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RESEARCH

Molecular classification and clinicopathological features of grade 3 endometrioid endometrial carcinoma

Grade 3 endometrioid tip endometrial karsinomun moleküler sınıflaması ve klinik-patolojik özellikleri

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Abstract

Purpose: This study investigates the molecular characteristics of grade 3 endometrioid endometrial carcinoma (EC) through immunohistochemical analysis of mismatch repair (MMR) proteins and p53, correlating molecular subtypes with clinicopathological features and survival outcomes.

Materials and Methods: We retrospectively analyzed 33 patients with surgically staged grade 3 endometrioid EC. Immunohistochemical analysis was performed to assess MMR protein (MLH1, MSH2, MSH6, PMS2) and p53 expression. Cases were classified into MMR-deficient (MMRd), p53 wild-type (p53wt), and p53 abnormal (p53abn) molecular subtypes. A comparative analysis was conducted on clinicopathological characteristics and survival outcomes across molecular subgroups.

Results: The molecular subtype distribution was: MMRd (36.4%), p53abn (15.2%), and p53wt (48.5%). Clinicopathological features, including age, stage, myometrial invasion, lymph node metastasis, and lymphovascular space invasion did not significantly differ across molecular subgroups. The p53abn group showed a non-significant trend toward reduced overall survival while disease-free survival was similar among the groups.

Conclusion: Routine IHC assessment is a practical approach to identify molecular subtypes, particularly MMRd tumors that may benefit from immunotherapy, and p53abn tumors that may warrant intensified treatment strategies.

Keywords: Endometrial carcinoma; molecular classification; immunohistochemistry.

Öz

Amaç: Bu çalışmada, mismatch repair (MMR) proteinleri ve p53'ün immünohistokimyasal analizi yoluyla grade 3 endometrioid endometrial karsinom (EC) moleküler özelliklerinin belirlenmesi, moleküler alt tiplerin klinik-patolojik özellikler ve sağkalım sonuçları ile ilişkilendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Cerrahi olarak evrelendirilmiş grade 3 endometrioid EC'li 33 hasta retrospektif olarak analiz edildi. MMR proteini (MLH1, MSH2, MSH6, PMS2) ve p53 ekspresyonunu değerlendirmek için immünohistokimyasal analiz yapıldı. Vakalar MMR eksikliği olan (MMRd), p53 wild tip (p53wt) ve p53 mutant (p53abn) moleküler alt tipler olarak sınıflandırıldı. Moleküler alt gruplar arasında klinik-patolojik özellikler ve sağ kalım sonuçları üzerine karşılaştırmalı bir analiz yapılmıştır.

Bulgular: Moleküler alt tip dağılımı şöyleydi: MMRd (%36.4), p53abn (%15.2) ve p53wt (%48.5). Yaş, evre, myometrial invazyon, lenf nodu metastazı ve lenfovasküler alan invazyonu gibi klinik-patolojik özellikler moleküler alt gruplar arasında anlamlı farklılık göstermedi. P53abn grubu genel sağkalımda azalma yönünde anlamlı olmayan bir eğilim gösterirken, hastalıksız sağkalım gruplar arasında benzerdi.

Sonuç: Rutin IHC değerlendirme, özellikle immünoterapiden fayda sağlayabilecek MMRd tümörleri ve yoğunlaştırılmış tedavi stratejileri gerektirebilecek p53abn tümörleri başta olmak üzere moleküler alt tipleri tanımlamak için pratik bir yaklaşımdır.

Anahtar kelimeler: Endometrial karsinom; moleküler sınıflama; immünohistokimya

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INTRODUCTION

Among gynecological malignancies in developed countries, endometrial carcinoma (EC) represents the most frequently diagnosed type, with worldwide prevalence showing an upward trajectory[1, 2]. Although most EC cases are diagnosed at early stages with favorable outcomes, a significant proportion, particularly those with grade 3 endometrioid histology, exhibit aggressive behavior associated with increased recurrence and mortality. According to the classification criteria established by the International Federation of Gynecology and Obstetrics (FIGO), tumors with solid growth patterns exceeding 50% of their volume are classified as Grade 3 endometrioid EC [3]. This histological grade has traditionally served as a key prognostic factor, guiding adjuvant treatment decisions. However, grade 3 endometrioid EC is a high risk and heterogeneous group, encompassing tumors with diverse molecular alterations and clinical behaviors. Histopathological grading alone is insufficient to fully characterize its biological diversity and predict prognosis. Recognizing the molecular characteristics of this group is also important in determining the treatment management.

Research conducted by The Cancer Genome Atlas (TCGA) consortium has transformed how we conceptualize EC biology, revealing four distinct molecular subtypes: DNA polimeraz epsilon (POLE) ultramutated, microsatellite instability-high (MSI-H)/mismatch repair deficient (MMRd), copy-number low (CNL)/p53 wild-type (p53wt), and copy-number high (CNH)/p53 abnormal (p53abn) each characterized by unique genomic landscapes, clinicopathological profiles, and prognostic trajectories [4]. Notably, the POLE ultramutated subtype, despite often presenting with high-grade histology, is associated with an exceptionally favorable prognosis, driven by mutations in the exonuclease domain of DNA polymerase epsilon. Conversely, the CNH/p53abn subtype, characterized by frequent TP53 mutations and extensive chromosomal instability, is consistently linked to the poorest clinical outcomes. The MMRd subtype, marked by deficient DNA mismatch repair mechanisms, exhibits an intermediate prognosis and is often associated with Lynch syndrome, a hereditary cancer predisposition. The CNL/p53wt subtype, also termed "no specific molecular profile" (NSMP), represents a large and biologically diverse group with intermediate prognostic features.

The clinical translation of molecular classification in EC has been greatly facilitated by the development of practical and cost-effective diagnostic tools, particularly immunohistochemistry (IHC) for MMR proteins and p53, and targeted sequencing assays for POLE mutations[5-7]. The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) algorithm, leveraging IHC and POLE sequencing, has emerged as a validated and widely adopted tool for refining risk stratification and informing adjuvant treatment strategies[8]. Recognizing the transformative potential of molecular classification, the 2023 FIGO staging system for endometrial cancer now incorporates molecular findings as integral components [9]. Numerous studies have robustly demonstrated the independent prognostic significance of molecular classification in EC, highlighting its superior predictive power beyond traditional clinicopathological factors, including stage, grade, and histology[10-12]. This situation is particularly important in the context of grade 3 EC, where histological grading alone may not adequately reflect the underlying biological heterogeneity and diverse clinical behaviors. For example, a subgroup of grade 3 endometrioid ECs harboring POLE mutations paradoxically exhibits a very favorable prognosis, while others characterized by p53abn exhibit aggressive behavior and poor outcomes independent of traditional clinicopathological risk factors. For this reason, the working group selected grade 3 endometrioid EC.

The present study evaluated the molecular profile of grade 3 EC using IHC for MMR proteins and p53, and correlated these molecular subtypes with clinicopathological features and survival outcomes in a single-institution cohort. This study will explore the utility of IHC-based molecular classification in refining risk stratification and potentially guiding treatment decisions in grade 3 endometrioid EC.

MATERIALS AND METHODS

Study design

Our retrospective analysis involved patients diagnosed with grade 3 endometrioid EC at Çukurova University Faculty of Medicine Department of Gynecologic Oncology and Medical Patology between 2010 and 2021. The study received

ethical approval by the faculty's Local Ethics Committee. This study adhered to the guidelines set forth by the Declaration of Helsinki. The Non-Interventional Clinical Research Ethics Committee at Cukurova University, Faculty of Medicine, granted approval (IRB number: 108, Date: February 12, 2021).

Sample and data collection

Patients were identified from the institutional pathology database. Inclusion criteria were histologically confirmed grade 3 endometrioid EC, surgical staging performed at the institution, complete clinical and follow-up data, and availability of sufficient tissue for IHC analysis. Patients were excluded if they had received neoadjuvant therapy, had synchronous primary malignancies, or had incomplete clinical data. During this period, 33 patients who met the inclusion and exclusion criteria were evaluated from among 80 patients diagnosed with grade 3 endometrioid adenocarcinoma.

Clinical and pathological data were extracted from medical records and pathology reports. The collected data included age, weight, body mass index (BMI), comorbid diseases (such as diabetes mellitus, hypertension, and others), menopausal status, parity, family history of cancer, FIGO stage (according to the 2009 FIGO staging system), lymphovascular space invasion (LVSI), myometrial invasion (MI, <50% or ≥50%), lymph node metastasis (LNM) and adjuvant therapy (chemotherapy, radiotherapy, or both). Overall survival (OS) measures time from diagnosis to death from any cause or the last follow-up, while disease-free survival (DFS) spans from diagnosis until recurrence or death, whichever occurs first.

IHC analysis

Archived pathology samples consisted of formalin-fixed, paraffin-embedded tissue (FFPE) blocks. We examined mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, PMS2) and p53 expression through immunohistochemical analysis of 4-µm tissue sections utilizing automated Ventana BenchMark XT technology (Ventana Medical Systems, Tucson, AZ) in accordance with manufacturer's recommendations. The prepared slides were stained using the iView Blue Detection Kit (Ventana) for p53 (Cellmarque, p53(D07) Mouse monoclonal antibody, Merck SA, Germany); MSH6 (Cellmarque, (44) Mouse monoclonal antibody, Merck SA, Germany); MSH2 (Cellmarque, (G219-1129) Mouse monoclonal antibody, Merck SA, Germany); MLH1 (Cellmarque, (G168-728) Mouse monoclonal antibody, Merck SA, Germany); and PMS 2 (GenomeMe, (IHK412) Mouse monoclonal antibody, BC, Canada) on a BenchMark XT (ISH protease 2, Ventana) automated staining device.

To evaluate MMR protein status, we determined whether tumor cell nuclei exhibited positive or negative immunoreactivity. Absence of any of the four MMR proteins indicated MMR deficiency (MMRd). The expression of intact MMR proteins was defined as nuclear staining in ≥1% of tumor cells. p53 expression was classified as follows: p53 wild-type (p53wt): Normal expression form, characterized by variable intensity of nuclear staining in tumor cells; p53 abnormal (p53abn): The presence of strong and diffuse nuclear staining in more than 80% of tumor cells is indicative of an overexpression pattern, while the complete absence of nuclear staining corresponds to a null pattern (Figure 1*)* [13].

Based on the IHC results, cases were classified into three molecular subgroups[14]:

1. MMRd: Loss of expression of one or more MMR proteins.
2. p53abn: Abnormal p53 expression (overexpression or null pattern).
3. p53wt: Normal expression of p53 and intact MMR protein expression. This group is equivalent to the NSMP group.

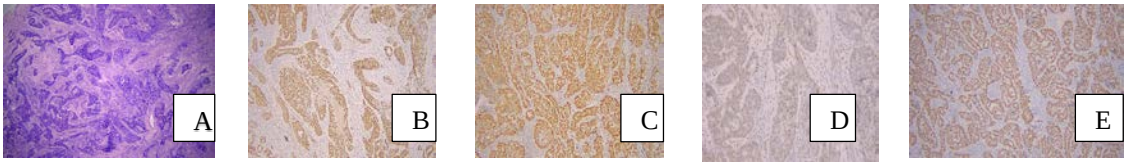

Figure 1. IHC staining samples of grade 3 endometrioid EC cases; A: Grade 3 endometrioid EC case (H&E x40), B: MSH2 intact in grade 3 EC case (IHCx100), C: MSH6 intact in grade 3 EC case (IHCx100), D: PMS2 intact in a grade 3 EC case (IHCx100), E: p53 abn in grade 3 EC case (IHCx100).

Statistical analysis

For the data analysis component of this research, we used IBM SPSS Statistics software (version 20.0, IBM Corporation, Armonk, New York). In our presentation of results, we expressed continuous data as either arithmetic means accompanied by standard deviations or as medians with their corresponding ranges, depending on data distribution characteristics. For categorical information, we summarized the data using numerical counts and corresponding percentage values as appropriate for the specific variable type.

When examining differences between the molecular subgroups, our analysis employed several statistical approaches. Categorical variable comparisons were conducted using either Chi-square testing or, when cell counts were insufficient, Fisher's exact test methodology. For the analysis of continuous variables, we selected either One-way Analysis of Variance (ANOVA) or the Kruskal-Wallis procedure, with the choice between these methods determined by whether the data satisfied normality distribution requirements. The assessment of Overall Survival (OS) and Disease-Free Survival (DFS) involved Kaplan-Meier survival curve estimation techniques. To determine whether statistically significant differences existed between the various subgroups in our survival analysis, we implemented the log-rank test. Throughout all analyses, we established statistical significance at the conventional threshold of $p<0.05$.

RESULTS

A total of 33 patients with grade 3 endometrioid EC met the inclusion criteria. Patients' mean age was 58.8 ± 9.0 years. One patient had previous breast cancer, and 17 patients (51%) had at least one systemic disease. 81.8% of our cases were post-menopausal.

Myometrial invasion (MI) exceeding 50% was observed in 79% of cases, while no MI was present in 2 cases (6.5%); no significant difference was observed between groups ($p = 0.548$). Similarly, lymphovascular invasion (LVAI) was positive in 27 cases (82%), with no significant intergroup difference ($p = 0.602$). Lymph node metastasis (LNM) was detected in 8 cases (24%), and no statistically significant difference was identified between the groups ($p = 0.920$). Nineteen of the cases were in

Table 1. Clinicoathological characteristics and comparison of the molecular subgroups.

Characteristic	Overall	MMRd (n=12)	p53abn (n=5)	p53wt (n=16)	p-value
Age (years)	58.8 ± 9.0	60.5 ± 10.3	59.2 ± 4.4	57.5 ± 9.3	0.707
Menopausal Status					0.155
Premenopausal	6 (18.2%)	1	0	5	
Postmenopausal	27 (81.8%)	11	5	11	
FIGO Stage					0.824
I	19 (57.6%)	7	3	9	
II	1 (3.0%)	1	0	0	
III	12 (36.4%)	4	2	6	
IV	1 (3.0%)	0	0	1	
Myometrial Invasion					0.548
<50%	5(16,1%)	2	0	3	
≥50%	26(79%)	10	4	12	
LVSI					0.602
Absent	6 (18.2%)	3	0	3	
Present	27 (81.8%)	9	5	13	
Lymph Node Metastasis					0.920
Absent	25 (75.8%)	9	4	12	
Present	8 (24.2%)	3	1	4	
Adjuvant Therapy					
Chemotherapy	18 (54,5)	4	3	11	0.802
Radiotherapy	22 (66,6)	6	5	11	0.391

FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymphovascular space invasion; MMRd: mismatch repair deficient; p53abn: p53 abnormal; p53wt: p53 wild-type.

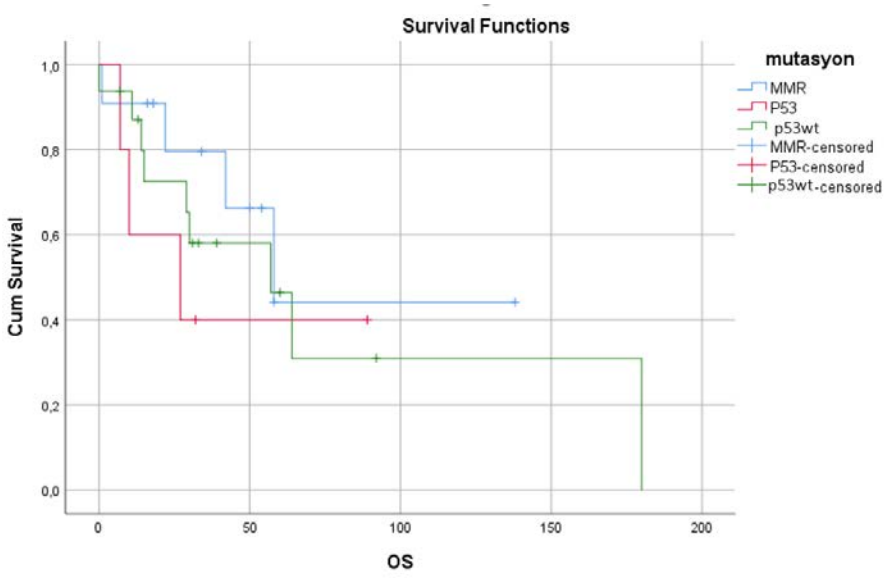

Figure 2. The Kaplan-Meier curves for overall survival (OS) according to molecular subgroup.

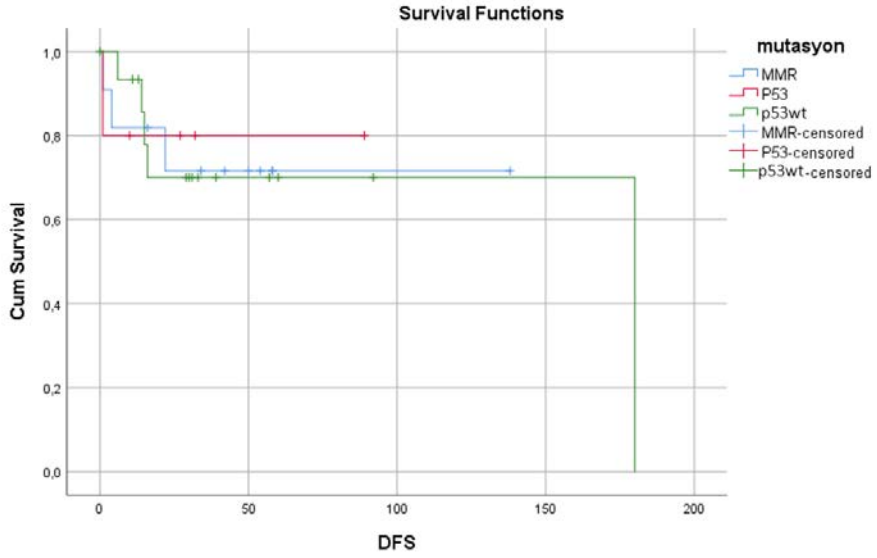

Figure 3. The Kaplan-Meier curves for (disease free survival) DFS according to molecular subgroup.

Stage I (57.6%), one in Stage II, 12 in Stage III (36.4%), and one in Stage IV (3%). The distribution of clinical stage did not differ significantly among the molecular subgroups (p = 0.824). In terms of adjuvant treatment, 18 (54.4%) of our patients received CT and 22 (66.6%) received RT. The groups did not differ significantly in the administration of adjuvant chemotherapy or chemoradiation (p = 0.802 and p = 0.391, respectively). Table 1 presents the

demographics and clinicopathological features of the patients according to their molecular subgroup.

Survival analysis revealed varying estimated overall survival durations across molecular subtypes, MMRd patients showed median OS of 58±15.2 months (95% CI=28.1-87.8), while p53abn cases demonstrated shorter survival at 27±18.6 months (95% CI=1-63), and p53wt individuals had median OS of 57±18.8 months (95% CI=20-93.3). Survival time did not differ significantly between the groups (p=0.383). The Kaplan-Meier curves for OS according to molecular subgroup are shown in Figure 2. Although there was a trend towards poorer OS in the p53abn group, the difference did not reach statistical significance. The Kaplan-Meier curves for DFS according to molecular subgroup are shown in Figure 3. DFS did not differ significantly among the molecular subgroups (p = 0.991).

DISCUSSION

This study investigated the molecular classification of grade 3 endometrioid EC using IHC for MMR proteins and p53, correlating these molecular subtypes with clinicopathological features and survival outcomes. Despite limitations in sample size and absent POLE sequencing, our findings confirm the molecular heterogeneity of grade 3 endometrioid EC while demonstrating both the potential and limitations of IHC-based classification for prognostication and treatment planning in this high-risk subgroup. Our patient population exhibited a molecular profile distribution of 36% MMRd, 15% p53abn, and 49% p53wt. While this generally corresponds with established literature, we observed a comparatively lower percentage of p53abn tumors, and an elevated proportion of p53wt cases relative to some published findings. The TCGA data, which primarily focused on endometrioid carcinomas, reported a p53abn frequency of approximately 26% in all grades and a higher frequency in high-grade serous carcinomas [4]. Subsequent studies utilizing IHC-based classification, such as the ProMisE project and its validation cohorts, have shown variable proportions of p53abn cases, ranging from 15% to 25% in unselected EC series [5-7]. The lower p53abn prevalence in our study could be attributed to several factors. First, our cohort included only grade 3 endometrioid tumors, while many other studies include all grades. Second, it is crucial to consider the absence of POLE sequencing. POLE-mutated tumors, despite often exhibiting high-grade histology, have an exceptionally favorable prognosis and typically show a wild-type p53 IHC pattern [15]. Without *POLE* testing, these cases are classified as p53wt/ NSMP, artificially inflating the size of this subgroup and potentially diluting the prognostic impact of the p53abn group. Third, interobserver variability in p53 IHC interpretation, despite consensus review, cannot be entirely excluded. Finally, genuine population differences in the prevalence of molecular subtypes may exist.

The lack of statistically significant differences in clinicopathological features between molecular subgroups in our study contrasts with some larger studies. While we observed trends consistent with the literature such as a higher proportion of advanced-stage disease and LNM in the p53abn group these were not statistically significant. In their extensive analysis of grade 3 endometrioid carcinomas, Bosse and colleagues[16] demonstrated significant correlations between p53abn molecular status and several clinicopathological parameters: advanced patient age, higher disease stage, non-endometrioid morphological features, and presence of lymphovascular invasion. Similarly, Kommoss et al. [7] reported associations between p53abn and advanced stage and higher grade in their validation cohort. Our limited sample size, particularly the small number of p53abn cases (n=5), likely reduced the statistical power to detect such associations.

The survival analysis, while not showing statistically significant differences between subgroups, revealed trends consistent with the established prognostic impact of molecular classification. The p53abn group exhibited the poorest OS, with a median survival of only 27 months, aligning with the known aggressive behavior of these tumors. The MMRd and p53wt groups had longer and not statistically different median survival times. The absence of statistical significance in survival differences is almost certainly a consequence of the limited sample size and relatively short follow-up, especially given the diverging survival curves. Larger studies with longer follow-up consistently demonstrate significant survival differences between molecular subgroups[10-12]. The PORTEC-3 trial, for example, showed that molecular classification significantly improved prognostic stratification in high-risk EC, with p53abn tumors having the worst prognosis and POLE-mutated tumors having the best, even within the high-grade subgroup[17]. In a study by Bayramoğlu et al.[18] evaluating the molecular classification of 97 high-

grade cases, the worst prognosis was observed in the p53abn group, while statistically significant differences were observed between the groups in terms of stage, LVSI, myometrial invasion and LNM. Zong et al.[19] performed molecular classification of 355 high-grade ECs and found that 52 patients (15.5%) changed risk groups, while 40 patients (11.9%) POLE mutation had a lower risk and 12 (3.6%) had a higher risk with p53abn. The authors concluded that molecular classification is important for risk stratification in this group of patients.

The clinical implications of these findings are significant despite the study's limitations. The identification of MMRd tumors, which comprise a substantial proportion (36%) of our grade 3 cohort, has immediate therapeutic relevance. MMRd/MSI-H tumors are known to be highly sensitive to immune checkpoint inhibitors, such as pembrolizumab and dostarlimab[20, 21]. The FDA has approved these agents for the treatment of advanced or recurrent MMRd/MSI-H solid tumors, regardless of histology, based on impressive response rates and durable clinical benefit. Therefore, routine IHC testing for MMR proteins in grade 3 endometrioid EC is crucial to identify patients who may benefit from immunotherapy.

The p53abn subgroup, while smaller in our cohort, represents a particularly challenging group with poor prognosis. These tumors often exhibit aggressive features, such as deep myometrial invasion, LVSI lymph node metastasis, and are less responsive to conventional chemotherapy and radiation. Identifying p53abn status may warrant more aggressive adjuvant treatment strategies, including combination chemotherapy and potentially targeted therapies. For instance, HER2 overexpression is observed in a subset of p53abn endometrial cancers, particularly serous carcinomas, and clinical trials are evaluating the efficacy of HER2-targeted agents in this context[22, 23]. Additionally, p53abn tumors may exhibit defects in homologous recombination DNA repair, making them potentially sensitive to Poly (ADP-ribose) polymerase (PARP) inhibitors [24].

The p53wt (NSMP) group, the largest in our study, remains the most heterogeneous and challenging to manage. This group likely includes a mixture of tumors with different underlying molecular drivers and prognoses. Further subclassification of this group, based on additional molecular markers such as CTNNB1 mutations, PIK3CA mutations, and L1CAM expression, may help to identify patients with different risks and treatment needs[8, 23, 25-26].

This study further demonstrates the feasibility and practicality of incorporating IHC-based molecular classification into routine pathology practice. IHC is widely available, relatively inexpensive, and can be performed on routinely processed FFPE tissue. The use of automated staining platforms and standardized interpretation guidelines enhances the reproducibility and reliability of the results. Despite the limitations of the retrospective design, the small sample size, and the absence of POLE sequencing, our study supports the molecular heterogeneity of grade 3 EC and advocates IHC-based molecular classification.

Incorporating IHC-based molecular classification into routine clinical practice refines risk stratification, identifies patients who may benefit from specific therapies, and ultimately improves outcomes for these high-risk endometrial cancer patients. The ongoing efforts to incorporate molecular classification into clinical guidelines and staging systems, such as the 2021 ESGO/ESTRO/ESP guidelines and the 2023 FIGO staging system, underscore the growing importance of personalized medicine in the management of endometrial cancer. Increased research in this area, along with a better understanding of the disease's molecular characteristics, will improve personalized medicine practices.

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