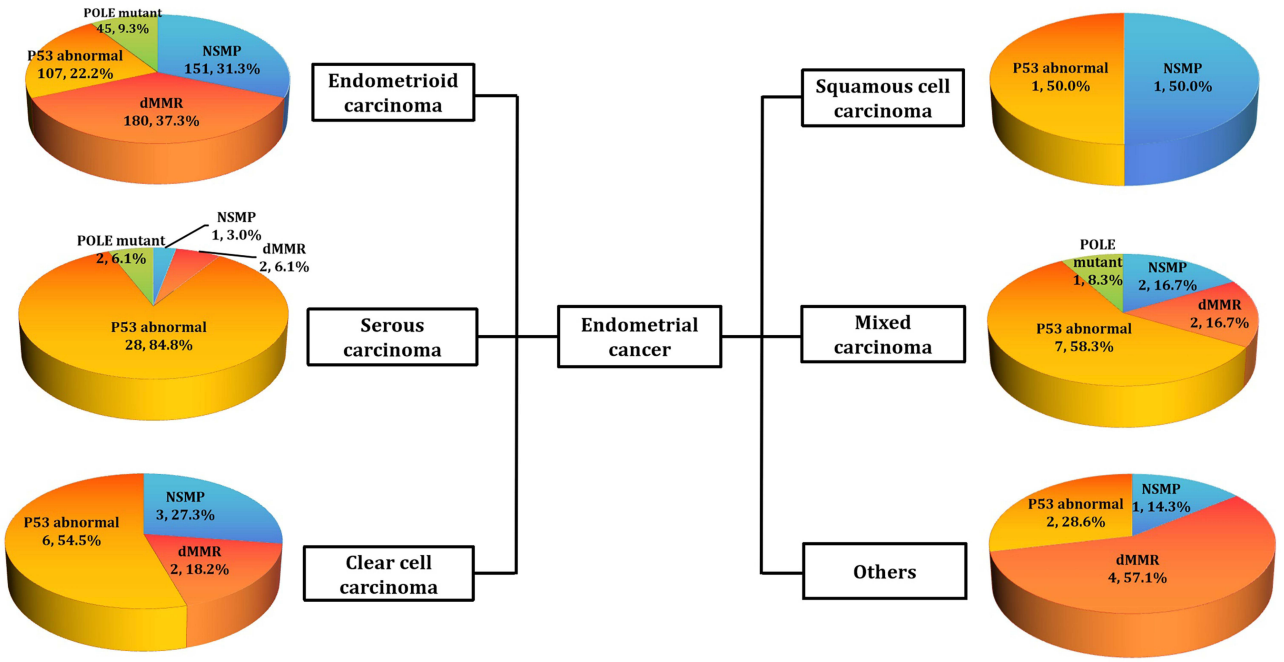

Figure 1 The proportion of molecular typing of different pathological types of endometrial cancer.
Abbreviations: POLE, DNA polymerase epsilon; dMMR, mismatch repair deficiency; NSMP, non-specific molecular profile.

carcinoma, the p53 abnormal molecular subtype has the highest proportion (54.5%), followed by NSMP (27.3%) and dMMR (18.2%). In mixed carcinoma, the p53 abnormal molecular subtype has the highest proportion (58.3%), followed by NSMP (16.7%), dMMR (16.7%), and POLE mutant (8.3%) (Figure 1). The distribution of molecular subtypes among patients with different histopathological types shows significant differences. Specifically, the proportion of POLE mutant type in endometrioid carcinoma is higher than that of other histological types, while the proportion of p53 abnormal type is relatively high in high-grade and highly invasive histological types such as serous carcinoma and clear cell carcinoma. The proportion of p53 abnormal subtype is also relatively high among patients with mixed carcinoma.

This study compared the various research results regarding the relationship between the molecular subtypes and histological types of endometrial cancer (Table 3). Most studies suggested that proportion of p53 abnormal was most in patients with serous carcinoma.[39–42] A study from the United States of America suggested that the proportion of POLE mutant type in endometrioid carcinoma is higher than that of other histological types.[39] The result of this study is consistent with it. A study conducted on a Finnish population indicated that the proportion of p53 abnormal among patients with endometrioid carcinoma was the highest.[43] It indicated that the proportion of molecular subtypes of endometrial cancer and their relationship with histological types vary among different studies.

Comparison of Clinicopathological Features Between Patients of Different Molecular Subtypes and Patients with NSMP, Respectively

There was statistically significant difference in distributions of tumor differentiation in dMMR vs NSMP ($p = 0.004$, $\chi^2 = 10.885$), and p53 abnormal vs NSMP ($p < 0.001$, $\chi^2 = 23.005$), respectively. Specifically, the proportions of poor tumor differentiation in the dMMR and p53 abnormal groups were higher than that in the NSMP group. In addition, the proportion of endometrioid carcinoma in the p53 abnormal group was lower than that in the NSMP group (69.0% vs 95.0%) ($p < 0.001$, $\chi^2 = 32.242$) (Table 4).

Table 3 Comparison of the Results of Different Studies on the Relationship Between Molecular Subtypes and Histological Types of Endometrial Cancer

Studies	Endometrioid Carcinoma	Serous Carcinoma	Clear Cell Carcinoma	Squamous Cell Carcinoma	Mixed Carcinoma	Others	References
Present study	Higher POLE mutant proportion vs other types	Proportion of p53 abnormal most	Proportion of p53 abnormal is second most				
Americans	Higher POLE mutant proportion vs other types	Proportion of p53 abnormal most	Proportion of p53 abnormal is second most				PMID: 37245486
A population from Zhejiang, China		Proportion of p53 abnormal most			Proportion of p53 abnormal most		PMID: 40302811
A population from Finland	Proportion of p53 abnormal most						PMID: 38303106
A population from Japan		Proportion of p53 abnormal most					PMID: 35002543
A study based on the data from Cancer Genome Atlas (TCGA)		Proportion of p53 abnormal is higher vs endometrioid carcinoma					PMID: 26556035

Abbreviation: POLE, DNA polymerase epsilon.

Discussion

In recent years, molecular typing of endometrial cancer has gradually been applied in clinical practice, providing a reference for the selection of diagnosis and treatment plans for patients.[44–46] However, the differences in pathological characteristics among different molecular subtypes of endometrial cancer still require more studies to confirm. This study analyzed the relationship of molecular subtypes and clinicopathological characteristics of 563 patients with endometrial cancer, and found that different molecular subtypes showed significant differences in histological type, and degree of tumor differentiation. These results were not only consistent with the conclusions of some studies,[30,47,48] but also further revealed that this relationship varies among different races and regions.

In this study, dMMR, p53 abnormal, POLE mutant, and NSMP molecular subtype accounted for 35.0%, 27.5%, 9.2%, and 28.2%, respectively. There is significant heterogeneity in the proportion of molecular typing of endometrial cancer among different races and regions.[49] The vast majority of studies suggested that the most common subtype of endometrial cancer is NSMP, followed by dMMR and p53 abnormal, with the fewest patients having POLE mutant.[29,50–56] However, other studies suggested that p53 abnormal is in the majority, followed by dMMR, NSMP, and POLE mutant.[57,58] In addition, other studies have shown that NSMP accounts for 70–80%, followed by dMMR and POLE mutant, and p53 abnormal is the least.[59] Compared with previous studies, in this study, except for the POLE mutant, which accounted for the lowest proportion (9.2%), there was no significant difference in the proportions of dMMR, p53 abnormal, and NSMP molecular subtypes, which could be said to be approximately 30% each. The differences existing among different studies may be related to the differences in different races and regions and the different numbers of research cases included in different studies.

In present study, the proportion of POLE mutant type in endometrioid carcinoma is higher than that of other histological types. The *POLE* gene, as a key proofreading enzyme encoding gene in the DNA replication process, the extremely high mutation burden caused by its mutation endows endometrioid carcinoma with unique biological

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Table 4 Comparison of Clinicopathological Features Between Patients of Different Molecular Subtypes and Patients with NSMP, Respectively

Clinicopathological Features	NSMP (n = 159)	dMMR		p53 Abnormal		POLE Mutant	
		dMMR (n = 197)	*p* values (dMMR vs NSMP)	p53 Abnormal (n = 155)	*p* values (p53 Abnormal vs NSMP)	POLE Mutant (n = 52)	*p* values (POLE Mutant vs NSMP)
Age (years)							
<55, n (%)	65(40.9%)	76(38.6%)	0.665 (χ^2= 0.195)	62(40.0%)	0.909 (χ^2= 0.025)	20(38.5%)	0.871 (χ^2= 0.095)
≥55, n (%)	94(59.1%)	121(61.4%)		93(60.0%)		32(61.5%)	
Reproductive history							
No, n (%)	8(5.0%)	5(2.5%)	0.261 (χ^2= 1.555)	2(1.3%)	0.104 (χ^2= 3.563)	1(1.9%)	0.458 (χ^2= 0.927)
Yes, n (%)	151(95.0%)	192(97.5%)		153(98.7%)		51(98.1%)	
Menopause							
No, n (%)	55(34.6%)	63(32.0%)	0.651 (χ^2= 0.237)	43(27.7%)	0.225 (χ^2= 1.523)	13(25.0%)	0.236 (χ^2= 1.461)
Yes, n (%)	104(65.4%)	133(67.5%)		110(71.0%)		38(73.1%)	
Histological type							
Endometrioid carcinoma, n (%)	151(95.0%)	180(91.4%)	1.000 (χ^2= 0.010)	107(69.0%)	<0.001 (χ^2= 32.242)	45(86.5%)	1.000 (χ^2= 0.109)
Non-endometrioid carcinoma, n (%)	8(5.0%)	10(5.1%)		44(28.4%)		3(5.8%)	
Tumor differentiation							
Well, n (%)	43(27.0%)	43(21.8%)	0.004 (χ^2= 10.885)	20(12.9%)	<0.001 (χ^2= 23.005)	12(23.1%)	0.268 (χ^2= 2.872)
Moderate, n (%)	103(64.8%)	107(54.3%)		76(49.0%)		27(51.9%)	
Poor, n (%)	9(5.7%)	32(16.2%)		32(20.6%)		6(11.5%)	
Muscular infiltration							
Endometrium, n (%)	25(15.7%)	38(19.3%)	0.477 (χ^2= 1.530)	16(10.3%)	0.651 (χ^2= 0.887)	5(9.6%)	0.744 (χ^2= 0.627)
<1/2 muscular layer, n (%)	97(61.0%)	105(53.3%)		83(53.5%)		27(51.9%)	
≥1/2 muscular layer, n (%)	29(18.2%)	30(15.2%)		27(17.4%)		6(11.5%)	
Lymphovascular invasion							
Absent, n (%)	125(78.6%)	146(74.1%)	0.867 (χ^2= 0.101)	104(67.1%)	0.196 (χ^2= 1.896)	30(57.7%)	0.442 (χ^2= 0.613)
Present, n (%)	20(12.6%)	21(10.7%)		26(16.8%)		7(13.5%)	
Perineural invasion							
Absent, n (%)	143(89.9%)	166(84.3%)	1.000 (χ^2= 0.859)	124(80.0%)	0.466 (χ^2= 1.148)	36(69.2%)	0.206 (χ^2= 3.886)
Present, n (%)	0(0)	1(0.5%)		1(0.6%)		1(1.9%)	
Disease stage							
I-II, n (%)	143(89.9%)	158(80.2%)	0.196 (χ^2= 1.919)	100(64.5%)	<0.001 (χ^2= 13.591)	40(76.9%)	0.214 (χ^2= 1.969)
III-IV, n (%)	16(10.1%)	28(14.2%)		36(23.2%)		3(5.8%)	

Abbreviations: dMMR, mismatch repair-deficient; POLE, DNA polymerase epsilon; NSMP, no specific molecular profile.

behaviors.[60] This mutant characteristic may make POLE mutant endometrioid carcinoma more sensitive to immunotherapy and platinum-based chemotherapy by influencing the immune infiltration pattern of the tumor microenvironment,[61,62] which also explains the molecular mechanism for the relatively good prognosis of patients with this subtype.

In this study, the proportion of p53 abnormal type is relatively high in high-grade and highly invasive histological types such as serous carcinoma and clear cell carcinoma. The *TP53* gene, as an important tumor suppressor gene, its functional deficiency or abnormal activation can disrupt the cell cycle regulation and DNA damage repair mechanisms, accelerating the malignant transformation and invasion process of tumors.[63,64] Serous carcinoma and clear cell carcinoma, as high-grade endometrial cancers, are often accompanied by high-frequency mutations or abnormal protein expression of the *TP53* gene, resulting in uncontrolled proliferation of tumor cells and enhanced anti-apoptotic ability, and thereby showing stronger invasiveness and metastatic potential.[65,66] Some studies showed that most p53 abnormal endometrial cancers have poor clinical outcomes.[67,68] The p53 abnormal accounts for only 15% of all endometrial cancer cases, but it makes up 50–70% of endometrial cancer deaths.[15] This is highly consistent with the biological characteristics of this subtype.

From the perspective of histogenesis, endometrioid carcinoma may have different pathogenesis pathways from serous carcinoma and clear cell carcinoma. POLE mutant endometrioid carcinoma mostly originates from estrogen-dependent endometrial hyperplasia, and its occurrence and development are relatively slow.[69] High-grade cancers related to p53 abnormal may bypass the early proliferative stage and directly originate from the malignant transformation of endometrial stem cells or metagenic cells.[70,71] This difference further explains the distribution preferences of the two molecular subtypes in different histological types.

Furthermore, although this study did not find a relationship between the patients' age and molecular subtypes, the association between the patients' age and molecular subtypes is equally worthy of attention. Some studies suggested that patients with POLE mutant type had a relatively younger age of onset,[72] while p53 abnormal type was more common in postmenopausal women.[73,74] It might be related to the differences in hormone levels and microenvironments among women of different age groups. The estrogen level in young women is relatively high, which may induce *POLE* gene mutations through certain mechanisms. However, due to the relatively strong immune function of young patients, the tumor progression is relatively slow. After menopause, the hormone levels in women are imbalanced. Moreover, as they age, the body's ability to repair DNA damage declines, making the *TP53* gene more prone to mutations and thus leading to the occurrence of tumors.[75]

This study has some limitations. First, the research was a single-center retrospective study with a relatively limited sample size. There might be selection bias, and the universality of the research results needs to be further verified. Second, this study only explored the relationship between molecular subtypes and common clinicopathological characteristics, and did not conduct in-depth analysis on some potential influencing factors, such as the tumor microenvironment and metabolic characteristics. In addition, this study did not analyze the relationship between molecular subtypes and the prognosis of patients. In the future, multi-center and large-sample prospective studies need to be carried out, combined with multi-omics techniques, to comprehensively and deeply explore the internal mechanisms of the clinicopathological characteristics of different molecular subtypes of endometrial cancer, providing a more solid theoretical basis for the precise diagnosis and individualized treatment of endometrial cancer.

Based on the results of this study, future research on molecular typing of endometrial cancer can be advanced from multiple dimensions. First, conduct multi-center, large-sample prospective studies, including patient cohorts from different regions, ethnic groups, and clinical treatment backgrounds, to verify the universality of the clinical and pathological characteristics of each molecular subtype in this study. Second, extend the follow-up period to clarify the long-term prognosis stability of the POLE mutant type and the potential risk stratification markers in the NSMP type. Third, combine multi-omics technologies (such as genomics, transcriptomics, and proteomics) to deeply explore the core driver genes and signaling pathways of each molecular subtype, especially exploring more precise sub-classification criteria for the more heterogeneous NSMP subtype, and evaluating the response differences of different subtypes of patients to specific treatment regimens. Additionally, optimize molecular classification detection techniques, develop low-cost, rapid combined detection Panels (such as POLE hotspot mutations + MMR protein + p53 immunohistochemistry), and establish standardized detection procedures to promote their popularization and application in primary medical

institutions, ultimately achieving the transformation of molecular typing from research to routine clinical diagnosis and treatment, and providing more precise individualized treatment strategies for patients.

Conclusions

The distribution of molecular subtypes among patients with different histopathological types shows significant differences. The proportion of POLE mutant type in endometrioid carcinoma is higher than that of other histological types, while the proportion of p53 abnormal type is relatively high in high-grade and highly invasive histological types such as serous carcinoma and clear cell carcinoma. In addition, the proportions of poor tumor differentiation in the dMMR and p53 abnormal groups were higher than that in the NSMP group. It reveals the intrinsic association between the molecular classification and histological characteristics of endometrial cancer. This relationship varies among different populations. Molecular typing can reduce the subjective differences in histological assessment. The results of this study provide valuable reference data for the diagnosis and prognosis evaluation of endometrial cancer in this region.

Data Sharing Statement

The data that support the findings of this study are available from any of the corresponding authors upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals and the informed consent from all the participants was obtained. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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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.

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