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ASSOCIATION OF CLINICOPATHOLOGIC CHARACTERISTICS WITH MISMATCH REPAIR PROTEINS AND P53 IMMUNOHISTOCHEMISTRY FINDINGS IN ENDOMETRIOID ENDOMETRIAL CARCINOMA

ENDOMETRİOİD ENDOMETRİAL KARSİNOMDA KLİNİKOPATOLOJİK ÖZELLİKLER İLE DNA UYUMSUZLUK ONARIMI PROTEİNLERİ VE P53 DURUMU ARASINDAKİ İLİŞKİ

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Abstract

Objective: This study aimed to evaluate the relationship between traditional prognostic clinicopathological features and the status of immunohistochemically assessed mismatch repair (MMR) proteins and p53 expression in endometrioid endometrial carcinoma (EEC).

Material and Methods: A total of 142 EEC patients who underwent hysterectomy and lymph node resection between 2018 and 2024 were included. Immunohistochemical analysis was performed for MLH1, MSH2, MSH6, PMS2, and p53.

Results: Our study showed that 66.2% of cases were MMR-proficient and 33.8% were MMR-deficient (dMMR). dMMR cases were significantly associated with higher International Federation of Gynecology and Obstetric (FIGO) Grade 3 tumours (33.3% vs. 10.6%) and cervical stromal invasion (39.6% vs. 23.4%). However, no significant association was found between dMMR and other parameters such as tumour size or lymphovascular invasion. For p53, 11.3% of cases showed mutation-type staining, whereas 88.7% showed the wild-type. p53 mutation-type staining demonstrated significant associations with multiple aggressive clinicopathological features, such as age, FIGO grade, tumour size, myometrial invasion depth, lymphovascular invasion, and cervical stromal invasion. No case exhibited both p53 mutation-type staining and loss of MMR proteins.

Öz

Amaç: Bu çalışmanın amacı, endometrioid endometrial karsinomda (EEK), geleneksel olarak prognostik klinikopatolojik özellikler ile immünohistokimyasal olarak değerlendirilen DNA Uyumsuzluk Onarımı (DUO) proteinleri ve p53 ekspresyonunun durumu arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: 2018-2024 yılları arasında histerektomi ve lenf nodu rezeksiyonu geçiren toplam 142 EEK hastası çalışmaya dahil edildi. MLH1, MSH2, MSH6, PMS2 ve p53 için immünohistokimyasal analiz yapıldı.

Bulgular: Çalışmamız, vakaların %66,2'sinin DUO-yeterli ve %33,8'inin DUO-yetersiz (DUOy) olduğunu gösterdi. DUOy vakalar, Uluslararası Jinekoloji ve Obstetrik Federasyonu (UJOF) Grade 3 tümörler (%33,3'e karşı %10,6) ve servikal stromal invazyon varlığı (%39,6'ya karşı %23,4) ile önemli ölçüde ilişkiliydi. Ancak, DUOy ile tümör boyutu veya lenfovasküler invazyon gibi diğer parametreler arasında önemli bir ilişki bulunmadı. p53 immünhistokimyasal incelemesinde, vakaların %11,3'ü mutasyon tipi boyama gösterirken, %88,7'si olağan tip boyanma gösterdi. p53 mutasyon tipi boyama, yaş, UJOF derecesi, tümör boyutu, miyometriyal invazyon derinliği, lenfovasküler invazyon ve servikal stromal invazyon dahil olmak üzere birden fazla agresif klinikopatolojik özellik ile anlamlı ilişki gösterdi. Vakaların hiçbirinde eş zamanlı p53 mutasyon tipi boyama ve DUO proteinlerinin kaybı görülmedi.

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Conclusion: MMR status and p53 expression in EECs are distinctly associated with key clinicopathological features, such as tumour FIGO grade and cervical stromal invasion. The association of the p53 mutation type with a broader range of aggressive factors underscores the importance of molecular classification in understanding EEC heterogeneity for prognostic evaluation and treatment strategies.

Keywords Endometrioid carcinoma · MSI · P53 · endometrial carcinoma

Sonuç: EEK'lerdeki MMR durumu ve p53 ekspresyonu, tümör UJOF derecesi ve servikal stromal invazyon gibi önemli klinikopatolojik özellikler ile belirgin şekilde ilişkilidir. p53 mutasyon tipi boyanmanın daha geniş bir agresif faktör yelpazesiyle ilişkisi, prognostik değerlendirme ve tedavi stratejileri için EEK heterojenliğini anlamada moleküler sınıflandırmanın önemini vurgulamaktadır.

Anahtar Kelimeler Endometrioid karsinom · MSI · P53 · endometrium karsinomu

INTRODUCTION

Endometrial carcinoma is the most prevalent malignancy affecting the female reproductive tract. The Cancer Genome Atlas Research Network developed a new classification system for endometrial cancer. This system categorises the disease into four groups: polymerase epsilon (POLE)-mutant, microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR), copy-number low (CN-L)/no specific molecular profile (NSMP), and copy-number high (CN-H)/p53-abnormal (1). This classification is based on the genetic characteristics of tumours, which helps determine the treatment strategies (2-15).

One of the most critical aspects in molecular classification is the status of microsatellite instability (MSI) and mismatch repair (MMR) proteins. MMR immunohistochemistry (MLH1, MSH2, MSH6, PMS2) and MSI (microsatellite instability) molecular analysis are used to define the MMR-deficient (MMRd) subgroup, which mainly consists of endometrioid endometrial carcinoma (EEC) (16). EEC is the most common subtype and is a highly heterogeneous group of tumours at the molecular level. Previous studies have also shown that lymphovascular invasion (LVI) and deep myometrial invasion are more common among MMRd tumours (17-22). Another molecular subgroup, the p53-abnormal group, is associated with a poor prognosis (1). p53 immunohistochemistry (IHC) is accepted as an accurate surrogate for TP53 mutation analysis (23).

This study aimed to evaluate the relationship between clinicopathological features traditionally known to have prognostic significance and the status of immunohistochemically assessed MMR proteins and p53 expression in EEC.

MATERIAL AND METHODS

A total of 142 patients diagnosed with endometrioid endometrial carcinoma (EEC) who underwent hysterectomy with bilateral salpingo-oophorectomy and lymph node resection were identified through a database search conducted at the Department of Pathology, Istanbul Faculty of Medicine from 2018 to 2024. Patients with synchronous tumours such as concurrent ovarian and endometrial primaries were excluded. Only cases with pure endometrioid histology were included, and tumours with non-endometrioid components were excluded to avoid histological heterogeneity. Clinicopathological parameters, including patient age, tumour International Federation of Gynecology and Obstetric (FIGO) grade, pathologic size of tumour, depth of myometrial invasion, LVI, microcystic, elongated, and fragmented (MELF) pattern of invasion, and cervical stromal involvement, were obtained through the patients' pathology reports.

A proper paraffin block containing the tumour was identified for each case, and immunostaining was performed on 4 µm paraffin-embedded tumour tissue sections. Immunohistochemistry was performed on consecutive whole-tissue sections of each case to evaluate the expression of MLH1, MSH2, MSH6, PMS2, and p53. The slides were stained on the Ventana Benchmark XT platform with the following commercially available antibodies: MLH1 (clone ES05, 1:100; DAKO, Buffalo Grove, IL), PMS2 (clone EP51, 1:75, DAKO, San Diego, CA, USA), MSH2 (clone FE11, 1:200, DAKO), MSH6 (clone EPR3945, 1:800, Genetex, Burlingame, CA, USA) and p53 (clone do-7, 1/100; Novocastra, AZ, USA). As internal controls, adjacent normal endometrial epithelial cells, lymphocytes, and endometrial stromal cells were evaluated. Using immunohistochemistry, tumours showing a loss of one or more mismatch repair (MMR) proteins were categorised as MMR-deficient (MMRd), whereas those exhibiting intact expression of all four MMR proteins were labelled as MMR-proficient (MMRp). The p53 staining pattern was interpreted as either the mutant-type characterised by strong and uniform nuclear staining (more than 80% of tumour cells), complete absence, or diffuse cytoplasmic staining or wild-type, indicated by variable staining present in less than 80% of the cells.

Categorical variables were assessed using the chi-square (χ^2) test or Fisher's exact test. Continuous variables were analysed using the Mann–Whitney U test. A p-value of <0.05 was considered indicative of statistical significance. All analyses

were performed using the Statistical Package for the Social Sciences (SPSS), version 31.0 (IBM SPSS Corp., Armonk, NY).

This retrospective study was approved by İstanbul University, İstanbul Faculty of Medicine, Clinical Research Ethics Committee (Date: 25.07.2025, No: 15).

RESULTS

A total of 142 patients with a diagnosis of EEC were included in this study. The mean age of these patients was 59.51 (20-84) years. The tumour grading distribution was as follows: FIGO Grade 1 (n=42, 29.6%), FIGO Grade 2 (n=74, 52.1%), and FIGO Grade 3 (n=26, 18.3%). Of these 142 cases, tumour size was <5 cm in 97 (68.3%) cases, while tumour size was ≥5 cm in 45 (31.7%) cases. Myometrial invasion was less than 50% in 69 (48.6%) cases, while it exceeded 50% in 73 (51.4%) cases. LVI was absent in 76 (53.5%) cases. Of the 66 cases exhibiting LVI, 45 (68.2%) demonstrated focal LVI (<5 vessels involved), and 21 (31.8%) demonstrated extensive LVI (≥5 vessels involved). The MELF invasion pattern was detected in 31 cases (21.8%), whereas it was not observed in 111 cases (78.2%). Cervical stromal invasion was identified in 41 (28.9%) cases and was not observed in the remaining 101 (71.1%) cases.

In the immunohistochemical analysis of MMR proteins, no loss of expression was detected with any antibody in 94 (66.2%) cases. Loss of MLH1-PMS2 expression was seen in 36 (25.4%) cases, loss of MSH2-MSH6 expression in 6 (4.2%) cases, and isolated loss of expression in 6 (4.2%) cases (Figure 1, 2). The distribution of the 6 cases with isolated loss of expression is as follows: 5 cases with isolated loss of MLH1 expression and 1 case with isolated loss of MSH6 expression. Thus, 94 (66.2%) cases were classified as pMMR, and 48 (33.8%) cases were classified as dMMR. In the group with pMMR, the distribution of cases as FIGO Grade 1, FIGO Grade 2, and FIGO Grade 3 was 35 (37.2%), 49 (52.1%), and 10 (10.6%), respectively. In contrast, in the group with dMMR, the distribution of cases by FIGO Grade was 7 (14.6%), 25 (52.1%), and 16 (33.3%), respectively, and this difference was statistically significant (p<0.001). While 22 (23.4%) of the pMMR cases had cervical stromal invasion, 19 (39.6%) of the dMMR cases had cervical stromal invasion (p=0.044). No statistically significant difference was found with other clinical and pathological parameters (Table 1).

Of the 142 cases, 126 (88.7%) showed wild-type staining with p53, while 16 (11.3%) showed mutation-type staining (Figure 3). When p53 mutation-type staining was compared with the clinicopathological data, statistically significant differences were observed regarding age (p=0.035), FIGO grade (p<0.001), tumour size (p<0.001), depth of myometrial invasion (p=0.045), LVI (p=0.018), cervical stromal invasion (p<0.001), and lymph node metastasis (p=0.004) (Table 2). When the LVI status was assessed as present versus absent, the association was statistically significant. However, when categorised as absent, focal, or extensive, the association did not reach statistical significance. No case showed both loss of MMR proteins and p53 mutation-type staining.

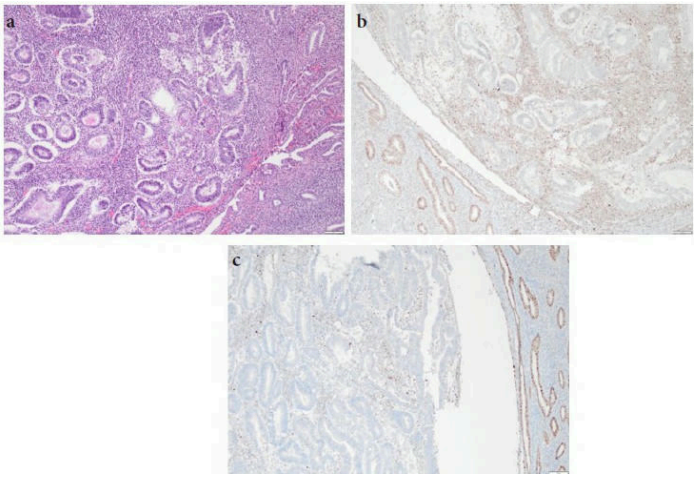

Figure 1. FIGO Grade 2 endometrioid carcinoma. a: hematoxylin and eosin, b: loss of MLH1 expression, c: loss of PMS2 expression

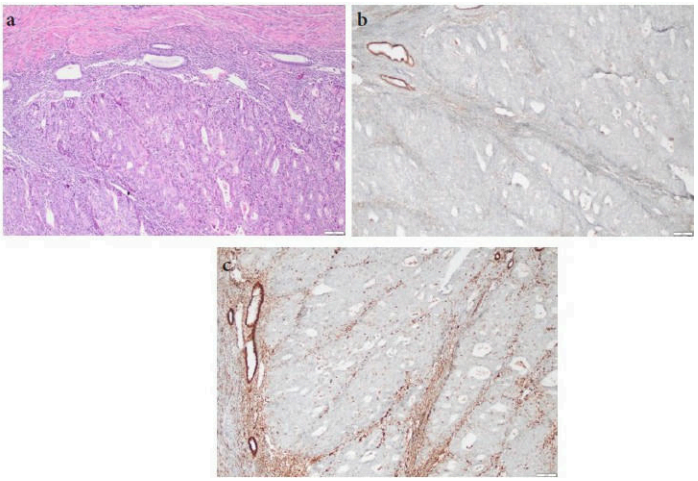

Figure 2. FIGO Grade 2 endometrioid carcinoma. a: hematoxylin and eosin, b: loss of MSH2 expression, c: loss of MSH6 expression

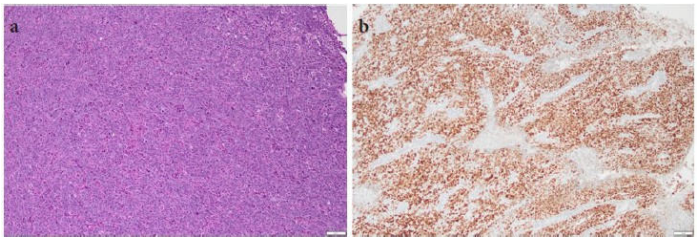

Figure 3. FIGO Grade 3 endometrioid carcinoma. a: hematoxylin and eosin, b: mutation-type staining with p53

Table 1. Clinicopathological characteristics according to the MMR proteins in endometrial cancer

	All patients (n=142) (%)	Proficient MMR (n=94) (%)	Deficient MMR (n=48) (%)	p
Age (mean)	59.51	58.7	61.2	0.143
FIGO Grade				**0.000***
1	42 (29.6)	35 (37.2)	7 (14.6)	
2	74 (52.1)	49 (52.1)	25 (52.1)	
3	26 (18.3)	10 (10.6)	16 (33.3)	
Pathologic tumour size				0.495
<5 cm	97 (68.3)	66 (70.2)	31 (64.6)	
≥5 cm	45 (31.7)	28 (29.8)	17 (35.4)	
Myometrial invasion				0.342
<50%	69 (48.6)	43 (45.7)	26 (54.2)	
≥50%	73 (51.4)	51 (54.3)	22 (45.8)	
Lymphovascular invasion				0.189
No	76 (53.5)	54 (57.4)	22 (45.8)	
Yes	66 (46.5)	40 (42.6)	26 (54.2)	
MELF pattern of invasion				0.823
No	111 (78.2)	74 (78.7)	37 (77.1)	
Yes	31 (21.8)	20 (21.3)	11 (22.9)	
Cervical stromal invasion				**0.044***
No	101 (71.1)	72 (76.6)	29 (60.4)	
Yes	41 (28.9)	22 (23.4)	19 (39.6)	
Lymph node metastasis				0.443
No	120 (84.5)	81 (86.2)	39 (81.3)	
Yes	22 (15.5)	13 (13.8)	9 (18.7)	

*p<0.05, MMR: mismatch repair, MELF: microcystic, elongated, and fragmented

DISCUSSION

The goal of this research is to analyse the correlation between clinicopathological characteristics, which are significant for prognosis, and the status of immunohistochemically evaluated MMR proteins (MLH1, MSH2, MSH6, PMS2) along with p53 expression in EEC.

In our study, 66.2% of the 142 endometrioid carcinoma cases evaluated were determined to be pMMR, and 33.8% were determined to be dMMR. This distribution is generally consistent with the rates reported in similar studies in the literature (17-20,24,25). Upon analysis of the relationships between MMR status and clinicopathological parameters, a statistically significant association was identified between MMR status and FIGO tumour grade (p<0.001). While the rate of FIGO Grade 3 tumours (33.3%) was significantly higher in the dMMR group than in the pMMR group (10.6%), the rate of FIGO Grade 1 tumours (37.2%) was higher in the pMMR group than in the dMMR group (14.6%). The rate of FIGO Grade 2 tumours was similar in both groups (52.1%).

In our study, dMMR cases were found to have a higher probability of cervical stromal invasion compared to pMMR cases (p=0.044). This finding provides additional information about the local dissemination potential of dMMR tumours. However, no statistically significant differences were found between other clinical and pathological parameters, such as age, tumour size, depth of myometrial invasion, LVI, MELF invasion pattern, and MMR status, in our study. In endometrioid carcinomas, there are reports from previous studies indicating that LVI and depth of myometrial invasion, which are classical factors known to be important for prognosis, have been observed more frequently among tumours showing MMRd; however, some studies have not found a statistically significant relationship between these histopathological features and MMR status, and findings on this matter are reported as contradictory or discordant in the literature (17-20). In particular, the lack of association between known prognostic factors, such as depth of myometrial invasion and LVI, and MMR status suggests that the prognostic effect of dMMR may be more closely related to specific features, such as FIGO grade or cervical invasion.

Table 2. Patient demographic data, symptoms, comorbidities, and associated cranial nerve palsy

	All patients (n=142) (%)	P53 wild type (n=126) (%)	P53 mutant (n=16) (%)	p
Age (mean)	59.51	58.9	64.1	**0.035***
FIGO Grade				**0.000***
1	42 (29.6)	41 (32.5)	1 (6.2)	
2	74 (52.1)	68 (54)	6 (37.5)	
3	26 (18.3)	17 (13.5)	9 (56.3)	
Pathologic tumour size				**0.000***
<5 cm	97 (68.3)	92 (73)	5 (31.2)	
≥5 cm	45 (31.7)	34 (27)	11 (68.8)	
Myometrial invasion				**0.045***
<50%	69 (48.6)	65 (51.6)	4 (25)	
≥50%	73 (51.4)	61 (48.4)	12 (75)	
Lymphovascular invasion				**0.018***
No	76 (53.5)	72 (57.1)	4 (25)	
Yes	66 (46.5)	54 (42.9)	12 (75)	
MELF pattern of invasion				0.751
No	111 (78.2)	99 (78.6)	12 (75)	
Yes	31 (21.8)	27 (21.4)	4 (25)	
Cervical stromal invasion				**0.000***
No	101 (71.1)	96 (76.2)	5 (31.2)	
Yes	41 (28.9)	30 (23.8)	11 (68.8)	
Lymph node metastasis				**0.004***
No	120 (84.5)	111 (88.1)	9 (56.3)	
Yes	22 (15.5)	15 (11.9)	7 (43.7)	

*p<0.05, MELF: Microcystic, elongated, and fragmented

Another important molecular marker is the TP53 mutation, which generally reflects the p53-abnormal phenotype that p53 IHC can detect. Studies have reported that p53-mutated EECs are generally associated with more advanced and invasive diseases and are the subgroup with the worst prognosis (26). In our study, according to p53 immunohistochemistry results, 88.7% of cases showed wild-type staining, while 11.3% showed mutation-type staining. p53 mutation-type staining showed statistically significant differences with clinicopathological features considered more aggressive, such as age, FIGO grade, tumour size, myometrial invasion depth, LVI, and cervical stromal invasion.

Previous studies have reported that traditional histopathological parameters, such as deeper myometrial invasion, presence of LVI, and cervical stromal invasion, are more frequently observed in the p53 abnormal group compared to the MMRd group (27). In our study, cases with p53 mutations were found to show statistically more significant associations with histopathological parameters compared to dMMR cases. This finding suggests that p53-mutated EECs, unlike MMR-deficient EECs, are generally associated with more advanced disease.

The study's limitations stem from its retrospective design and the constrained sample size. However, the number of patients in the study is sufficient for both the study's purpose and statistical analysis. One of the limitations of our study is the lack of a POLE sequence, which is not yet widely applied. POLE sequencing is an expensive test, and new mutations are being identified in the literature daily. Another limitation is the limited number of patients in the p53 mutant subgroup. However, in endometrioid endometrial carcinomas, the frequency of p53 mutations ranges between 10% and 20% in previous studies. In our study, the rate of cases with p53 mutation-type staining was 11.3%.

CONCLUSION

Our study has demonstrated that MMR status and p53 expression in EECs are differentially associated with key clinicopathological features, including tumour FIGO grade and cervical stromal invasion. Notably, the association of the p53

mutation type with a broader range of aggressive clinicopathological factors highlights the importance of molecular classification in understanding endometrioid carcinoma heterogeneity. These findings are valuable for the prognostic evaluation of EEC patients and for determining future treatment strategies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University, İstanbul Faculty of Medicine, Clinical Research Ethics Committee (Date: 25.07.2025, No: 15).

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Author Contributions: Conception/Design of Study- A.B., S.Ö.; Data Acquisition- A.B., S.B., A.Ü., A.T.; Data Analysis/Interpretation – A.B., S.B.; Drafting Manuscript- A.B., S.B., A.Ü., A.T.; Critical Revision of Manuscript- A.B., S.Ö.; Final Approval and Accountability- A.B., S.B., A.Ü., A.T., S.Ö.; Supervision- S.Ö.

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