

# Value of Molecular Typing Combined with Integrated Positron Emission Tomography/Magnetic Resonance Imaging in Risk Stratification of Endometrial Cancer

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**Objective:** In this study, we investigated the value of molecular typing combined with integrated positron emission tomography (PET)/magnetic resonance imaging (MRI) semi-quantitative indices in endometrial cancer risk stratification.

**Methods:** A retrospective study was conducted on 86 patients who were pathologically diagnosed with endometrial cancer and underwent surgical treatment after curettage at the Department of Obstetrics and Gynecology, Xuanwu Hospital, Capital Medical University between January 2017 and March 2023. Prior to surgery, each patient underwent integrated PET/MRI examination. The postoperative samples were subjected to pathological diagnosis, immunohistochemistry, and POLE gene sequencing. The differences in clinicopathological features between the four molecular subtypes and the differences in integrated PET/MRI semi-quantitative indexes (SUV max, ADC min) between the four molecular subtypes were analyzed. The cutoff value of molecular typing combined with integrated PET/MRI semi-quantitative indices for endometrial cancer risk stratification was determined.

**Results:** There were statistically significant differences in pathological types and tumor grades among the four molecular subtypes of endometrial cancer. The values of the four integrated PET/MRI semi-quantitative indices (SUV max and ADC min) of the molecular subtypes were statistically different. The SUV max was greater in the p53abn mutation group than in the POLE mutation group ( $P < 0.05$ ). The ADC minimum of the POLE mutation group and the MMR-d group was lower than the NSMP group ( $P < 0.05$ ). Molecular typing combined with the integrated PET/MRI semi-quantitative SUV max index can predict the low/medium risk group of endometrial cancer and the medium-high/high risk group, and the cut-off value of SUV max for predicting the risk of early endometrial cancer was 14.72 (sensitivity 66.7%, specificity 68.7%).

**Conclusion:** Molecular typing combined with integrated PET/MRI semi-quantitative indicators is useful to achieve risk stratification in patients diagnosed with endometrial cancer and guide individualized treatment.

**Keywords:** endometrial cancer, integrated PET/MRI, individualized treatment, molecular typing

## Introduction

Endometrial cancer (EC) is a malignant tumor originating from the endometrium, that is more prevalent in elderly women. The incidence of endometrial cancer in malignant tumors of the female genital tract can reach 20%–30%. With the evolution of the modern lifestyle and the extension of life expectancy, the global incidence of EC has been increasing annually and has become prevalent in younger women over the past two decades.<sup>1</sup>

Patients diagnosed with endometrial cancer are typically treated with surgery. The scope of surgery is determined by a comprehensive preoperative evaluation. Diagnostic curettage is performed to determine the pathological diagnosis to obtain histological subtypes and grades, and iconography is used for preoperative staging. With the development of precision medicine, the standard pathomorphological classification is no longer adequate for clinical diagnosis and treatment. Along with the advancement of genomics research, molecular classification of endometrial cancer is being

carried out to provide more tumor biological information. In 2013, the Cancer Genome Atlas Program (TCGA) conducted a large-scale, comprehensive, and integrated genomic analysis of 373 cases of endometrial cancer, which was divided into four molecular subtypes based on different clinicopathological and molecular characteristics, namely POLE exonuclease domain mutations (POLE) exonuclease domain mutations (POLE mut), microsatellite instability-high mutation (MSI-H), copy number abnormalities-low (CN-L), and copy number abnormalities-high (CN-H). Among these four molecular subtypes, the POLE mutant type had the best prognosis, followed by the CN-L type, MSI-H type, and CN-H type, which had the worst prognosis.<sup>2</sup>

Nevertheless, the widespread clinical utilization of TCGA molecular typing diagnostic technology has been impeded by its high cost. In 2015, McConechy et al<sup>3</sup> sought to simplify the TCGA detection method. They accomplished this by employing immunohistochemical staining for mismatch repair (MMR) proteins and p53 protein, as well as sequencing the POLE gene. This simplified approach was extended beyond endometrial cancer to include non-endometrioid adenocarcinoma. As a result, they introduced the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE). In 2020, the National Comprehensive Cancer Network (NCCN) guidelines officially included molecular typing into the guidelines.<sup>4</sup> The 2022 European Society of Gynaecological Oncology (ESGO) guidelines incorporated pathological factors and molecular subtypes, redefined the prognostic risk level of EC, and indicated that molecular typing had begun to be formally applied to guide clinical treatment.<sup>5</sup> Although molecular typing can alter risk stratification, it cannot replace morphological assessment. The guidelines recommend that patients with endometrial cancer should undergo enhanced magnetic resonance imaging (MRI) before surgery. If distant metastases are suspected, a whole-body positron emission tomography-computed tomography (PET-CT) can be performed.<sup>6</sup> Currently, the most commonly used preoperative imaging examination for endometrial cancer is the newly emerging integrated positron emission tomography/magnetic resonance imaging (PET/MRI). Through integrated scanning imaging, it combines the precise anatomical positioning capability of MRI for high contrast resolution of pelvic soft tissue and leverages the advantages of PET in providing functional metabolic information of lesions.<sup>7</sup> Apparent diffusion coefficient (ADC) is a quantitative index of diffusion-weighted imaging. A decrease in ADC is observed in malignant tumor cells. Normal tissue exhibited a greater ADC value. Therefore, ADC values are frequently employed for tumor diagnosis and prognosis evaluation. The maximum standard uptake value (SUV max) is the most frequently employed semi-quantitative index of PET examinations, reflecting the highest glucose metabolism in tumor tissues. SUV max is highly correlated with tumor cell metabolism, tumor cell proliferation rate, tumor tissue grade, and tumor type, and can therefore be used for tumor diagnosis and prognosis evaluation.

The purpose of this study was to investigate the clinicopathological characteristics of different molecular subtypes of endometrial cancer and the difference of semi-quantitative indexes of integrated PET/MRI between different molecular subtypes, and to explore the value of molecular typing combined with integrated PET/MRI for risk stratification of patients with endometrial cancer.

## Materials and Methods

### Research Material

A retrospective study was conducted on patients who were pathologically diagnosed with endometrial cancer following diagnostic curettage or hysteroscopy in the Department of Obstetrics and Gynecology, Xuanwu Hospital, Capital Medical University from January 2017 to March 2023 and received surgical treatment in the Department of Obstetrics and Gynecology. Prior to surgery, each patient underwent integrated PET/MRI examination in the Department of Nuclear Medicine. Postoperative paraffin specimens were analyzed in the Department of Pathology for pathological diagnosis and immunohistochemical staining. The POLE gene sequencing was conducted at the Beijing Physical and Chemical Center. This study was conducted with the approval of the ethics committee of our hospital, and each patient signed an informed consent prior to admission.

The patients included in the study met the following criteria: A. Patients diagnosed with endometrial cancer by pathological results of diagnostic curettage or hysteroscopy; B. Patients who underwent preoperative integrated PET/MRI examination; C. Patients who underwent surgical treatment in our hospital two weeks after PET/MRI examination; D. Patients whose postoperative pathological specimens were tested for molecular typing.

Patients with any of the following criteria during the study were excluded: A. Preoperative neoadjuvant chemotherapy, radiotherapy, or hormone therapy; B. Complicated with other pelvic malignant tumors such as cervical cancer or ovarian cancer; C. The integrated PET/MRI imaging failed to be completed for various reasons, such as metal foreign bodies in the body, obesity, claustrophobia, and inadequate breathing training; D. Due to various reasons, the patient was unable to tolerate endometrial cancer staging procedures; E. Postoperative pathological core tissue without tumor or absence of tumor.

## Research Methods

### Integrated PET/MRI Examination

Before undergoing surgery, an integrated PET/MRI exam was administered to every patient in this study. The tracer used was <sup>18</sup>F-fluorodeoxyglucose produced by Atomic High-tech Co., Ltd. Fasting blood glucose levels < 8 mmol/L were measured at least 6 hours before the examination. Before the scan, the imaging reagent was injected intravenously, and after 1 hour of rest, PET-MRI imaging was performed on the whole body. Integrated PET/MRI scanning protocol: 6 minutes per bed, scanning 4–5 beds each time with a bed overlap of 24%. Time-of-flight (TOF) technology is utilized, and images are reconstructed using a rapid iterative algorithm (OSEM). The integrated PET/MRI examination takes a total of 60 minutes. The scanned images are anonymously stored on the post-processing workstation of General Electric Company in the United States. Two expert radiologists independently interpreted the imaging results. The demographic profile, medical history, pathological results, and other imaging data of patients were not obtained during the interpretation process. The imaging report results were interpreted based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) endometrial cancer surgical pathological staging and the following procedures: primary lesion identification, measurement of lesion-related indicators such as size, standard uptake value (SUV), apparent diffusion coefficient (ADC), and so on. The subsequent staging was performed in accordance with the FIGO 2009 surgical pathological staging criteria and meticulously documented. The target area of interest was delineated along the local radioactive concentration area of the lesion, and the maximum standard uptake value SUV max and ADC min were calculated.

### Surgical Methods

All surgical procedures were performed in the Department of Obstetrics and Gynecology, Xuanwu Hospital, Capital Medical University. The surgical procedure was either open gastrectomy or laparoscopic and included but was not limited to the following procedures: total hysterectomy, bilateral adnexectomy, sentinel lymph node biopsy, or systematic lymph node resection through open gastrectomy or laparoscopy. Comprehensive surgical staging of endometrial serous carcinoma and uterine carcinosarcoma, including omentectomy, peritoneal biopsy, and lymph node staging were conducted. For patients with stage III–IV, maximum tumor cytoreductive surgery was considered where feasible.<sup>8</sup>

### Molecular Typing Detection and Analysis Process

Molecular typing of postoperative pathological specimens: spot mutations in exons 9–14 of POLE gene were detected. The criteria for POLE mut type were P286R, V411L, S297F, A456P, and S459F spot mutations of the POLE gene.<sup>9,10</sup> Immunohistochemical staining: All immunohistochemical staining were conducted in the pathology department of our hospital. The interpretation of immunohistochemical staining results is as follows: Positive expression of MMR protein is localized in the cell nucleus, with positive internal controls (lymphocytes and normal tissue cells within the tissue). Any clear nuclear staining intensity higher than the background in tumor cells can be considered positive. If the internal controls are positive but there are no detectable signals or light gray or brown nuclear discoloration in tumor cells, it is considered negative. If  $\geq 1$  of the 4 proteins is not expressed, it is classified as MMRd type, while all 4 MMR proteins being positive are classified as pMMR type (intact mismatch repair function). Interpretation of p53 protein: ① Diffuse strong nuclear staining in over 80% of tumor cells; ② Positive staining in internal controls (lymphocytes and normal tissue cells within the tissue) while tumor cell nuclei are completely negative; ③ Three expression patterns fall under p53-abn type: diffuse moderate or strong cytoplasmic staining and no nuclear staining, among others; ④ Strong to weak variable nuclear staining in tumor cells is interpreted as wild-type expression; ⑤ Subclonal p53 expression involves at least one or more staining patterns, typically

a combination of wild-type and one or more mutant patterns, or a mixture of two different mutant patterns, with each pattern present in at least 5% of tumor cells. The image shows the immunohistochemical staining results for p53 protein. (Figure 1).

Analysis process: The analysis of molecular typing conformed to the standard diagnostic procedure for molecular typing outlined in the 5th edition classification.<sup>11</sup> First, the mutation type was determined by sequencing the POLE gene. The expressions of MLH1, PMS2, MSH2, and MSH6 were then detected using immunohistochemical staining to determine the MMR-d status of the tissue. The results of p53 immunohistochemical staining were used to determine whether the tumor was p53-abn or no specific molecular profile (NSMP) type (Figure 2).

## Observation Indicators

The demographic profile of patients was collected: age, height, weight, BMI, fertility history, complications, surgical pathological stage.

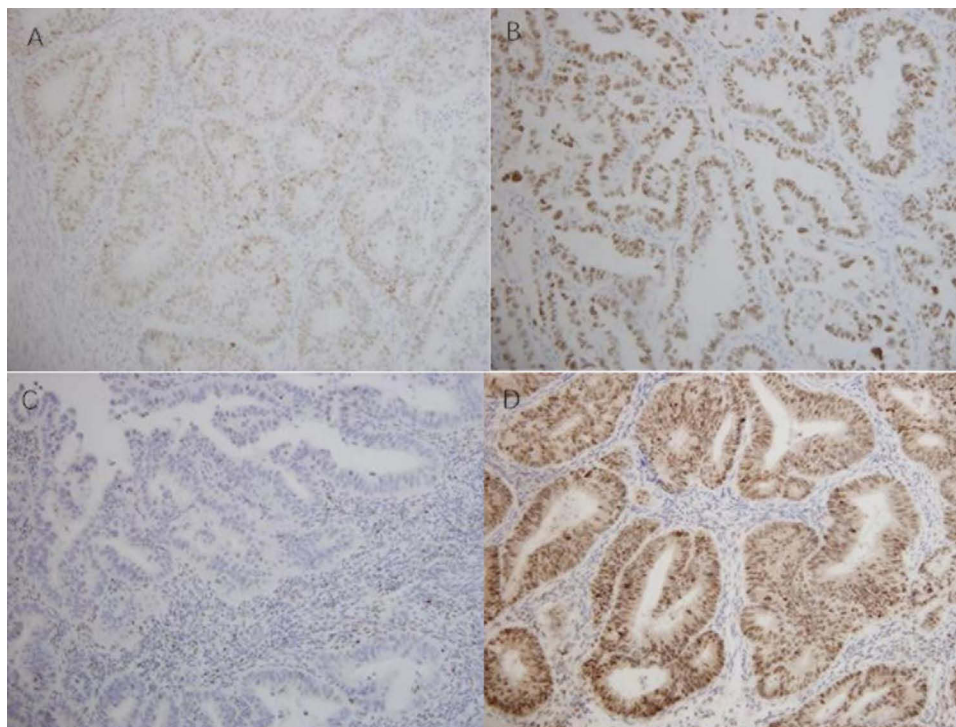
Integrated PET/MRI data: imaging staging, PET/MRI semi-quantitative indices SUV max, ADC min.

Postoperative pathological information: histopathological type, tumor grade, primary lesion size, pathological stage, lymphovascular space invasion (LVSI) infiltration, and so on.

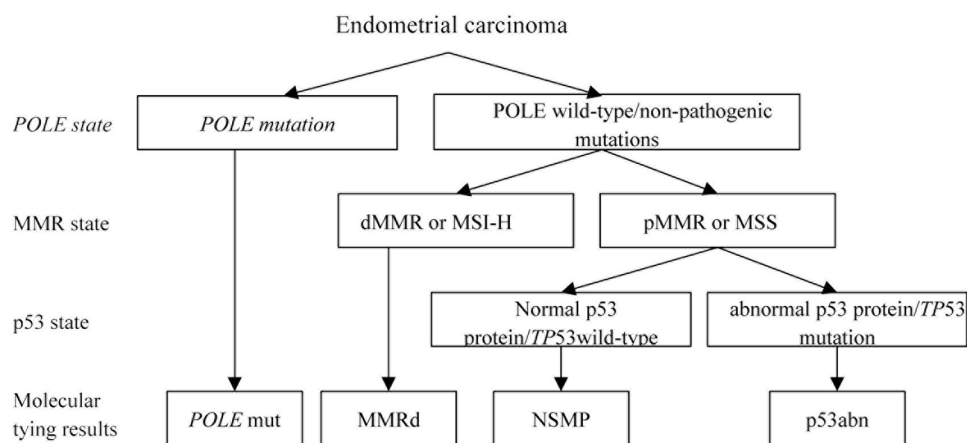
Molecular typing detection results: POLE gene mutation, p53; MLH1, PMS2, MSH2, MSH6 protein staining results.

## Statistical Method

Statistical analysis was conducted using SPSS 26.0 software. The quantitative data are expressed as mean  $\pm$  standard deviation or median. Qualitative data are expressed as frequency and percentage. The chi-squared test or Fisher's exact test was used to analyze the composition ratio. The receiver operating characteristic (ROC) curve and area under the ROC (AUC) were used to assess the predictive value of imaging indices (SUV max, ADC min) for risk stratification of early (FIGO I-II) endometrial cancer, and to investigate the cut-off value of imaging indicators. A *P* value  $<$  0.05 was considered statistically significant.



**Figure 1** The immunohistochemical staining results for p53 protein. (A) Wild-type p53, varying proportions and intensities of nuclear staining in tumor cells; (B) Aberrant nuclear overexpression of p53, strong nuclear staining in tumor cells compared to internal controls; (C) Complete loss of p53 expression, no p53 staining in tumor cell nuclei, with internal controls showing variable but moderate to strong staining. (D) Subclonal p53 mutation, with partial tumor cell cytoplasm showing diffuse moderate or strong positivity and no nuclear staining, accompanied by abnormal nuclear overexpression in some tumor cells. (Original magnification  $\times 20$ ).



**Figure 2** Recommended molecular typing detection pathway.

## Results

General characteristics of the patients: Based on the inclusion and exclusion criteria, 86 patients diagnosed with endometrial cancer in our hospital were finally retrospectively analyzed. Of the 86 patients analyzed, 82 (95.25%) underwent laparoscopic surgery and 4 (4.65%) underwent open gastrectomy. Among the 86 patients, 6 patients (6.98%) were unable to tolerate anesthesia and comprehensive staging procedure due to advanced age and comorbidities. Therefore, only total hysterectomy + double attachment resection was performed. Finally, 68 patients (79.07%) underwent comprehensive staging of endometrial cancer (total uterus + double attachments + pelvic lymph node dissection + para-aortic lymph node dissection), and 12 patients (13.95%) underwent total hysterectomy + double attachments + sentinel lymph node biopsy. None of the patients presented any residual lesion at the resection margin. Among the 86 patients with endometrial cancer, there were 74 cases (86.04%) of endometrial carcinoma, 3 cases (3.49%) of clear cell carcinoma, 3 cases (3.49%) of serous carcinoma, 3 cases (3.49%) of carcinosarcoma, and 3 cases (3.49%) of mixed adenocarcinoma. Among all patients with endometrial carcinoma, 12 cases (16.22%) were in Grade I, 57 cases (77.03%) were in Grade II, 5 cases (6.75%) were in Grade III. Based on the FIGO 2009 surgical pathological staging of endometrial cancer, 62 (72.09%) of the 86 patients were in FIGO Stage IA, 12 (13.95%) were in FIGO Stage IB, and 5 cases (5.81%), 6 cases (6.98%) and 1 case (1.16%) were in FIGO Stages II, III, and IV, respectively.

## Clinicopathological Characteristics of Endometrial Cancer Patients with Four Molecular Subtypes

Among the 86 patients in this study, there were 6 cases (6.98%) of POLE gene mutations, 24 cases (27.91%) of MMR-d type, 14 cases (16.28%) of p53abn type, and 42 cases (48.83%) of NSMP type, which is comparable to the proportion reported in literature.<sup>12</sup> There were significant differences in pathological types ( $P = 0.041$ ) and histological grades ( $P = 0.002$ ) among the four molecular subtypes of endometrial cancer. There were differences in the integrated PET/MRI semi-quantitative indices SUV max ( $P = 0.019$ ) and ADC ( $P = 0.003$ ) among the four molecular subtypes. There was no statistical difference between the four molecular subtypes in the remaining clinicopathological features (Table 1). The chi-squared test was then used to compare the two groups: the p53abn group consisted primarily of non-endometrial carcinoma, whereas the NSMP group comprised primarily of endometrial carcinoma. The difference between the two groups was statistically significant ( $P < 0.05$ ). In terms of tissue grading, p53abn had predominantly G3, while NSMP had predominantly G2, and the difference was statistically significant ( $P < 0.05$ ). The p53abn mutation group had a greater maximum SUV value than the POLE mutation group ( $P < 0.05$ ). The ADC min value of the POLE mutation group and MMR-d group was lower than that of the NSMP group ( $P < 0.05$ ).

There were 6 patients with POLE gene mutation, 1 of whom had abnormal nuclear overexpression of p53 in immunohistochemical staining, that is, bimolecular characteristics. Considering the high mutation state, it was classified as POLE gene mutation type based on the molecular typing detection process subsequently causing P53 gene mutation, as determined by the molecular typing detection process. The pathological types in this group were all endometrial carcinoma, and the FIGO stages

**Table 1** Clinicopathological Characteristics of the Four Molecular Subtypes of Endometrial Carcinoma

Parameter		POLEmut (n=6)	MMR-d (n=24)	p53abn (n=14)	NSMP (n=42)	P
Age		58.00±7.13	57.08±10.38	63.00±8.02	60.19±10.15	0.313
BMI(kg/m <sup>2</sup> )		27.51±3.78	25.94±4.18	25.21±3.27	26.84±4.61	0.531
Immediate family members of the patient	No	6(100.00)	18(75.00)	12(85.71)	30(71.43)	0.368
Malignant tumor	Yes	0(0.00)	6(25.00)	2(14.29)	12(28.57)	
Complicated gynecological diseases	No	2(33.33)	14(58.33)	9(64.29)	28(66.67)	0.452
Benign tumor	Yes	4(66.67)	10(41.67)	5(35.71)	14(33.33)	
Complicated hypertension	No	3(50.00)	14(58.33)	4(28.57)	16(38.10)	0.259
And/or diabetes	Yes	3(50.00)	10(41.67)	10(71.43)	26(61.90)	
Preoperative CA125		11.74(9.1,17.2)	16.01(13.2,21.4)	15.60(9.9,72.8)	17.72(14.0,28.2)	0.245
FIGO stage	I-II	6(100.00)	21(87.50)	12(85.71)	40(95.24)	0.477
	III-IV	0(0.00)	3(12.50)	2(14.29)	2(4.76)	
Pathological type	Endometrial carcinoma	6(100.00)	20(83.33)	9(64.29)	39(92.86)	0.041
	Non-endometrial carcinoma	0(0.00)	4(16.67)	5(35.71)	3(7.14)	
Tissue grade	G1	2(33.33)	2(9.09)	0(0.00)	8(19.51)	0.002
	G2	4(66.67)	16(72.73)	7(53.85)	32(78.05)	
	G3	0(0.00)	4(18.18)	6(46.15)	1(2.44)	
Muscle infiltration	<1/2	6(100.00)	16(66.67)	11(78.57)	34(80.95)	0.297
	≥1/2	0(0.00)	8(33.33)	3(21.43)	8(19.05)	
	No	5(83.33)	17(70.83)	11(78.57)	38(90.48)	0.233
	Yes	1(16.67)	7(29.17)	3(21.43)	4(9.52)	
Size of lesion	<2cm	4(66.67)	6(25.00)	3(21.43)	21(50.00)	0.05
	≥2cm	2(33.33)	18(75.00)	11(78.57)	21(50.00)	
SUVmax		11.98±7.59	18.59±11.25	19.57±12.28	12.30±5.81	0.019
ADCmin		554.17±219.58	438.09±139.08	609.20±203.98	723.46±151.16	0.003

**Abbreviation:** SUV, standard uptake value.

were all IA. In this molecular subtype group, 2 cases had histopathological grade of G1, 4 cases had histopathological grade of G2, 1 case had lymphatic vascular invasion, and there were no cases of lymph node metastasis.

MMR protein deletion was detected in 24 patients diagnosed with MMR-d. Among them, there were 3 cases of single MMR protein deletion, 3 cases of MSH6 deletion, 21 cases of double MMR protein deletion, including 15 cases of PMS2 and MLH1 deletion and 6 cases of MSH6 and MSH2 deletion. In this group, there were 5 patients with MMR-d combined with abnormal expression of p53, that is, cases with bimolecular characteristics, 2 cases revealed MLH1 and PMS2 protein deletion and p53 overexpression, 1 case revealed MSH2 and MSH6 protein deletion and p53 overexpression, 1 case revealed MSH6 protein deletion and p53 subclonal mutation, and 1 case revealed MSH6 protein deletion and p53 overexpression. These 5 patients were classified into MMR-d type based on the molecular typing detection process. Endometrial carcinoma was found in 20 (83.33%) of the 24 patients in this group and the remaining 4 (16.67%) had non-endometrial carcinoma. There were 18 cases in FIGO stage I (75.00%), 3 cases in FIGO stage II (12.50%), 2 cases in FIGO stage III (8.33%), and 1 case in FIGO stage IV (4.17%). The G1, G2, and G3 histological grades involved 2 cases (9.09%), 16 cases (72.73%), and 4 cases (18.18%), respectively. There were 8 cases (33.33%) of deep muscle invasion, 7 cases (29.17%) of lymphatic vascular invasion, and no cases of lymph node metastasis. In this group, 1 patient had Lynch syndrome-related endometrial cancer. The patient was found having sigmoid colon lesions during intraoperative exploration, and radical resection of sigmoid colon cancer was performed during the operation. Next generation sequencing (NSG) was conducted on the paraffin specimens of patients with poorly differentiated adenocarcinoma of the sigmoid colon confirmed by postoperative pathology. The results suggested that MLH1 may cause germline gene mutation, so it was diagnosed as Lynch syndrome.

Twenty out of the 86 patients had abnormal p53 protein expression, and 1 case had a POLE gene mutation, which was classified as a POLE gene mutation type. The remaining 5 cases involved MMR protein deletion. Based on the recommended

molecular typing detection path, these 5 cases were classified as MMR-d type. There were 14 cases of p53abn type, including 11 cases of p53 abnormal nuclear overexpression, 1 case of p53 abnormal complete deletion expression, 2 cases of p53 subclonal expression, 1 case of p53 wild-type expression combined with p53 nuclear overexpression, and 1 case of p53 nuclear overexpression combined with p53 cytoplasmic abnormal expression. In this molecular subtype, there were 11 cases (78.57%) of FIGO stage I, 1 case (7.14%) of FIGO stage II, and 2 cases (14.29%) stage III. There were 5 cases (35.71%) of non-endometrial carcinoma, 6 cases (46.15%) of grade G3 endometrial carcinoma, 3 cases (21.43%) of lymphatic vascular invasion, and 1 case of lymph node metastasis, which included pelvic lymph node combined with para-aortic lymph node metastasis.

There was no spot mutation in the POLE gene of 42 patients, and the expression of the four MMR proteins was complete. Immunohistochemical staining revealed that the p53 protein was wild-type expression and was classified as NSMP type. In this classification, there were 39 cases (92.56%) in FIGO I stage, 1 case (2.38%) in FIGO II stage and 2 cases (4.76%) in FIGO stage III. NSMP type accounted for the highest proportion of all endometrial cancer (48.83%). The age distribution span of patients was the largest. The histopathological types involved endometrial carcinoma, carcinosarcoma and mixed carcinoma. In this group, 40 cases (95.24%) were graded as G1-2, 8 cases (19.05%) were accompanied by deep myometrial invasion, 4 cases (9.52%) were LVSI positive, and no lymph node metastasis was observed.

## Correlation Analysis of SUV Max and ADC Min Values of Integrated PET/MRI to Evaluate the Risk Stratification of Early (FIGO I-II) Endometrial Cancer

The 2022 ESGO guideline integrates pathological factors (pathological type, tumor grade, stage, myometrial invasion, lymphovascular invasion) and molecular subtypes and redefines the prognostic risk level of EC.<sup>13</sup> The changes in risk stratification reflected in molecular typing were POLE mut and p53abn. The FIGO stage I–II POLE mut type was downgraded to the low-risk group, and the stage III POLE super mutant type was also categorized as low-risk group; however, additional treatment safety data are required. The high-risk group was expanded to include patients with stage I p53abn endometrial carcinoma with myometrial invasion. Intraoperative sentinel lymph node biopsy is possible for patients in the low-to-moderate risk category. Systemic lymphadenectomy is not advised for the low-to-moderate risk group. A sentinel lymph node biopsy is not required for patients without myometrial invasion. Systematic lymphadenectomy and sentinel lymph node biopsy are alternative treatment options for patients in the medium-high/high risk category.<sup>14</sup>

In this study, 79 patients diagnosed with FIGO stage I–II were categorized based on the ESGO risk grouping included in the molecular typing, including 54 cases in the low/medium risk group and 25 cases in the medium-high/high risk group. The statistical results revealed that the average SUV max for the low/medium risk group was  $12.39 \pm 7.34$ , and the average SUV max in the medium-high/high risk group was  $19.87 \pm 10.51$ . The SUV max was significantly lower in the low/medium risk group than in the medium-high/high risk group, and the difference was statistically significant ( $P = 0.001$ ). The difference between mean ADC min value of  $582.58 \pm 207.19 \text{ mm}^2/\text{s}$  in the early low/medium risk group and mean ADC min value of  $578.15 \pm 195.62 \text{ mm}^2/\text{s}$  in the medium-high/high risk group was not statistically significant ( $P = 0.95$ ).

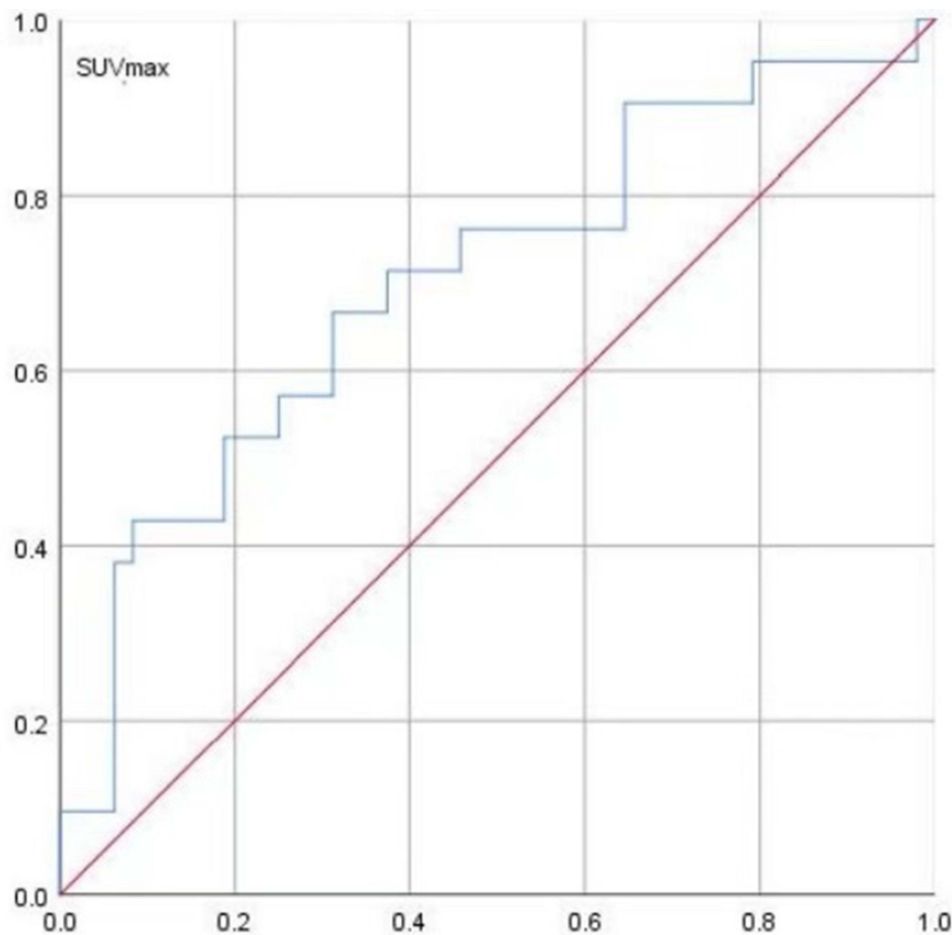
In conclusion, the results demonstrated that SUV max can be used to predict early endometrial cancer risk stratification (Table 2).

We used the area under the ROC curve (AUC) to evaluate the value of the integrated PET/MRI semi-quantitative index SUV max value in predicting the risk stratification of early endometrial cancer. An AUC value  $> 0.5$  has diagnostic value—the greater the AUC value, the higher the diagnostic accuracy. The AUC value of SUV max was 0.702, and the predictive value was higher (Figure 3).

**Table 2** Correlation Analysis of Semi-Quantitative Parameters of Integrated PET/MRI in Early Endometrial Cancer Risk Stratification

	Low/Medium Risk Group	Medium-High/High Risk Group	F	P
SUV max	12.39±7.34	19.87±10.51	13.251	0.001
ADC min	582.58±207.19	578.15±195.62	0.004	0.95

**Abbreviations:** SUV, standard uptake value; ADC, apparent diffusion coefficient.



**Figure 3** The value of SUVmax in predicting the risk stratification of early endometrial cancer.

The statistical results revealed the SUV max cut-off value for predicting the risk of early endometrial cancer was 14.72 (sensitivity 66.7%, specificity 68.7%, Youden's index 0.354), that is, SUV max > 14.72 can be predicted as medium-high/high risk group, while SUV max < 14.725 can be predicted as low/medium risk group. In clinical practice, the SUV max cut-off value can be used to predict the risk stratification of patients with early endometrial cancer prior to endometrial cancer surgery, to guide the selection of surgical methods.

## Discussion

Endometrial cancer is a tumor with strong heterogeneous pathological and molecular characteristics. With the limitations of standard clinical classification and histological diagnosis, it is anticipated that the proposed molecular classification can more accurately reflect the molecular biological behavior of tumors and result in a more refined clinical risk stratification. This suggests that clinicians should not only make a clear diagnosis of endometrial cancer, but also carry out risk stratification to guide individualized treatment.

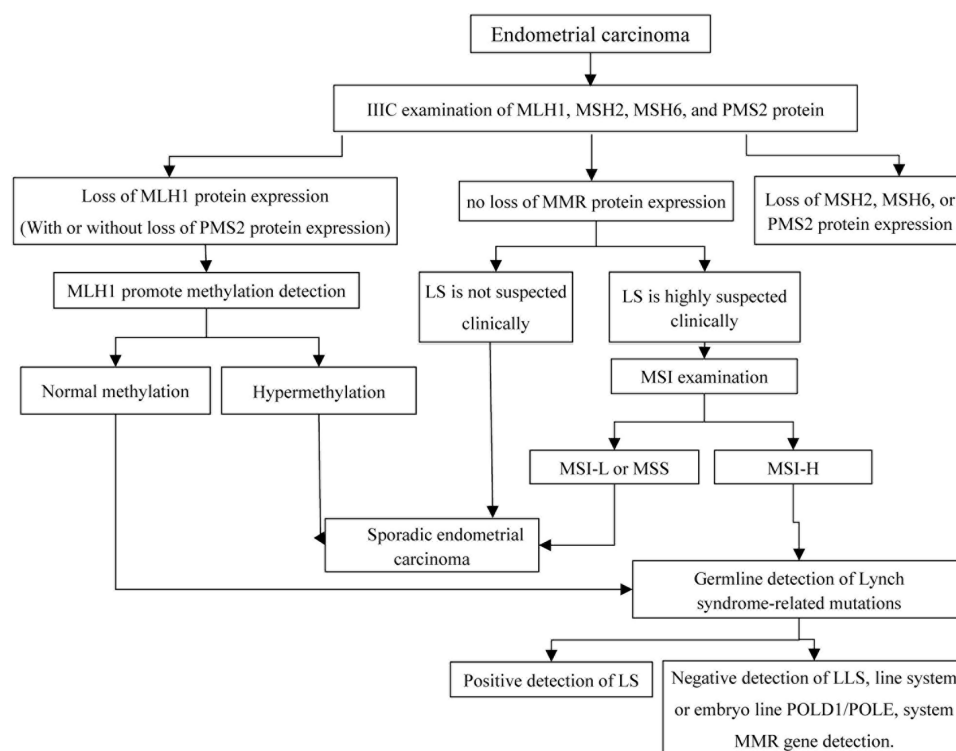
Currently, experts in China concur on molecular typing detection for all patients diagnosed with endometrial cancer. POLE mutant type has the best prognosis, most of which are endometrial carcinoma. The patients are relatively young, and the majority have FIGO stage I. Although the tumor grade is mostly G2–G3, the prognosis is favorable and the recurrence rate is low.<sup>15</sup> It is estimated that between 6–8% of all patients with endometrial cancer have a POLE mutation.<sup>16</sup> In this study, there were 6 patients (6.98%) diagnosed with POLE mutation. All patients were in FIGO stage IA, and the tumor grades were G1–G2. One patient had lymphatic vascular invasion, but no lymph node metastasis or recurrence at the end of the follow-up period. Currently, the 2022 ESGO guidelines recommend that patients with



FIGO stage I–II POLE mutant endometrial cancer should be downgraded following adjuvant postoperative therapy.<sup>5</sup> Therefore, accurate identification of pathogenic mutations in the POLE gene is crucial for the classification of EC molecular typing. For patients diagnosed with POLE gene mutation, those with fertility requirements can consider preserving fertility.<sup>17</sup> If there is no myometrial invasion, there is no need for lymph node dissection. Although patients with stage III POLE mutations are divided into low-risk groups, additional safety information is required.

In this group, there were 24 cases (27.91%) of MMR-d subtype. Loss of MLH1 or MSH2 protein expression existed in pairs, that is, MLH1 combined with PMS2 loss or MSH2 combined with MSH6 loss. PMS2 and MSH6 can be removed independently.<sup>18</sup> MMR protein detection or MMR gene sequencing can aid in screening patients with Lynch syndrome, interpreting the prognosis of patients diagnosed with endometrial cancer, and directing follow-up treatment. In this study, one patient was found to have a sigmoid colon space-occupying lesion by preoperative integrated PET/MRI evaluation. The sigmoid colon lesion was evaluated during the surgery, and the surgical procedure was performed concurrently. Postoperative pathology confirmed that the resected specimen was a poorly differentiated adenocarcinoma of the sigmoid colon. Immunohistochemical staining revealed that MLH1 was combined with PMS2 protein deletion, and additional NGS testing confirmed MLH1 germline gene mutation. (Figure 4)

Among the four molecular subtypes, the P53 mutant is the most heterogeneous. Most p53abn endometrial carcinomas are serous and high-grade endometrial carcinomas, but they also include other histological types and low-grade tumors, and have the worst clinical outcomes. Although p53abn endometrial carcinomas account for only 15% of all endometrial cancer cases, they account for 50–70% of the mortality rate in patients with endometrial cancer.<sup>19</sup> Different molecular types have vastly different prognoses and treatments, so it is crucial to correctly identify patients with p53 mutations. There were 13 patients with p53 mutations in this study. Compared to the other three groups, the proportion of non-endometrial carcinoma, tumor grade G3, and the lymph node metastasis rate were higher. Among the 20 patients diagnosed with abnormal p53 expression in our study group, 1 patient was found to have POLE gene mutation (POLEmut-p53ab), and 5 patients were found to have MMR protein deletion (MMRd-p53abn), that is, bimolecular characteristic. León-Castillo et al confirmed that the manifestations of MMRd-p53abn and POLEmut-p53abn endometrial



**Figure 4** Lynch syndrome screening process.

carcinoma were similar to those of MMRd and POLE mut endometrial carcinoma, through large-scale studies.<sup>20</sup> These results indicated that TP53 mutation was a late event in the progression of POLE mut and MMR-d tumors and does not affect clinical outcomes. This also highlighted the importance of interpreting p53 IHC results in MMR and POLE states.

Patients diagnosed with NSMP have no specific molecular markers and have a moderate prognosis, accounting for the largest proportion of the four molecular subtypes. In this study, 42 patients (48.83%) were included in the NSMP group, which had the largest age distribution and the most extensive histopathological types (including endometrial carcinoma, carcinosarcoma, and mixed carcinoma). Finding new classification indicators facilitates a more precise classification of NSMP subtypes in clinical practice. Currently, CTNNB1 gene exon 3 mutation has become a new prognostic marker in the NSMP subtype.

Although molecular typing is of great value in assessing the prognosis of patients with endometrial cancer, it cannot completely replace morphological evaluation and preoperative imaging examination. The 2022 ESGO guideline incorporates the prognostic grade of EC determined by molecular typing, and continues to account for tumor staging, myometrial invasion, and lymphatic vascular invasion. By conducting a preoperative curettage, tumor pathological types and molecular typing information can be obtained and preoperative staging can be performed using imaging examination. Integrated PET/MRI, a new imaging technology, is increasingly utilized in the clinical diagnosis and treatment of gynecological malignant tumors. The value of PET/MRI in preoperative staging, evaluation of myometrial invasion, cervical interstitial infiltration, lymph node metastasis and distant metastasis, as well as evaluation and prognosis of endometrial cancer has been gradually confirmed.<sup>21</sup> Integrated PET/MRI can not only achieve preoperative staging of endometrial cancer, but also provide metabolic information of tumors and detect early lesions in addition to ensuring precise anatomical localization, while conventional imaging examinations are mainly based on morphological change.<sup>22</sup> Therefore, it provides important reference data for clinicians to determine the extent of surgical resection, guide postoperative radiotherapy and chemotherapy, guide the formulation of radiotherapy scope, and assess the prognosis of patients.

PET/MRI and MRI were used to measure the maximum SUV and minimum ADC, respectively. SUV max and ADC min are considered to be related to the pathological type, tumor size, and prognosis of endometrial cancer. A 2014 meta-analysis of 771 patients by Ghooshkhaneh confirmed that the SUV max of patients with endometrial cancer with high-risk factors (ie, tissue grade G3, lymphatic vascular infiltration, cervical infiltration, and deep myometrial infiltration) were higher than that of patients without risk factors, and suggested that the SUV max of preoperative primary tumor lesions appeared to be an independent prognostic marker for recurrence and death.<sup>23</sup> Wang et al measured the ADC values in preoperative MRIs of EC lesions and discovered that the ADC value of the p53 mutation group was significantly higher than that of the non-p53 mutation group. When the cutoff value of ADC mean was  $820.6 \times 10^{-6} \text{ mm}^2/\text{s}$ , the AUC was 0.787, and the predictive value was moderate (accuracy 74.5%, sensitivity 53.8%, specificity 94.4%, positive predictive value 93.3%, negative predictive value 58.6%). The distinction between integrated PET/MRI semi-quantitative indicators for the four molecular subtypes of endometrial cancer has not been reported previously. In this study, the differences in SUV maximum and ADC minimum between the four subtypes of molecules were analyzed. SUV max of the p53abn mutation group was higher than that of the POLE mutation group ( $P < 0.05$ ), and ADC of the POLE mutation group and MMR-d group was lower than that of the NSMP group ( $P < 0.05$ ). This study further demonstrated the utility of integrated PET/MRI semi-quantitative indicators included in molecular typing, in predicting the risk grouping of ESGO endometrial cancer.

## Conclusion

The emergence of molecular typing facilitates a deeper comprehension of the heterogeneity of endometrial cancer, elucidates the difference in prognosis between the same clinical classification and the same histopathological type and is more objective and repetitive than the traditional classification. However, it is essential to evaluate histological risk factors (pathological type, histological grade, degree of myometrial invasion, lymphatic vascular invasion, etc.) and preoperative staging combined with imaging examination. As a new technology, integrated PET/MRI has many advantages in the diagnosis and treatment of malignant gynecological tumors, but more clinical data and further clarification of its indications are required to bring it more in line with the principles of health economics. In conclusion, the future of EC diagnosis and treatment lies in the use of integrated PET/MRI indicators in combination with clinicopathological features and molecular typing to stratify the risk of EC and guide the formulation of surgical and adjuvant treatment plans.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Xuanwu Hospital Capital Medical University ([2019]030). A written informed consent was obtained from all participants.

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## Disclosure

The authors report no conflicts of interest in this work.

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