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Original Article

Clinicopathological characteristics of endometrial carcinoma with different molecular subtypes and their correlation with lymph node metastasis

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Abstract: Endometrial carcinoma (EC) is one of the three major malignancies of the female reproductive organs. With intense research of tumor molecular mechanisms and development of precision medicine in recent years, the traditional pathomorphological classification fails to meet the needs of clinical diagnosis and treatment for EC. This study aims to analyze the correlation of different Proactive Molecular Risk Classifier for Endometrial Cancer molecular subtypes with lymph node metastasis (LNM) and other clinical features in EC. 120 treatment-naive EC patients with surgery were enrolled in this study. The molecular subtypes of these patients were classified as follows by Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) molecular subtyping: mismatch repair deficiency (MMRd) in 22 cases (18.33%), polymerase epsilon exonuclease domain mutation (POLE EDM) in 2 cases (1.67%), p53 wild-type (p53-wt) in 64 cases (53.33%), and p53 abnormal (p53-abn) in 32 cases (26.67%). The clinicopathological features of 120 patients were retrospectively analyzed. Statistical significance was identified among the four molecular subtypes in terms of histological classification, International Federation of Gynecology and Obstetrics (FIGO) staging, pathological grading, and LNM. Among the enrolled cases, 26 had LNM and 94 had no lymph node involvement. According to the multivariate Logistic regression analysis, p53 wt (P=0.008, OR=0.078, 95% CI: 0.012-0.510) was a protective factor for LNM in EC patients, while poorly differentiated histology (P=0.001, OR=15.137, 95% CI: 3.013-76.044) was a risk factor. ProMisE classification system, being more objective and reproducible, can provide an important reference for preoperative decision-making. The patients with p53 wt by ProMisE had a low risk of LNM in preoperative diagnostic curettage specimens, while there was a higher risk of LNM among the patients with poorly differentiated EC.

Keywords: Endometrial carcinoma, ProMisE molecular subtyping, lymph node metastasis, pathological features

Introduction

Endometrial carcinoma (EC) is one of the most common malignancies arising in the female reproductive system, with an incidence ranking behind breast cancer, lung cancer and colorectal cancer [1, 2]. In recent years, the prevalence of EC has increased and has shown an increasing trend in younger individuals, which may be related to obesity, aging population, and use of unopposed estrogens [3-5]. Bokhman JV [6] first proposed to classify EC into estrogen-dependent (type I) or non-estrogen-dependent (type II). Type I EC accounts for 80%-90% of cases, also known as endometrioid adenocarcinoma, which is related to well- and moderately-differentiated tumors with a good prognosis [7]. Type II EC accounts for only 10-20%, with p53 mutations as a main feature, including special types such as serous adenocarcinoma, clear cell carcinoma, and carcinosarcoma, which are poorly differentiated with a poor prognosis [8]. At present, surgical treatment is the first choice for EC clinically, and the decision foe supplementary chemoradiotherapy and hormone therapy is made depending on pathological typing and staging [9, 10]. The prognosis of surgically treated patients with early-stage EC is good, with a 5-year overall survival (OS) rate of 90% without metastasis. However, some early-stage low-risk patients still experience recurrence. The overall survival rate of high-risk EC is

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about 50%. Even with postoperative chemoradiotherapy, the median OS time of high-risk EC is only 37 months, while the median progression-free survival (PFS) time is only 13 months [11]. The fatality rate of EC also showed an increasing trend, which may be related to the advanced stage of the disease [12]. Lymph node metastasis (LNM) is the main metastatic modality of EC and an independent risk factor for patient prognosis [13]. Lymph node dissection is a common way to treat LNM in EC but with a high risk of postoperative complications [14]. For patients with a low risk of LNM, lymph node dissection has not been recommended [15]. However, because the preoperative risk assessment system of LNM in EC has not been established yet, there is still some controversy about whether to perform lymph node dissection. Therefore, there is an urgent need for individualized precision therapy based on molecular characteristics.

Since The Cancer Genome Atlas (TCGA) database integrated the features of tumor genomics, transcriptomics and proteomics of endometrioid adenocarcinoma and serous carcinoma and classified EC into four molecular subtypes: Polymerase Epsilon ultramutated (POLE mut), microsatellite instability (MSI) hypermutated (MSI-H), copy-number low (CNL)/microsatellite stability, and copy-number high (CNH)/serous-like in 2013, molecular subtyping has been found to better predict prognosis [16]. Although TCGA molecular subtyping is comprehensive and accurate, the testing process is complex and costly, making it difficult to popularize in primary hospitals. Therefore, scholars have developed the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) typing system [17]: POLE hypermutated, mismatch repair deficient (MMRd), no specific molecular profile (NSMP), and p53 abnormal (p53-abn). The results of molecular sequencing combined with immunohistochemistry found that this typing system was highly consistent with the TCGA analysis, and was more practical and convenient for clinical promotion. Moreover, new therapeutic schemes based on this molecular subtyping, such as targeted therapy, immunotherapy, and combination therapy, have brought new hope to EC patients [18, 19].

In recent years, EC molecular subtyping has been gradually applied in clinical practice, providing a reference for prognosis judgment and treatment scheme selection. Therefore, based on ProMisE molecular subtyping, this study explores its correlation with the clinical characteristics and LNM of EC patients, thus providing a theoretical basis for in-depth clinical study, understanding the underlying molecular basis of EC, and serving as a potential clinical treatment guide.

Data and methods

Study population

This is a retrospective study, selecting 120 patients who were initially diagnosed with EC and surgically treated in the Beijing Tsinghua Chang Gung Hospital, School of Clinical Medicine, Tsinghua University from January 2015 to June 2023. Inclusion criteria: (1) Patients who were diagnosed with EC (endometrioid adenocarcinoma, papillary serous carcinoma, clear cell carcinoma, etc.) by histopathological examination, and the diagnosis met the relevant standards of the "National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (V.1.2020)", with all the HE and immunohistochemical stained pathological sections reviewed and diagnosed by two qualified pathologists; (2) Within 10 days before operation, staging and histological subtyping were performed according to the International Federation of Obstetrics and Gynecology (FIGO) staging system. All patients were tested for estrogen receptor (ER), progesterone receptor (PR), and carbohydrate antigen 125 (CA125); (3) ProMisE molecular subtyping was performed by high-throughput sequencing for all patients; (4) Patients were aged ≥18 and ≤80; (5) With complete follow-up and clinical data. Exclusion criteria: (1) Patients who underwent other treatment other than surgery, such as radiotherapy and neoadjuvant chemotherapy; (2) Aged <18 or >80 years old; (3) With incomplete medical records or test results; (4) With mental and psychological disorders. This study was approved by the Beijing Tsinghua Chang Gung Hospital Ethics Committee.

Patient data collection

Patients' clinical data, including general data such as age, body mass index (BMI), menopausal status, underlying diseases, and patho-

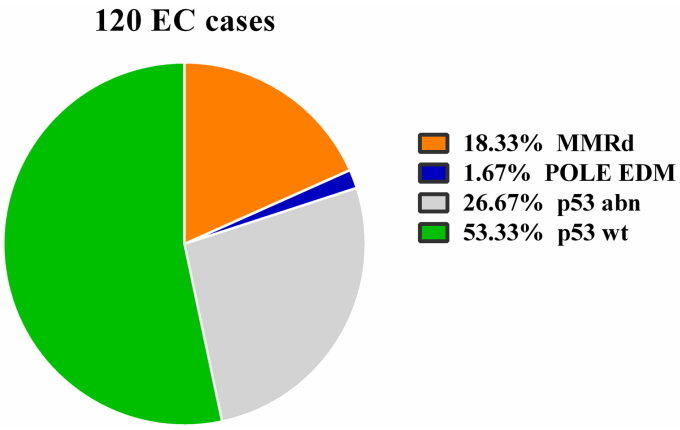

Figure 1. Proportions of ProMisE molecular subtypes in 120 patients with EC. Note: MMRd: mismatch repair deficiency; POLE EDM: polymerase epsilon exonuclease domain mutation; p53 abn: p53 abnormal; p53 wt: p53 wide-type.

logical data such as preoperative serum levels of CA125 and Ki-67, clinical stage, histological classification, pathological grade, LNM, tumor diameter (maximum diameter measured in postoperative gross specimen), lymphovascular space invasion (LVSI), muscular infiltration, ER, and PR, were collected.

Research methods

The expression of MMR proteins, including MLH1, MSH2, MSH6, and PMS2, was analyzed by immunohistochemistry testing. The positive expression of the MMR protein is localized in the nucleus, and when it is completely negative in tumor cells, it is interpreted as loss of the MMR protein, which can be presented as a simultaneous loss of one or more proteins (MMRd subtypes). A POLE gene mutation test would be performed without MMR protein loss. The exon 9-14 regions of POLE exonuclease are sequenced, and the mutations are classified as POLE hypermutated (POLE EDM). p53 protein expression was detected by immunohistochemistry in those who had no POLE mutations. p53 positive or inactivated patients were interpreted as p53 mutant (p53 abnormal) and classified as p53 abn subtype, while p53 wild-type was classified as p53 wt subtype.

In addition, all patients underwent immunohistochemical detection of Ki-67 and PD-L1. PD-L1: The combined positive score (CPS) was used, which is calculated as the sum of the number of PD-L1 positive tumor cells and tumor-associated immune cells in every 100 tumor cells, with CPS<1 considered negative and CPS≥1 considered positive.

Statistical methods

SPSS 25.0 software was used for data analysis. Count data, described as the number of cases (percentage), were comparatively analyzed with the chi-square test or Fisher's exact probability test. Factors associated with the risk of LNM in EC were determined by Multivariate Logistic regression. P<0.05 was the threshold of significance.

Results

Pathological and clinical features

A total of 120 EC patients undergoing surgery were enrolled in this study, with a median age of 60.5 years (range from 18-78 years). 120 EC patients were staged according to FIGO staging as follows: stage I (48 cases), stage II (23 cases), stage III (35 cases), and stage IV (14 cases), with 95 cases of endometrioid adenocarcinoma and 25 cases of non-endometrioid carcinoma. Among the 120 EC patients, the proportions of four molecular subtyping were POLE EDM in 2 cases, MMRd in 22 cases, p53 wt in 64 cases, and p53 abn in 32 cases (**Figure 1**). The immunohistochemical staining patterns of MMR protein in MMRd patients and p53 in typical cases are shown in **Figures 2** and **3**, respectively.

ProMisE molecular subtyping and clinicopathological features

The differences in FIGO staging, pathological grading, and LNM among patients with four molecular subtypes were statistically significant (all P<0.05). However, no marked differences were observed in age, menopausal status, histological classification, myometrial invasion depth, tumor diameter, and preoperative CA125, ER, PR, PD-L1, and Ki-67 expression among the four molecular subtypes (all P>0.05), as shown in **Table 1**.

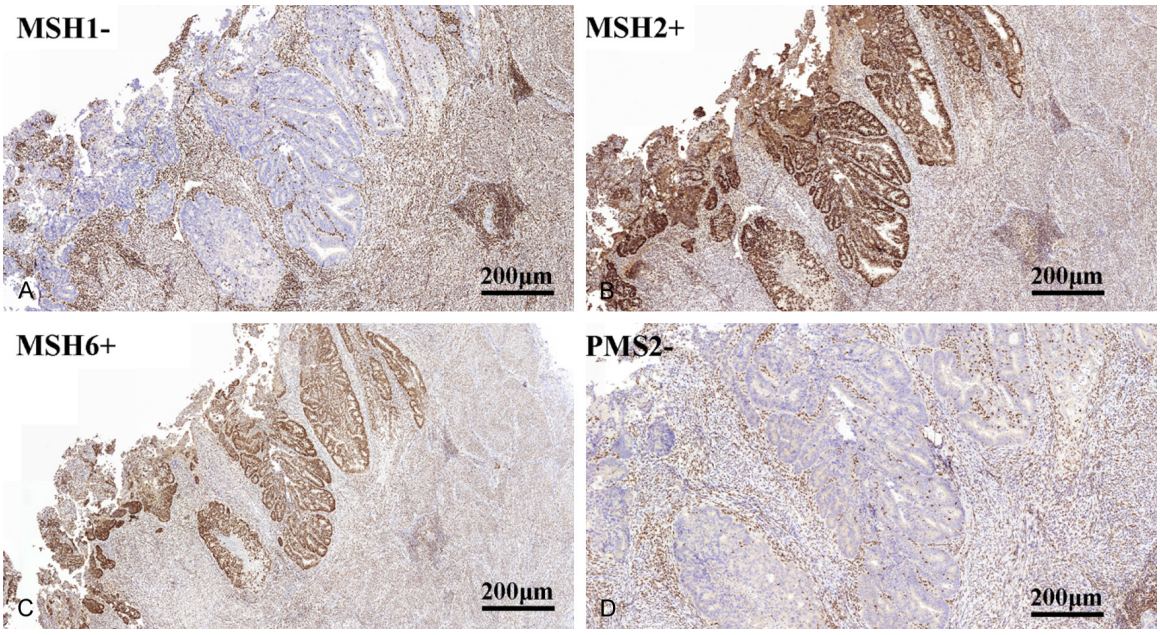

Figure 2. Immunohistochemical staining of four MMR proteins in MMRd subtype cases. A: Case with MSH1-; B: Case with MSH2+; C: Case with MSH6+; D: Case with PMS2-.

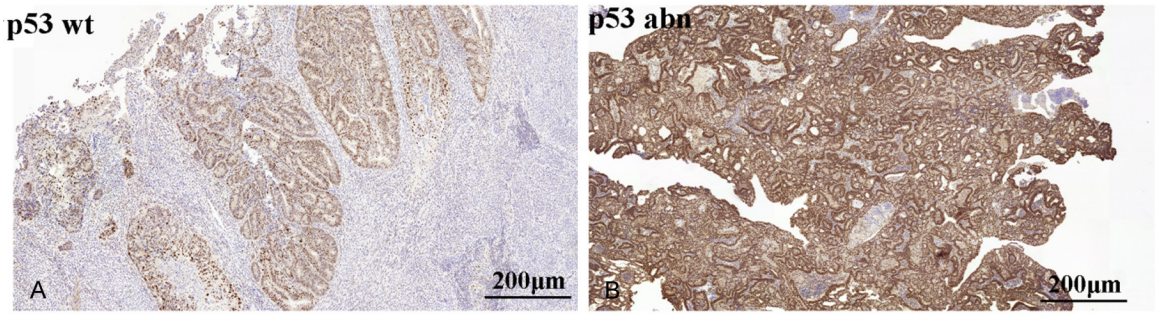

Figure 3. p53 immunohistochemical staining diagram. A: p53 wt case; B: p53 abn case. Note: p53 abn: p53 abnormal; p53 wt: p53 wide-type.

Clinical features of LNM

According to histopathological findings, there were 26 patients with LNM and 94 patients without lymph node involvement. Statistical significance (all P<0.05) was observed in the variations of FIGO staging, tumor grading, myometrial invasion depth of 50% or more, and levels of CA125, ER, PR, and Ki-67 between patients with LNM and those without, as indicated in **Table 2**.

Molecular subtypes and LNM

The ProMisE molecular subtyping analysis revealed MMRd and p53 expression between patients with LNM and those without (P<0.05; 38.5% vs 12.8%). Conversely, MMR positive and p53 wt expressions were significantly less common in patients with LNM (P<0.05; 19.2% vs 62.8%). There were no significant differences observed in POLE EDM between the two groups. Details are provided in **Table 3**.

Multivariate Logistic regression analysis of LNM in EC patients

Using LNM as the dependent variable (without =0, with =1) and the factors with statistical difference indicated by P<0.1 in **Table 2** as independent variables, i.e., FIGO staging (I-II =0, III-IV =1), pathological grading (moderately differ-

Table 1. Relationship between four molecular subgroups and clinicopathological features

Characteristics	n	MMRd (n=22)	POLE EDM (n=2)	p53 abn (n=32)	p53 wt (n=64)	F	P
Age (years)	120					1.563	0.068
≤50	46	8 (36.4)	1 (50.0)	15 (46.9)	22 (34.4)		
>50	74	14 (63.6)	1 (50.0)	17 (53.1)	42 (65.6)		
BMI (kg/m^2)	120					10.616	0.101
≤24	53	14 (63.6)	0 (0)	9 (28.1)	30 (46.9)		
24-28	49	5 (22.7)	2 (100.0)	18 (56.3)	24 (37.5)		
≥28	18	3 (13.7)	0 (0)	5 (15.6)	10 (15.6)		
Menopause	77	15 (68.2)	1 (50.0)	17 (53.1)	44 (68.8)	2.610	0.456
Pausimenia	92	19 (86.4)	1 (50.0)	21 (65.6)	51 (79.7)	4.335	0.228
Hypertension	48	11 (50.0)	2 (100.0)	12 (37.5)	23 (35.9)	4.440	0.218
Diabetes mellitus	43	8 (36.4)	2 (100.0)	10 (31.3)	23 (35.9)	3.877	0.275
Histological typing	120					12.719	0.176
Endometrioid adenocarcinoma	95	21 (95.5)	2 (100.0)	24 (75.0)	48 (75.0)		
Papillary serous carcinoma	13	0 (0)	0 (0)	7 (21.9)	6 (9.4)		
Clear cell carcinoma	4	0 (0)	0 (0)	1 (3.1)	3 (4.7)		
Mixed carcinoma	8	1 (4.5)	0 (0)	0 (0)	7 (10.9)		
FIGO staging	120					36.703	<0.0001
I-II	71	11 (50.0)	2 (100.0)	6 (18.8)	52 (81.3)		
III-IV	49	11 (50.0)	0 (0)	26 (81.3)	12 (18.8)		
Pathological grading	120					17.416	0.008
Well differentiated	20	6 (27.3)	0 (0)	1 (3.1)	13 (20.3)		
Moderately differentiated	72	10 (45.4)	0 (0)	20 (62.5)	42 (65.6)		
Poorly differentiated	28	6 (27.3)	2 (100.0)	11 (34.4)	9 (14.1)		
Myometrial invasion depth (%)	120					0.155	0.985
<50	64	11 (50.0)	1 (50.0)	17 (53.1)	35 (54.7)		
≥50	56	11 (50.0)	1 (50.0)	15 (46.9)	29 (45.3)		
Maximum tumor diameter (cm)	120					7.983	0.239
<2	29	4 (18.2)	2 (100.0)	8 (25.0)	15 (23.4)		
2-5	61	12 (54.5)	0 (0)	14 (43.7)	35 (54.7)		
>5	30	6 (27.3)	0 (0)	10 (31.3)	14 (21.9)		
Lymph node metastasis	120					17.253	0.000
Yes	26	10 (45.5)	1 (50.0)	10 (31.3)	5 (7.8)		
No	94	12 (54.5)	1 (50.0)	22 (68.7)	59 (92.2)		
CA125 (U/mL)	120					3.185	0.364
≤35	77	11 (50.0)	1 (50.0)	20 (62.5)	45 (70.3)		
>35	43	11 (50.0)	1 (50.0)	12 (37.5)	19 (29.7)		
ER	120					0.358	0.949
Positive	105	19 (86.4)	2 (100.0)	28 (87.5)	55 (85.9)		
Negative	15	3 (13.6)	0 (0)	4 (12.5)	9 (14.1)		
PR	120					1.905	0.592
Positive	107	21 (95.5)	2 (100.0)	29 (90.6)	55 (85.9)		
Negative	13	1 (4.5)	0 (0)	3 (9.4)	9 (14.4)		
PD-L1	120					3.138	0.371
Positive	66	10 (45.5)	1 (50.0)	15 (46.9)	40 (62.5)		
Negative	54	12 (54.5)	1 (50.0)	17 (53.1)	24 (37.5)		
Ki-67 (%)	120					4.327	0.228
≤50	75	12 (54.5)	0 (0)	21 (65.6)	42 (65.6)		
>50	45	10 (45.5)	2 (100.0)	11 (34.4)	22 (34.4)		

Note: MMRd: mismatch repair deficiency; POLE EDM: polymerase epsilon exonuclease domain mutation; p53 abn: p53 abnormal; p53 wt: p53 wide-type.

Table 2. Comparison of clinical characteristics between patients with lymph node metastasis and those without lymph node involvement

Characteristic	Lymph node metastasis (n=26)	Non-lymph node metastasis (n=94)	χ^2	P
Age (years)			0.222	0.638
≤50	11 (42.3)	35 (37.2)		
>50	15 (57.7)	59 (62.8)		
BMI (kg/m^2)			1.891	0.389
≤24	11 (42.3)	42 (44.7)		
24-28	13 (50.0)	36 (38.3)		
≥28	2 (7.7)	16 (17.0)		
Menopause	16 (61.5)	61 (64.9)	0.099	0.752
Pausimenia	18 (69.2)	74 (78.7)	1.026	0.311
Hypertension	10 (38.5)	38 (40.4)	0.033	0.856
Diabetes mellitus	9 (34.6)	34 (36.2)	0.021	0.884
Histological typing			4.131	0.248
Endometrioid adenocarcinoma	21 (80.8)	74 (78.7)		
Papillary serous carcinoma	3 (11.5)	10 (10.6)		
Clear cell carcinoma	2 (7.7)	2 (3.2)		
Mixed carcinoma	0 (0)	8 (8.5)		
FIGO staging			5.890	0.015
I-II	10 (38.5)	61 (64.9)		
III-IV	16 (61.5)	33 (35.1)		
Pathological differentiation			28.862	<0.0001
Well differentiated	0 (0)	20 (21.3)		
Moderately differentiated	10 (38.5)	62 (66.0)		
Poorly differentiated	16 (61.5)	12 (12.7)		
Myometrial invasion depth			6.790	0.009
<50	8 (30.8)	56 (59.6)		
≥50	18 (69.2)	38 (40.4)		
Maximum tumor diameter (cm)			1.560	0.458
<2	4 (15.4)	25 (26.6)		
2-5	14 (53.8)	47 (50.0)		
>5	8 (30.8)	22 (23.4)		
CA125 (U/mL)			6.897	0.009
≤35	11 (42.3)	66 (70.2)		
>35	15 (57.7)	28 (29.8)		
ER			4.742	0.029
Positive	26 (100.0)	79 (84.0)		
Negative	0 (0)	15 (16.0)		
PR			4.033	0.045
Positive	26 (100.0)	81 (86.2)		
Negative	0 (0)	13 (13.8)		
PD-L1			1.049	0.306
Positive	12 (46.2)	54 (57.4)		
Negative	14 (53.8)	40 (42.6)		
Ki-67 (%)			5.774	0.016
≤50	11 (42.3)	64 (68.1)		
>50	15 (57.7)	30 (31.9)		

Table 3. Relationship between ProMisE molecular subtyping and LNM

	Lymph node metastasis		χ^2	P
	With (n=26)	Without (n=94)		
MMRd			8.982	0.003
Yes (n=22)	10 (38.5)	12 (12.8)		
No (n=98)	16 (61.5)	82 (77.2)		
POLE EDM			0.962	0.327
Yes (n=2)	1 (3.8)	1 (1.1)		
No (n=118)	25 (96.2)	93 (98.9)		
p53			8.889	0.003
abn (n=32)	10 (38.5)	22 (23.4)		
wt (n=64)	5 (19.2)	59 (62.8)		

Note: MMRd: mismatch repair deficiency; POLE EDM: polymerase epsilon exonuclease domain mutation; p53 abn: p53 abnormal; p53 wt: p53 wide-type.

entiated =0, poorly differentiated =1, and well differentiated =2), ProMisE molecular subtyping (MMRd =0, p53 wt =1, POLE EDM =2, and p53 abn =3), myometrial invasion (<50% =0, ≥50% =1), CA125 (≤35 =0, >35 =1), ER (negative =0, positive =1), PR (negative =0, positive =1), and Ki-67 (≤50% =0, >50% =1), binary Logistic regression analysis was performed. p53 wt (P=0.008, OR=0.078, 95% CI: 0.012-0.510) was a protective factor for LNM in EC patients, while poorly differentiated histology (P=0.001, OR=15.137, 95% CI: 3.013-76.044) was a risk factor, as shown in **Table 4**.

Discussion

EC has great clinical heterogeneity. The traditional Bokhman's dualistic model and histopathological classification can not fully reflect the biological characteristics of the tumor due to overlaps between different types of histological characteristics [20]. The ProMisE molecular typing protocol, derived from the TCGA algorithm, first determines the MMRd subtype through immunohistochemical detection of MMR proteins, recommending further second-generation gene sequencing for suspected Lynch syndrome (LS) patients for diagnosis. LS, previously referred to as hereditary nonpolyposis colorectal cancer, results from germline mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) and represents the most prevalent cause of hereditary cancer susceptibility, with a predisposition to colorectal cancer, EC and other malignancies [21-23]. The POLE EDM subtype was identified through sequencing of the POLE gene in suspected LS patients. Finally, the p53 abn and p53 wt subtypes were determined by immunohistochemical analysis of the p53 protein.

This study employed the ProMisE protocol to evaluate 120 EC patients including 95 cases of endometrioid adenocarcinoma. The proportions of POLE EDM, MMRd, p53 abn, and p53 wt subtypes accounted for 1.67%, 18.33%, 26.67%, and 53.33%, respectively, aligning with the corresponding proportions of 12%, 30%, 18%, and 40% reported in the 5th edition of the WHO classification. The composition ratios between the two datasets were largely comparable, with the exception of a minor discrepancy in the POLE hypermutated subtype, which may be attributed to the limited sample size of this study. Previous research indicated that POLE hypermutated EC typically characterized by occurrence in relatively young patients, early FIGO stage, and high tumor grade [24]. The MMRd subtype exhibits similarities to the POLE hypermutated subtype, whereas the p53 abn subtype encompasses serous carcinoma and the majority of G3 endometrioid adenocarcinomas [25]. The findings of this study largely align with existing literature. Variations in the proportion of molecular subtypes across different studies may be attributed not only to differences in detection methodologies, but also to variations in the pathological types.

The correlation between molecular subtyping of EC and traditional clinicopathological features remains a focal point of clinical research. In this study, variations were observed in histological classification, FIGO staging, pathological grading, and LNM among patients with different ProMisE molecular subtypes. Conversely, no differences were detected in ER and PR expression, potentially due to the limited number of pathological types included. The molecular subtyping of certain rare pathological types holds greater significance for elucidating the fundamental nature of the disease. Travaglino et al. [26] conducted a meta-analysis of 231 cases of uterine carcinosarcoma across four studies, categorizing them according to the TCGA molecular subtypes. Their findings indicated that the CNH subtype was predominant in carcinosarcoma. In the same year, the

Table 4. Multivariate Logistic regression analysis results of LNM in patients with EC

Variables	β	S.E.	Wald	P	OR	95% CI
FIGO staging	-0.005	0.822	0.000	0.995	0.995	0.199-4.980
Molecular subtyping (control: MMRd)			7.421	0.060		
p53 wt	-2.545	0.955	7.102	0.008	0.078	0.012-0.510
PLOE EDM	-3.214	2.037	2.489	0.115	0.040	0.001-2.180
p53 abn	-1.479	0.916	2.605	0.106	0.228	0.038-1.373
Pathological grading (control: moderately differentiated)			10.885	0.004		
Poorly differentiated	2.717	0.824	10.885	0.001	15.137	3.013-76.044
Well differentiated	-19.417	7723.279	0.000	0.998	0.000	-
Myometrial invasion ≥50%	1.350	0.704	3.681	0.055	3.859	0.971-15.328
CA125>35 U/mL	0.736	0.693	1.125	0.289	2.087	0.536-8.123
ER positive	17.499	8357.120	0.000	0.998	39772317.06	-
PR positive	19.869	9131.980	0.000	0.998	425615869.4	-
Ki-67>50%	0.802	0.691	1.347	0.246	2.229	0.576-8.634

Note: MMRd: mismatch repair deficiency; POLE EDM: polymerase epsilon exonuclease domain mutation; p53 abn: p53 abnormal; p53 wt: p53 wide-type.

research team applied TCGA molecular subtyping to 73 cases of undifferentiated/dedifferentiated EC, identifying MSI in 44% of cases, POLE hypermutation in 12.4%, p53 mutation in 18.6%, and p53 wild-type in 25% [27]. These results highlight a significant distinction between EC and other high-risk histological types. Therefore, more pathological types need to be included for related research in the future.

EC patients with LNM are correlated with increased chemical resistance, higher recurrence rates, and poorer prognosis. Consequently, vigilant monitoring of LNM during treatment is imperative. Currently, there is ongoing debate regarding the necessity and extent of lymph node dissection in the management of early-stage EC. Jamieson et al. [28] investigated the relationship between ProMisE molecular subtyping and LNM in a cohort of 172 EC patients, identifying a significant association between molecular subtyping and LNM (P= 0.004). Notably, the p53 abn subtype exhibited the highest rate of LNM, underscoring the critical importance of molecular subtyping for treatment decision-making and prognostic evaluation. In this study, the expression status of p53 was significantly correlated with LNM, with lymph node involvement observed in 38.5% of cases of the p53 abn subtype, compared to 19.2% of cases of the p53 wt subtype. Mariani et al. [29] conducted an analysis of lymph node dissection specimens from 82 EC patients and determined that p53 mutation served as an independent predictor of LNM. The findings of this study suggest that p53 wt functions as a protective factor, indicating that p53 mutations are associated with a higher risk of LNM compared to wild-type p53. Furthermore, a systematic review and meta-analysis concluded that the presence of lymph node metastases appears to be influenced by molecular classification. Specifically, p53-abnormal group exhibited the highest rate of lymph node involvement, whereas the POLE-mutated group demonstrated the lowest rate [30].

In addition, this study identified poor differentiation a risk factor for LNM in EC patients. Low differentiation is traditionally recognized as a risk factor for LNM in EC and is associated with an unfavorable prognosis [31]. In 2022, the European Society for Medical Oncology incorporated molecular subtyping into the risk stratification, categorizing all stages and grades of p53 abn with myometrial invasion as high-risk. Therefore, lymph node staging is imperative for EC of the p53 abn subtype, and postoperative adjuvant therapy is recommended [32]. Additionally, this study did not corroborate the role of CA125, ER, and PR as risk factors for LNM in EC patients. However, some literature suggests a correlation between preoperative CA125 levels and LNM in EC patients [33]. EC is a hormone-regulated malignancy, where ER-negative, high-grade tumors typically exhibit a higher proliferation rate, whereas ER-positive, low-grade tumors generally demonstrate a lower proliferation rate [34]. However, the results are contrary to our observations. This

discrepancy may be attributed to the limited sample size or the loss of statistical significance of the variable following multivariate inclusion in the regression analysis and adjustment for confounders. Existing studies have demonstrated that only the combination of ER, PR, Ki-67, and P53 serves as a statistically significant predictor of lymph node metastasis [35].

In conclusion, ProMisE molecular subtyping plays a significant role in guiding the treatment of EC. The p53 mutation (abn subtype) in ProMisE typing of EC is closely associated with LNM, thereby facilitating more precise treatment strategies for patients undergoing preoperative diagnostic curettage. Nonetheless, it is imperative to integrate molecular subtyping with histological classification and FIGO grading to prevent both under-treatment and over-treatment in clinical practice. This study is subject to several limitations. The findings may be biased due to its design as a single-center retrospective analysis with an inadequate sample size. Additionally, the pathological types of the included samples are both limited and unevenly distributed. Moreover, this study did not incorporate a "multimolecular signature" EC analysis, nor did it conduct a survival-related prognostic analysis. Consequently, a prospective clinical study with a larger sample size is warranted for further validation.

Disclosure of conflict of interest

None.

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