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Original Article

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The relationship between histopathological data and molecular alterations with oncological outcomes in endometrioid-type endometrial cancers and a novel POLE mutation

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ABSTRACT

Objective: To identify molecular subgroups in endometrioid endometrial cancer (EEC), evaluate their association with clinicohistopathological characteristics, and define low-intermediate risk groups by integrating these parameters.
Methods: This retrospective-cohort study included 1,040 patients who underwent surgery between January 2000 and June 2022. Among 900 EEC cases, 72 recurred. Patients with tumor recurrence (n=62) and those without (n=52) were matched. POLE exons 9–14 were examined using Sanger sequencing. p53 and mismatch repair (MMR) protein expression were assessed via immunohistochemistry.
Results: The molecular subgroups were POLE mutation (POLE-mut) 5%, mismatch repair-deficient (MMR-d) 43%, p53 mutation (p53-mut) 5%, and non-specific molecular profile (NSMP) 42%. 5% of cases displayed multiple molecular mutations. POLE-mut were more prevalent in high-grade tumors (p=0.026). MMR-d tumors exhibited higher rates of lymphovascular space invasion and myometrial invasion ≥50% (p=0.032, p=0.020). No recurrences occurred in POLE-mut tumors (p=0.002), while MMR-d was significantly associated with recurrence (p=0.002). Median disease-free survival (DFS) for MMR-d, p53-mut, and NSMP were 34, 49, and 107 months, respectively. Median overall survival (OS) for these groups was 128, 102, and 181 months. Multivariate Cox-regression analysis employing the Backward-Stepwise method identified stage as the strongest predictor of DFS, and grade and stage as predictors of OS.
Conclusion: POLE mutations were linked to the most favorable molecular prognostic factor. NSMP cases showed the longest DFS and OS, while p53-mut had the shortest OS. Except for POLE, molecular features alone were insufficient for establishing risk groups, highlighting the continued importance of histopathology in EEC management.

Keywords: POLE; Endometrioid Type Endometrium Cancer; Molecular Classification; p53; MMR-d

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Synopsis
This study identified POLE mutations as the strongest prognostic factor in endometrioid endometrial cancer, with no recurrences observed. Other molecular traits were less definitive, reaffirming the critical role of tumor stage and grade in guiding clinical decisions.

INTRODUCTION

Endometrial cancer (EC) is the most prevalent malignancy among gynecological cancers [1]. Surgical intervention, including hysterectomy, bilateral salpingo-oophorectomy, and lymphatic assessment is the conventional treatment for EC. Following surgery, factors such as histological subtype, tumor grade, depth of myometrial invasion (MI), and lymphovascular space invasion (LVSI) status are considered in assessing tumor recurrence and survival outcomes. Consequently, low, intermediate, and high-risk groups have been delineated in terms of recurrence and prognosis for patients with EC, taking into account these histopathologic factors [2]. Patients are mostly assigned to adjuvant treatments based on risk groups that are primarily determined by employing these histopathological markers after hysterectomy. The long-running discussion has centered on the place of adjuvant therapy after surgery in the non-high-risk group, which makes up around 75% of EC cases.

Prognostic variables based on histopathology are acknowledged to be insufficient, particularly in low-intermediate risk groups, and may be inadequate in determining the prognosis of patients. This circumstance complicates the selection of patients who require additional treatment, sometimes leading to either under-treatment or overtreatment. Consequently, undertreated patients face an increased risk of disease recurrence, while over-treated individuals incur additional morbidity and costs.

Recent studies have demonstrated a link between the molecular features of EC and its prognosis [3]. Moreover, there have been some reports advocating for the utilization of molecular characteristics of tumor tissue in determining risk groups. Taking these findings into consideration, current and upcoming researches are investigating the efficacy of molecular characteristics in guiding adjuvant treatment planning. Current limited data indicate that employing histopathological and molecular characteristics to delineate new risk groups and reassess treatment options based on these categories is essential.

This retrospective cohort study evaluated the relationship between the clinico-histopathological characteristics of patients and the molecular profile of tumors, as well as the impact of the tumor's molecular profile on oncological outcomes in patients with endometrioid-type EC. Our objective is to elucidate the impact of molecular changes on the clinical management of patients.

MATERIALS AND METHODS

A retroprospective evaluation was conducted on 1,040 patients who underwent surgery and followed up at the Istanbul University Cerrahpasa–Cerrahpasa Faculty of Medicine, Department of Gynecologic Oncology between January 2000 and June 2022. Among them, 900 patients (86.5%) displayed endometrioid-type histology. Cases lacking regular follow-up

data for at least 6 months, non-endometrioid type EC cases, individuals who had previously received pelvic radiotherapy, those who underwent chemotherapy within 6 months before the operation, and cases with synchronous malignancies were excluded from the study. During the study, 828 endometrioid endometrial cancer (EEC) cases were found to be disease-free, whereas 72 instances had recurrences and these patients with recurrent disease were accepted as the study group.

Out of the 72 tumor tissue blocks from hysterectomy specimens in the recurrent group, 62 were accessible from the pathology archive. Individuals in the control group were selected proportionally to match the distribution of each target variable in the recurrence group. Random sampling was conducted among individuals without recurrence while adhering to the predefined proportions. To prevent the same individual from being selected multiple times, duplicate entries were removed. Considering the characteristics of patients with tumor recurrence, such as age, menopausal status, grade, stage, type of surgery, date of surgery, MI depth, and LVSI status, 150 of the 828 cases with EECs without recurrence were randomly chosen as control group and tumor tissue blocks of 52 patients were reached in this group. So, the results of 114 cases forming 62 patients with recurrent disease (study group) and 52 patients without recurrent disease (control group) were evaluated.

Two gyno-pathologists reassessed all tissue blocks of 114 cases, and they noted each result aligned with the original pathology report. After this evaluation, 3 sections were taken from each tumor tissue embedded in paraffin, one for hematoxylin-eosin staining and others for molecular profile assessment. The immunohistochemical staining method for p53 and mismatch repair (MMR) proteins (PMS2, MLH1, MSH2, MSH6), and the Sanger Sequencing method for the POLE gene were used for detection of tumor molecular profile status of patients. Details regarding molecular profile assessment methods are shown in the supplement.

All data were statistically evaluated using Excel (Microsoft, Redmond, WA, USA) and SPSS Version 26 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to look at the normal distribution of continuous variables. Continuous variables showing a normal distribution (e.g., age) were compared using the Student's t-test (independent sample t-test). For heterogeneous continuous variables, the Mann-Whitney U test was employed. The χ^2 test or Fisher's exact test was used to evaluate the association between clinicopathological traits and molecular alterations (categorical data).

Kaplan-Meier test was used to statistically evaluate the oncological outcomes (disease-specific survival, disease-free survival [DFS], and overall survival [OS]). Patients who survived until the last follow-up were indicated. Cox proportional hazard models were used to assess the prognostic value of each factor, using the backward stepwise method. All reported p-values are based on 2-tailed tests with $p<0.05$ considered statistically significant.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

1. Ethics approval

This study was reviewed and approved by the Ethics Committee of Istanbul University-Cerrahpasa (ethics approval number: E-83045809-604.01.02-22628).

RESULTS

The clinicopathological characteristics of all patients are presented in **Table 1**. In the study group, the mean age was 61.34, and a majority of the patients had tumors larger than 2 cm, similar to those in the control group. Within the study group, 53% of patients had MI ≥50% and 60% of patients had a positive LVSI. Nodal spread was noted in 7% of patients who did not recur and in 13% of patients who did ($p>0.05$). Rates of adjuvant treatments given to both groups were also similar. Briefly, there were no statistically significant differences in terms of clinicopathological characteristics among study and control groups.

Molecular profile status of patients was evaluated with Sanger sequencing and immunohistochemical methods. At immunohistochemical evaluation, the rate of p53 mutation (p53-mut), mismatch repair-deficient (MMR-d), and non-specific molecular profile (NSMP) were found as 10.5% (12/114), 47% (54/114), and 42% (48/114) in the whole group, respectively. More than one molecular subtypes (multiple classifiers) were detected in 6 (5%) cases.

Table 1. The clinicopathological characteristics of the cases

Feature	Study group (n=62)	Control group (n=52)	p-value
Mean age (yr)	61	61	0.719
Tumor size (cm)			0.105
<2	5 (8.1)	11 (21.2)	
≥2	57 (91.9)	41 (78.8)	
Grade			0.980
I	24 (38.7)	23 (44.2)	
II	30 (48.4)	18 (34.6)	
III	8 (12.9)	11 (21.2)	
LVSI			0.531
Yes	37 (59.7)	27 (51.9)	
No	25 (40.3)	25 (48.1)	
MI (%)			0.979
<50	29 (46.8)	24 (46.2)	
≥50	33 (53.2)	28 (53.8)	
Cervical involvement			0.033
Yes	12 (19.4)	3 (5.8)	
No	50 (80.6)	49 (94.2)	
Nodal spread			0.336
Yes	8 (12.9)	4 (7.7)	
No	54 (87.1)	48 (92.3)	
Type of nodal spread			
ITC	0	0	
Micrometastasis	0	1	
Macrometastasis	8	3	
Surgical technique			0.100
Open	53 (85.5)	39 (75.0)	
MIS	9 (14.5)	13 (25.0)	
Laparoscopic	4	13	
Robotic	5	0	
Lymphadenectomy			0.210
Yes	48 (77.4)	45 (86.5)	
No	14 (22.6)	7 (13.5)	
Adjuvant treatment			0.743
Yes	40 (64.5)	32 (61.5)	
No	22 (35.5)	20 (38.5)	

Values are presented as number (%) not otherwise specified.
ITC, invasive tumor cell; LVSI, lymphovascular space invasion; MI, myometrial invasion; MIS, minimal invasive surgery.
Underlined p-values indicate statistically significant differences ($p<0.05$) between study and control groups in the respective variables.

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After excluding patients with multiple mutations from the cohort, the number of patients with a single mutation was as follows: POLE in 5 individuals, MMR-d in 49 individuals, and p53-mut in 6 individuals.

Sanger sequencing identified 8 out of 114 (7%) cases with POLE-muts. Notably, all instances with POLE-muts were from the group that did not have tumor recurrence. These mutations include c.1231G>T (p.V411L), c.1382C>T (p.S461L), c.857C>G (p.P286R), c.1231G>T (p.V411L), and c.1331T>A (p.M444K). In one case, a novel mutation, not previously reported for EC, was detected. This mutation was observed in exon 14 of the POLE gene and is identified as c.1368_1370dup (p.T457dup) (**Fig. 1**).

Among the cases with tumor recurrence, 2 patients exhibited p53-muts and MMR-d together (p53-mut + MMR-d). In the cases without tumor recurrence, one showed p53-mut and MMR-d (p53-mut + MMR-d), another displayed p53-mut and POLE-mut (p53-mut + POLE-mut), and 2 cases were characterized by p53 presence, POLE-mut, and MMR-d (p53 + POLE-mut + MMR-d). Based on literature data, these patients with multiple molecular profiles were regrouped under a single mutation assuming that they would behave similarly to mutations associated with better prognosis. Cases with p53-mut + MMR-d were counted as MMR-d, excluding them from the p53 group. Cases showing p53-mut+POLE-mut were counted as POLE-mut and cases with p53+POLE-mut+MMR-d were also counted as POLE-mut and the relationship between clinicopathologic characteristics-oncologic results and molecular profile status was evaluated based on this rearranged groups.

The relationship between molecular profile status and clinicopathologic characteristics of patients is presented in **Table 2**.

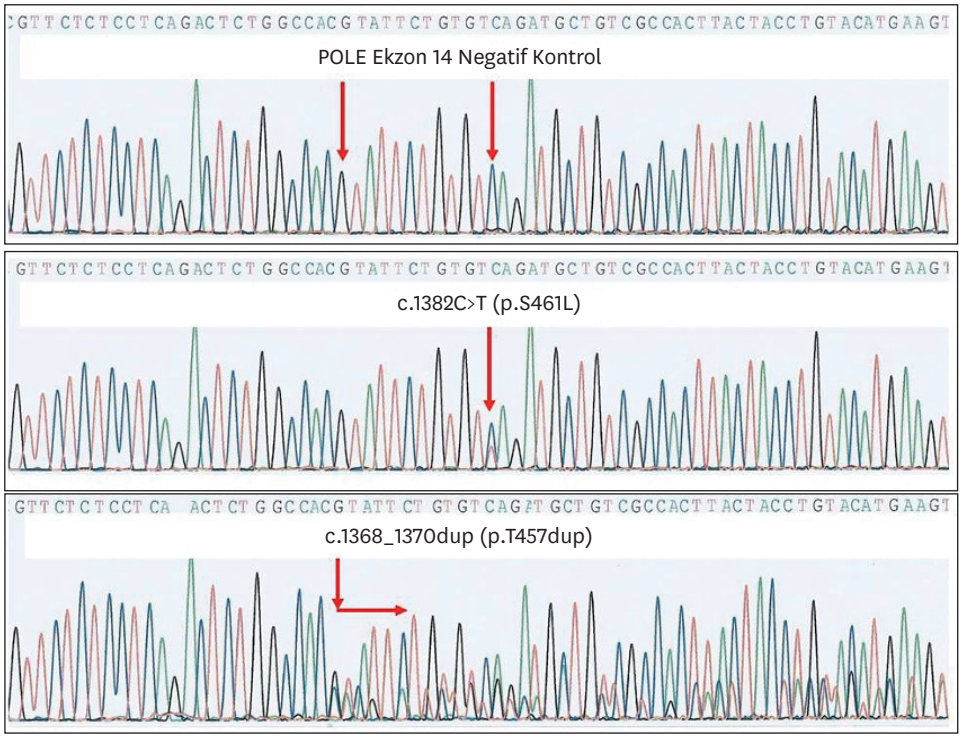

Fig. 1. Sanger sequencing for POLE gene exon 14; negative control and a novel POLE mutation for endometrial cancer.

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Table 2. The effect of clinicopathological characteristics of patients on molecular profile status

Characteristics	POLE		p53		MMR status		NSMP	
	POLE-mut	POLEwild	p53-mut	p53wild	MMR-d	MMR-p	NSMP	Non-NSMP
Age (yr)								
≤60	3	50	4	49	23	30	23	30
>60	5	56	2	59	29	32	25	36
p-value	0.720		0.414		0.708		0.795	
Tumor size (cm)								
<2	1	15	1	15	3	13	10	6
≥2	7	91	5	93	46	52	39	59
p-value	1.000		0.567		0.062		0.081	
Grade								
I + II	4	91	4	91	43	52	44	51
III	4	15	2	17	9	10	4	15
p-value	0.026		0.261		0.866		0.042	
LVSI								
Yes	4	45	3	46	28	28	14	35
No	4	61	3	62	24	41	34	31
p-value	0.723		1.000		0.032		0.011	
MI (%)								
<50	4	49	3	50	18	35	28	25
≥50	4	57	3	58	34	27	20	41
p-value	1.000		1.000		0.020		0.031	
Stage								
I + II	7	87	6	88	40	54	41	53
III + IV	1	19	0	20	12	8	7	13
p-value	1.000		0.588		0.155		0.478	
Nodal spread								
Yes	1	11	0	12	7	5	4	8
No	7	93	6	96	45	57	44	58
p-value	1.000		1.000		0.376		0.759	

Cases exhibiting multiple molecular mutations were categorized into a single molecular subgroup, based on the assumption that they would act in a manner similar to mutations associated with a more favorable prognosis.
LVSI, lymphovascular space invasion; MI, myometrial invasion; MMR, mismatch repair; MMR-d, mismatch repair-deficient; MMR-p, mismatch repair-proficient; NSMP, non-specific molecular profile; p53-mut, p53 mutation; p53wild, p53 wild-type; POLE-mut, POLE mutation; SD, standard deviation.
Underlined p-values indicate statistically significant differences ($p<0.05$) between study and control groups in the respective variables.

No significant correlation was found between age and molecular profile distributions. POLE-muts were more frequently observed in higher-grade tumors (p=0.026). MMR-d was detected mostly in tumors larger than 2 cm but this relation is insignificant (p=0.261). A markedly elevated incidence of MMR-d tumors was noted in instances with positive LVSI and with ≥50% MI (p=0.032 and p=0.020, respectively). No correlation was observed between p53 status and the tumor's stage or grade. Molecular alterations demonstrated no significant impact on stage and nodal spread.

Molecular profile status was compared in recurrent and non-recurrent patients (**Table 3**). POLE-muts were seen solely in cases without tumor recurrence (p=0.02). On the other hand, those with MMR-d had a higher frequency of tumor recurrences (p=0.02). In contrast, no significant correlation was found between NSMP/p53 status and tumor recurrence.

Among the 12 patients showing p53-muts, 6 of them concurrently exhibit one or 2 additional molecular profiles. To further evaluate the relationship between molecular subtypes and tumor recurrence, these cases, showing multiple molecular profiles from each group, were excluded from the cohort, and statistical analysis was repeated. Similarly, a higher incidence of recurrences in MMR-d instances was shown to be significant (p=0.011), as the absence of tumor recurrence in patients with POLE-muts (p=0.015). Once more, there was no

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Table 3. Molecular profile distributions in the study and control group

Molecular profile	Study group (n=62)	Control group (n=52)	p-value
POLE			0.002
POLE-mut	0 (0.0)	8 (15.4)	
POLEwild	62 (100.0)	44 (84.6)	
MMR			0.002
MMR-d	36 (58.1)	16 (30.8)	
MMR-p	26 (41.9)	36 (69.2)	
p53			0.684
p53-mut	4 (6.5)	2 (3.8)	
p53wild	58 (93.5)	50 (96.2)	
NSMP			0.075
Yes	22 (35.5)	26 (50.0)	
No	40 (64.5)	26 (50.0)	

Values are presented as number (%). Cases exhibiting multiple molecular mutations were categorized into a single molecular subgroup, based on the assumption that they would act in a manner similar to mutations associated with a more favorable prognosis.
MMR, mismatch repair; MMR-d, mismatch repair-deficient; MMR-p, mismatch repair-proficient; NSMP, non-specific molecular profile; p53-mut, p53 mutation; POLE-mut, POLE mutation.

discernible link (p-values=0.691 and 0.082, respectively) between tumor recurrence and instances exhibiting p53-muts or NSMP.

Additionally, our study examined the relationship between the site of the first recurrence and the molecular profile. When cases were categorized into 2 groups based on pelvic and extrapelvic recurrences, no significant association was identified between either recurrence group and any molecular profile.

This study examined the correlation between molecular profile status and oncological outcomes. The median follow-up duration in our research was 65 months. The cohort had a median DFS of 47 months. Upon stratification by molecular distribution, this duration was 34 months for MMR-d, 49 months for p53-mut, and 107 months for NSMP. None of the cases with POLE-mut experienced tumor recurrence. When comparing DFS durations based on molecular profile, a statistically significant difference was found (p=0.002) (**Fig. 2**).

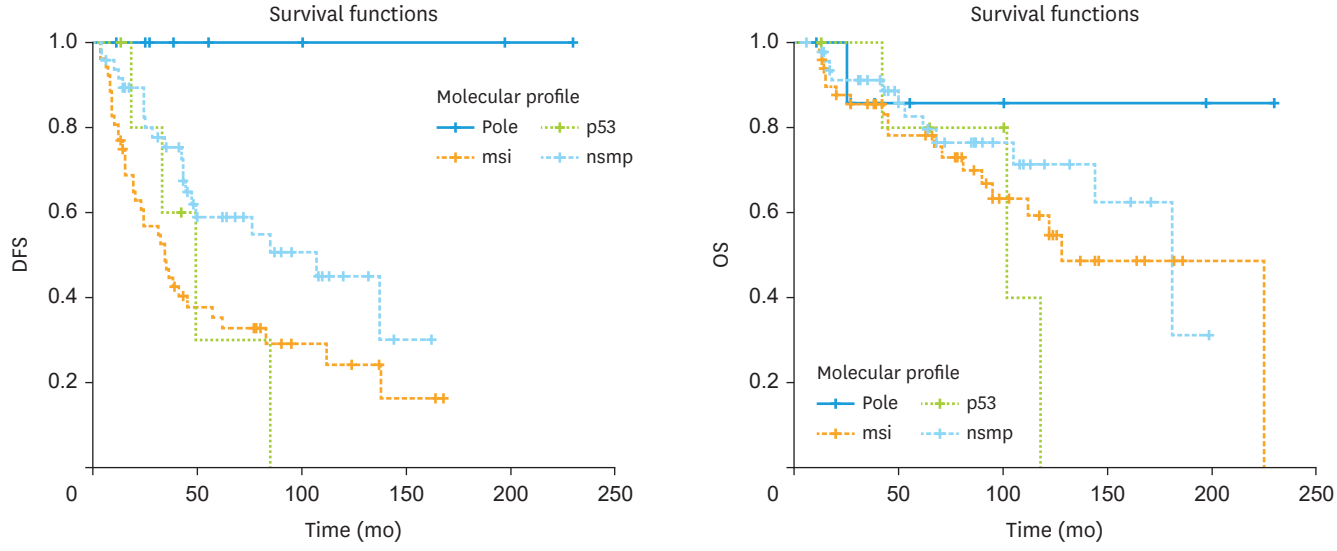

Fig. 2. Relationship between molecular profile distribution and DFS, relationship between molecular profile distribution and OS.
DFS, disease-free survival; OS, overall survival.

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Upon excluding the POLE group and reassessing the impact of the other 3 groups on DFS, it was similarly observed that the difference was significant, with the best outcome observed in the NSMP group.

The relationship between molecular profiles and OS is depicted in **Fig. 2**. The longest OS was observed in the group exhibiting POLE-muts (mean: 200 months; median survival not calculated due to only one death case). Conversely, the shortest median survival was observed in cases with p53-muts (mean: 96 months, median: 102 months). Following this group, in ascending order, were cases with MMR-d (median: 128 months) and cases classified as NSMP (median: 181 months). In conclusion, it was found that the NSMP group had the longest median OS. However, 5-year OS rates were found to be 80%, 50%, 44%, and 66% for POLE-mut, p53, MMR-d, and NSMP, respectively (p>0.05).

Finally, the predictive impact of clinicopathological traits and molecular profiles on oncological outcomes was investigated in multivariate Cox analysis with the backward stepwise method. The variables that are included in the multivariate analysis were age (≤60, >60), LVSI status (present/absent), Grade, MI status (<50%, ≥50%), Stage (I + II, III + IV), POLE-mut (present/absent), p53-mut (present/absent), MMR status (deficient/proficient), NSMP (present/absent). The overall significance of the Cox analysis was determined to be p=0.002. Initially, the association of these variables with tumor recurrence was examined, and Cox regression analysis was performed based on DFS. In the analysis, stage of the tumor was shown to be the most significant variable (p=0.012) (odds ratio [OR]=1.488).

Thereafter, Cox regression analysis was used to investigate the connection between the same factors and OS. The backward stepwise approach study revealed that grade and stage were the most significant predictive parameters (p=0.010, p=0.001) (OR=1,686; OR=1.867).

DISCUSSION

The identification of 4 distinct molecular characteristics independent of histopathological features in EC has sparked discussions regarding the distribution and prognostic implications of these molecular traits in the disease. Considering the practical challenges associated with the techniques employed for molecular assessment in the The Cancer Genome Atlas (TCGA) project, the ProMisE (Vancouver) research group in 2015 and the TransPORTEC (Leiden) research group in 2016 published findings suggesting that ECs could be categorized into 4 groups with minor distinctions [4,5]. In these classifications, molecular evaluations were conducted using immunohistochemistry and Sanger sequencing techniques, as in our study.

A systematic review published by Jumaah et al. [6] in 2020 investigated the frequency of the POLE gene and its prognostic value in EC. The authors evaluated 25 studies, noting that, similar to our research, Sanger sequencing was utilized to detect tumor mutations in the exonuclease domains of exons 9–14 of the POLE gene in most of these studies. This meta-analysis reported that 8.5% of ECs harbor POLE-muts. The majority of POLE-mut tumors exhibited endometrioid histology and were identified at early stages. Paradoxically, the same study indicated that POLE-mut tumors were more frequently found in grade 3 tumors (51.5%) and they presented with reduced MI (OR=1.48, 95% confidence interval [CI]=0.99–2.20). In our study, POLE-muts were statistically significantly found in high-grade

tumors. Additionally, POLE-mut tumors were observed to be at earlier stages (stages 1–2) in 87.5% of cases, however, this finding is also consistent with tumors lacking POLE-muts. Conversely, our analysis revealed that MI depth and LVSI positivity did not have a statistically significant impact on POLE-mut status. In another study, analyzing 599 EC cases, 38 cases (6.3%) were found to have POLE-muts, with a higher prevalence noted in International Federation of Gynecology and Obstetrics (FIGO) stage I tumors (86%) and grade III tumors (57.9%) [7]. Similar to our research, this study also found no statistically significant relationship between stage and the distribution of POLE-muts. Some studies have reported that POLE-muts are more frequently observed in younger age groups [8]. However, in our research, no significant correlation was found between POLE-mut status and age.

The prevalence of MMR-d in ECs ranges from 30%–40% in the literature [3,9-13]. Our study found a higher rate compared to previous studies, possibly due to differences in case selection, as some studies included non-endometrioid cancers and variations in methodology. In the study by Kim et al. [14] involving 492 cases of EEC, MMR-d was detected in 144 tumors (29%). The majority of MMR-d cases (76%) consisted of tumors with MLH-1/PMS-2 loss, as observed in our study as well. In the same study, it was found that MMR-d tumors had a higher incidence of being high-grade and LVSI positivity. According to the NRG Oncology/Gynecologic Oncology Group (GOG) study, higher tumor grade and the presence of LVSI were associated with both epigenetic MMR defects and potential MMR mutations [15]. Our study found a statistically significant higher rate of LVSI positivity in MMR-d tumors, consistent with existing literature. We divided patients into 2 groups based on tumor grade: grade I + II (low) and grade III (high), with grade III considered aggressive. In this study, MMR-d positivity in our study was more prevalent in low-grade tumors (grade I: 33%, grade II: 50%, grade III: 17%), however, this finding is not statistically significant.

In numerous studies, the presence of p53-muts in non-endometrioid type ECs and high-grade ovarian cancers has been found at significantly high rates [3,16,17]. From another perspective, the presence of p53-mut in a tumor could be considered a marker of poor prognostic characteristics. The rate of p53-muts in EECs varies across studies. For example, in the TCGA cohort, 26% of EC cases were classified in the copy number high group and most of these tumors were found to be associated with p53-muts [3]. Another large-sample study, conducted with 452 patients, identified p53-muts in 12.2% of cases [4]. In other studies, the rate of p53-muts has been observed in the range between 8%–26% [18,19]. In our study, pure p53-muts were detected in 5% (10.5% if included patients with multiple classifiers) of the EEC cases. These differences in p53-mut rates across studies may be due to varying patient selection criteria, such as including only high-risk patients, all endometrial histologies, or, as in our study, exclusively EECs.

In the literature, p53-mutated tumors are more frequently observed in older patients and are associated with high-grade and aggressive histopathological parameters (e.g., diffuse LVSI, lymph node metastasis, advanced stage) [20]. For instance, in a study published by Talhouk et al. [21] in 2017, the average age of patients with p53-mutated tumors was 71, and it was found that these tumors were significantly more common in older patients. The same study reported that p53-muts were more prevalent in grade 3 tumors (96.5%), tumors with LVSI positivity (61.3%), lymph node metastasis (14.5%), and advanced-stage tumors (stage 2–4: 55.8%). In our investigation, we discovered that p53-muts were less common in high-grade (grade III) tumors than in low-grade (grades I–II) tumors. p53-muts were more prevalent in patients aged <60, but not statistically significant. Also, all p53-mut

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cases in our cohort were detected at stages I–II. We were unable to identify a statistically significant correlation between clinicopathologic features and p53 status, which contradicts existing literature. Different patient selection criteria may explain this discrepancy. Many investigations covered all endometrial histologies with over 20% of individuals having non-endometrioid malignancies. Our study included almost 80% of low-risk individuals with grade I–II and stage I–II cancers.

In our study, the NSMP group (42% of all cases), predominantly consisted of low-grade (92%), early-stage (85%), and without nodal involvement (92%) tumors. Additionally, NSMP cases showed low MI depth and LVSI-negativity ($p<0.05$). Similarly, the vast majority of cases in the NSMP group had grade I + II tumors ($p=0.073$). According to TCGA, cases with low copy number and low mutation burden, not exhibiting other molecular profiles, comprise 39% of EC cases [3]. The ProMisE validation study reported that this group constituted 50.4% of all cases [4]. In a study published by the NRG Oncology/GOG group in 2018, which included 982 patients, 49% of cases were classified as NSMP [22]. These rates are consistent with our findings. The number of studies in the literature investigating the relationship between clinicopathological data and NSMP status is limited. Further research is needed to delineate this group of patients.

The primary objective of classifying EC based on molecular profiles is to determine the prognostic significance of these parameters and assess their impact on oncological outcomes. According to the Vancouver cohorts, the PORTEC-1 and 2 subgroups, TCGA, Ohio, Calgary, Singapore, and the combined PORTEC-NGO results, patients with POLE-muts represent the group with the best prognosis [3,8,23-26]. Although POLE-mut tumors are often classified as grade 3 in some studies, including our own, survival analyses emphasize that these tumors are associated with better oncological outcomes [6]. Another study published by Bosse et al. [27], which included 381 EC cases, found that POLE-mut cases had significantly better DFS (hazard ratio [HR]=0.23, $p=0.017$), followed by MMR-d cases (HR=0.61, $p=0.052$) and NSMP cases (HR=1), respectively. In contrast, p53-mutant tumors were associated with the worst DFS (HR=1.92, $p=0.007$). The TransPORTEC data demonstrated that the DFS curves for the MSI and POLE-mut subgroups overlapped, while the p53-mut and NSMP subgroups showed similar, yet poorer, DFS outcomes [5]. In this study, the 5-year DFS rates were found to be 93% for POLE-mut, 95% for MSI, 52% for NSMP, and 42% for p53-mut. However, The TransPORTEC study also included the evaluation of non-endometrioid tumors. Siegenthaler et al. [28] reported in their study that overall, the median time to first recurrence was 16 months (95% CI-12–20); with the shortest median time in MMR-d patients, with 13 months (95% CI-5–21), followed by p53abn (14 months, 95% CI-10–18), NSMP (16 months, 95% CI-12–20), and POLE-mut (25 months, 95% CI-6–84), with no significant differences ($p=0.224$). In another study, Ruscelli et al. [20] evaluated 219 EC cases and found that POLE-mut tumors exhibited no recurrence, indicating an excellent prognosis, while MMR-d and NSMP tumors had intermediate prognoses, and p53-mut tumors had the worst prognosis.

In our investigation, which exclusively involved EEC, in POLE-mut patients recurrence was not observed, throughout a median follow-up duration of 65 months, consistent with several studies. The NSMP group had a statistically significant enhancement in median DFS (107 months) relative to the p53-mut group (49 months) and the MMR-d group (34 months). The median OS duration was also the longest in NSMP at 181 months, followed by MMR-d at 128 months and p53 at 102 months.

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It has long been known that the main prognostic factors in EC are the histopathological characteristics of tumor tissue. Therefore, we evaluated the prognostic effects of molecular profile status alongside histopathologic characteristics using multivariate Cox analysis with the backward stepwise method. In our analysis, stage was found to be the most significant prognostic factor for tumor recurrence. A similar analysis for OS revealed that grade and stage were the most significant predictive factors for OS. Cox analysis showed no molecular profile status had a significant effect on DFS or OS.

However, the primary common characteristic of the studies, including our own, is that the presence of POLE-muts significantly improves prognosis. Excluding the p53-mut, the impact of MMR-d and NSMP on the prognosis of EC varies between research.

Many of these studies show that the p53-mut negatively affects prognosis when compared to other molecular variables. However, it is important to acknowledge that, although limited, there are discrepancies in the findings regarding the role of p53 across the literature. With the release of studies indicating the predictive value of molecular profile distribution in EC, there is a growing consensus, particularly regarding POLE status, that molecular characteristics should be used to define risk groups. A guideline published in 2021 by European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/ European Society of Pathology recommended the incorporation of molecular profiles including POLE, MMR-d, and p53 status in the classification of EC risk groups [29]. According to this guideline, the presence of POLE-muts, in conjunction with histopathological data, is used to define low-risk cases, while cases with MMR-d and NSMP molecular characteristics predominantly fall into the intermediate-risk group and p53-mutant cases into the high-risk group. Lately, FIGO introduced a new staging system for EC particularly regarding the role of histopathological findings [30]. In this updated system, the importance of molecular profiling is noted only in the footnotes, with the recommendation of POLE-mut and p53-mut status could influence staging.

In cases of EC, the question of whether all mutations should be evaluated in each case remains a subject of debate. For example, in the Promise classification, the initial step involves assessing whether there is any loss of MMR proteins. Subsequently, in patients without such loss, POLE-muts were examined. However, drawing from studies that hypothesize that patients with MMR-d accompanied by POLE-mut may behave similarly to the POLE-mut group, we also included these patients in the better-prognosis POLE-mut group. This raises the question of whether it might be more clinically advantageous to first screen all patients for POLE-muts and then evaluate additional mutations sequentially, based on prognosis from favorable to poor.

The limitations of our study include the relatively small sample size and the extended study period. Despite the intended aim to include more instances, the difficulty in acquiring enough relevant tumor tissue blocks due to paraffin degradation is the main cause for these limits. Molecular analyses on tissue blocks preserved for many years may have brought some hurdles to the molecular profiling procedure. On the other hand, the strengths of the study are that all patients underwent surgery and were followed up at a single center, and a large number of recurrent EEC cases were included in the analysis. Only including endometrioid-type tumors is another strength of this study. Furthermore, the control group was chosen based on histopathology data from the study group, assuring statistical matching between the 2 groups in terms of independent characteristics and thereby reducing bias. Finally,

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another strength of the study is the comprehensive evaluation of all molecular features in all instances, with no selection bias.

In conclusion, our study showed that POLE-mut was the most important prognostic factor among tumor molecular profiles, with none of the POLE-mut patients had tumor recurrence. NSMP patients had the longest median DFS and OS. In contrast, p53-mut patients had the lowest median OS. So, it cannot be conclusively stated that molecular characteristics, other than the presence of POLE-muts, are definitive for determining risk groups. Additionally, we found that stage and grade significantly affect the DFS and OS, compared to all other histopathological characteristics and molecular profiles of tumors.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. PUBMED | CROSSREF
2. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol 2016;27:16-41. PUBMED | CROSSREF
3. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73. PUBMED | CROSSREF
4. Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol 2018;29:1180-8. PUBMED | CROSSREF
5. Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol 2015;28:836-44. PUBMED | CROSSREF
6. Jumaah AS, Salim MM, Al-Haddad HS, McAllister KA, Yasseen AA. The frequency of POLE-mutation in endometrial carcinoma and prognostic implications: a systemic review and meta-analysis. J Pathol Transl Med 2020;54:471-9. PUBMED | CROSSREF
7. Imboden S, Nastic D, Ghaderi M, Rydberg F, Rau TT, Mueller MD, et al. Phenotype of POLE-mutated endometrial cancer. PLoS One 2019;14:e0214318. PUBMED | CROSSREF
8. Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, ter Haar N, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. J Natl Cancer Inst 2015;107:402. PUBMED | CROSSREF
9. Backes FJ, Leon ME, Ivanov I, Suarez A, Frankel WL, Hampel H, et al. Prospective evaluation of DNA mismatch repair protein expression in primary endometrial cancer. Gynecol Oncol 2009;114:486-90. PUBMED | CROSSREF
10. Goodfellow PJ, Billingsley CC, Lankes HA, Ali S, Cohn DE, Broaddus RJ, et al. Combined microsatellite instability, MLH1 methylation analysis, and immunohistochemistry for Lynch syndrome screening in endometrial cancers from GOG210: an NRG Oncology and Gynecologic Oncology Group Study. J Clin Oncol 2015;33:4301-8. PUBMED | CROSSREF
11. Zighelboim I, Goodfellow PJ, Gao F, Gibb RK, Powell MA, Rader JS, et al. Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. J Clin Oncol 2007;25:2042-8. PUBMED | CROSSREF
12. MacDonald ND, Salvesen HB, Ryan A, Iversen OE, Akslen LA, Jacobs IJ. Frequency and prognostic impact of microsatellite instability in a large population-based study of endometrial carcinomas. Cancer Res 2000;60:1750-2. PUBMED
13. Risinger JI, Berchuck A, Kohler MF, Watson P, Lynch HT, Boyd J. Genetic instability of microsatellites in endometrial carcinoma. Cancer Res 1993;53:5100-3. PUBMED
14. Kim SR, Tone A, Kim RH, Cesari M, Clarke BA, Eiriksson L, et al. Understanding the clinical implication of mismatch repair deficiency in endometrioid endometrial cancer through a prospective study. Gynecol Oncol 2021;161:221-7. PUBMED | CROSSREF

15. McMeekin DS, Tritchler DL, Cohn DE, Mutch DG, Lankes HA, Geller MA, et al. Clinicopathologic significance of mismatch repair defects in endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. J Clin Oncol 2016;34:3062-8. PUBMED | CROSSREF
16. Na K, Sung JY, Kim HS. TP53 mutation status of tubo-ovarian and peritoneal high-grade serous carcinoma with a wild-type p53 immunostaining pattern. Anticancer Res 2017;37:6697-703. PUBMED | CROSSREF
17. Momeni-Boroujeni A, Dahoud W, Vanderbilt CM, Chiang S, Murali R, Rios-Doria EV, et al. Clinicopathologic and genomic analysis of TP53-mutated endometrial carcinomas. Clin Cancer Res 2021;27:2613-23. PUBMED | CROSSREF
18. Imboden S, Nastic D, Ghaderi M, Rydberg F, Siegenthaler F, Mueller MD, et al. Implementation of the 2021 molecular ESGO/ESTRO/ESP risk groups in endometrial cancer. Gynecol Oncol 2021;162:394-400. PUBMED | CROSSREF
19. Devereaux KA, Weiel JJ, Pors J, Steiner DF, Ho C, Charu V, et al. Prospective molecular classification of endometrial carcinomas: institutional implementation, practice, and clinical experience. Mod Pathol 2022;35:688-96. PUBMED | CROSSREF
20. Ruscelli M, Maloberti T, Corradini AG, Rosini F, Querzoli G, Grillini M, et al. Prognostic impact of pathologic features in molecular subgroups of endometrial carcinoma. J Pers Med 2023;13:723. PUBMED | CROSSREF
21. Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. Cancer 2017;123:802-13. PUBMED | CROSSREF
22. Cosgrove CM, Tritchler DL, Cohn DE, Mutch DG, Rush CM, Lankes HA, et al. An NRG Oncology/GOG study of molecular classification for risk prediction in endometrioid endometrial cancer. Gynecol Oncol 2018;148:174-80. PUBMED | CROSSREF
23. Bellone S, Bignotti E, Lonardi S, Ferrari F, Centritto F, Masserdotti A, et al. Polymerase ε (POLE) ultra-mutation in uterine tumors correlates with T lymphocyte infiltration and increased resistance to platinum-based chemotherapy in vitro. Gynecol Oncol 2017;144:146-52. PUBMED | CROSSREF
24. Wong A, Kuick CH, Wong WL, Tham JM, Mansor S, Loh E, et al. Mutation spectrum of POLE and POLD1 mutations in South East Asian women presenting with grade 3 endometrioid endometrial carcinomas. Gynecol Oncol 2016;141:113-20. PUBMED | CROSSREF
25. Hussein YR, Weigelt B, Levine DA, Schoolmeester JK, Dao LN, Balzer BL, et al. Clinicopathological analysis of endometrial carcinomas harboring somatic POLE exonuclease domain mutations. Mod Pathol 2015;28:505-14. PUBMED | CROSSREF
26. Talhouk A, Hoang LN, McConechy MK, Nakonechny Q, Leo J, Cheng A, et al. Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: earlier prognostic information to guide treatment. Gynecol Oncol 2016;143:46-53. PUBMED | CROSSREF
27. Bosse T, Nout RA, McAlpine JN, McConechy MK, Britton H, Hussein YR, et al. Molecular classification of grade 3 endometrioid endometrial cancers identifies distinct prognostic subgroups. Am J Surg Pathol 2018;42:561-8. PUBMED | CROSSREF
28. Siegenthaler F, Lindemann K, Epstein E, Rau TT, Nastic D, Ghaderi M, et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification. Gynecol Oncol 2022;165:230-8. PUBMED | CROSSREF
29. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021;31:12-39. PUBMED | CROSSREF
30. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023;162:383-94. PUBMED | CROSSREF