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Research Article

Mismatch Repair Deficiency as a Predictor of Lymph Node Metastasis in Endometrioid Endometrial Carcinoma

Endometrioid Endometriyal Karsinomda Lenf Nodu Metastazının Bir Göstergesi Olarak Mismatch Repair (MMR) Eksikliği

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Abstract

To investigate the clinicopathologic characteristics and prognostic outcomes of mismatch repair (MMR) protein expression in patients with endometrioid endometrial carcinoma (EEC). This retrospective study included 197 patients with histologically confirmed EEC who underwent primary surgical staging between 2014 and 2020. MMR status was determined by immunohistochemistry for MLH1, PMS2, MSH2, and MSH6, classifying tumors as MMR-deficient (MMRd) or MMR-proficient (MMRp). Clinicopathologic variables and survival outcomes were compared between groups. Multivariate logistic regression identified independent predictors of LN metastasis. Overall (OS) and progression-free survival (PFS) were assessed. Of the 197 patients included, 67 (34.0%) had MMRd tumors, and 130 (66.0%) had MMRp tumors. No significant differences were observed between MMRd and MMRp groups in age (p=0.083), grade (p=0.149), FIGO stage (p=0.172), depth of myometrial invasion (p=0.295), and LVSI (p=0.474). LN metastasis was significantly more frequent in MMRd tumors (13.4%) compared to MMRp tumors (5.4%) (p=0.05). In multivariate analysis, grade 3 (RR=0.177, 95% CI: 0.084–0.374, p<0.001), deep myometrial invasion (>50%) (RR=0.427, 95% CI: 0.270–0.673, p=0.003), and MMR deficiency (RR=0.570, 95% CI: 0.352–0.922, p=0.050) were independently associated with LN metastasis. MMR status was not a significant predictor of LVSI or survival outcomes. Our findings indicate that MMR deficiency is an independent predictor of LN metastasis in EEC. However, MMR status did not significantly impact overall or progression-free survival.

Keywords: Endometrial Neoplasms, Immunohistochemistry, Lymph Node Metastasis, Mismatch Repair Deficiency, Prognosis.

Özet

Bu çalışmanın amacı, endometrioid endometriyal karsinom (EEC) hastalarında mismatch repair (MMR) protein ekspresyonunun klinikopatolojik özelliklerini ve prognostik sonuçlarını araştırmaktır. Bu retrospektif çalışma, 2014–2020 yılları arasında primer cerrahi evreleme yapılmış ve histolojik olarak EEC tanısı doğrulanmış 197 hastayı kapsamaktadır. MMR durumu, MLH1, PMS2, MSH2 ve MSH6 için immünohistokimya ile değerlendirildi ve tümörler MMR-deficient (MMRd) veya MMR-proficient (MMRp) olarak sınıflandırıldı. Klinikopatolojik değişkenler ve sağkalım sonuçları gruplar arasında karşılaştırıldı. Çok değişkenli lojistik regresyon analizi, bağımsız lenf nodu metastazı öngördürücülerini belirledi. Kaplan-Meier ve log-rank analizleri genel sağkalım (OS) ve progresyonsuz sağkalımı (PFS) değerlendirdi. Toplam 197 hastanın 67'sinde (%34,0) MMRd tümör, 130'unda (%66,0) MMRp tümör saptandı. MMRd ve MMRp grupları arasında yaş (p=0,083), derece (p=0,149), FIGO evresi (p=0,172), miyometriyal invazyon derinliği (p=0,295) ve lenfovasküler alan invazyonu (LVSI) (p=0,474) açısından anlamlı fark bulunmadı. Lenf nodu metastazı, MMRd tümörlerde (%13,4) MMRp tümörlere kıyasla (%5,4) anlamlı derecede daha sık görüldü (p=0,05). Çok değişkenli analizde, derece 3 (RR=0,177, %95 GA: 0,084–0,374, p<0,001), derin miyometriyal invazyon (>50%) (RR=0,427, %95 GA: 0,270–0,673, p=0,003) ve MMR eksikliği (RR=0,570, %95 GA: 0,352–0,922, p=0,050) LN metastazı ile bağımsız olarak ilişkili bulundu. MMR durumu, LVSI veya sağkalım sonuçları için anlamlı bir öngördürücü değildi. Sonuçlarımız, MMR eksikliğinin EEC'de LN metastazı için bağımsız bir öngördürücü olduğunu göstermektedir. Bununla birlikte, MMR durumu genel ya da progresyonsuz sağkalımı anlamlı derecede etkilememektedir.

Anahtar Kelimeler: Endometriyal Neoplaziler, İmmünohistokimya, Lenf Nodu Metastazı, Mismatch Repair Eksikliği, Prognoz.

Introduction

The DNA mismatch repair (MMR) system is a conserved genomic maintenance mechanism that identifies and corrects base–base mismatches and insertion–deletion loops arising during DNA replication. It is primarily mediated by the MLH1, MSH2, MSH6, and PMS2 proteins. Functional inactivation of this pathway, termed mismatch repair deficiency (MMRd), results in microsatellite instability (MSI), a hypermutable state characterized by widespread alterations in short tandem repeat sequences (1,2).

Endometrial carcinoma (EC), the most common gynecologic malignancy in developed countries, exhibits MMRd in approximately 25–30% of cases, a higher than that observed in many other solid tumors (3,4). While the majority of MMRd cases are sporadic, driven by MLH1 promoter hypermethylation, a clinically significant minority (3–5%) arises from germline mutations in MMR genes, consistent with Lynch syndrome (5,6). Owing to this dual clinical significance, universal MMR testing is recommended for all newly diagnosed ECs to facilitate both Lynch syndrome screening and therapeutic stratification (7). Beyond its role in hereditary cancer detection, MMR status has predictive value in the immunotherapy era. MMRd tumors, due to their high mutational burden and resultant neoantigen load, exhibit enhanced immunogenicity and are particularly susceptible to immunotherapy (8).

The Cancer Genome Atlas (TCGA) molecular classification, operationalized clinically through surrogate models such as ProMisE, has further refined EC risk stratification by dividing tumors into four subtypes: POLE-ultramutated (excellent prognosis), p53-abnormal (poor prognosis), MMRd (intermediate prognosis), and no specific molecular profile (NSMP) (9). However, the categorization of MMRd tumors as having an "intermediate" prognosis likely oversimplifies a more nuanced clinical trajectory. While some studies link MMRd to adverse features, including high-grade histology, advanced stage, and lymphovascular space invasion (LVSI), others report increased recurrence rates or no significant difference in overall survival (OS) (10-12). A few studies even suggest favorable outcomes, possibly related to immune-mediated tumor control (13,14).

LN metastasis is a paramount prognostic determinant in EC, yet its association with MMR status has yielded conflicting results. Given the ongoing controversies and the clinical importance of nodal status in EC management, the current study aimed to assess the association between MMR status and clinicopathologic outcomes, as well as LN metastasis and survival, in patients with EEC.

Material and Method

Study Design and Study Population

This retrospective study was conducted following approval from the Institutional Review Board of Kartal City Hospital (Approval number: 2025/010.99/17/34, date: 25/06/2025). The hospital's electronic database was queried to identify all patients who underwent primary surgical staging for EEC between January 2014 and December 2020. Inclusion criteria for the study were a histologically confirmed diagnosis of EEC and the availability of MMR immunohistochemistry (IHC) results, which were performed as part of routine clinical care. Patients with non-endometrioid histologies or those who received neoadjuvant therapy prior to surgery were excluded from the analysis.

Data Collection

A comprehensive retrospective review of electronic medical records and pathology reports was performed to extract data for all eligible patients. The collected variables included demographic information such as age, body mass index (BMI), and presence of comorbidities. Pathologic data were recorded according to the 2023 International Federation of Gynecology and Obstetrics (FIGO) staging system. Histopathologic features included tumor grade, depth of myometrial invasion, LVSI, and LN metastasis. The expression status of estrogen receptor (ER) and progesterone receptor (PR) was also documented.

Immunohistochemistry and MMR Status Classification

Formalin-fixed, paraffin-embedded tissue blocks from hysterectomy specimens were used for IHC analysis. Standardized protocols were employed to assess the expression of the four MMR proteins using primary antibodies against *MLH1, MSH2, MSH6, and PMS2*. MMR protein loss was defined by the complete, unequivocal absence of nuclear staining in viable tumor cells, in the presence of positive nuclear staining in internal control cells, such as non-neoplastic endometrial glands, stromal cells, or infiltrating

lymphocytes.19 Based on the IHC results, tumors were classified into two groups: MMRd: Defined by the loss of nuclear expression of one or more of the four MMR proteins. MMRp: Defined by intact nuclear expression of all four MMR proteins.

Study Outcomes and Definitions

The primary outcome included the association of MMR status with clinicopathologic and survival outcomes. Secondary outcomes of the study were the association between MMR status (MMRd vs. MMRp) and the presence of LN metastasis. OS was defined as the time interval from the date of primary surgery to the date of death from any cause or the date of last follow-up. Progression-free survival (PFS) was defined as the time from the date of primary surgery to the date of first documented disease recurrence or death from any cause, whichever occurred first.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 25 (IBM, Armonk, NY, USA). Descriptive statistics were used to summarize cohort characteristics; categorical variables were reported as frequencies and percentages, while continuous variables were presented as means with standard deviations (SD). To compare clinicopathologic features between the MMRd and MMRp groups, the Chi-square test or Fisher's exact test was used for categorical variables, and the independent samples t-test was used for continuous variables.

To identify independent predictors of lymph node metastasis, a multivariate logistic regression analysis was performed. The model included MMR status (deficient vs. proficient) as the primary variable of interest, along with established clinicopathologic risk factors for nodal involvement, specifically tumor grade and depth of myometrial invasion. Results from the regression analysis are presented as Odds Ratios (ORs) with corresponding 95% confidence intervals (CIs). For survival analysis, Kaplan-Meier curves were generated to estimate OS and PFS, and the log-rank test was used to compare survival distributions between the MMRd and MMRp groups. For all statistical tests, a two-sided p-value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 197 patients with endometrial cancer were included. The mean age at diagnosis was 60.11 ± 9.54 years, and the mean BMI was 32.35 ± 6.32 kg/m². The majority of tumors were early-stage (FIGO stage I, 74.1%), and 8.1% (n=16) had LN metastasis (Table 1).

Table 1. Clinicopathologic characteristics and expression pro les of MMR proteins of endometrioid endometrial cancer patients (n=197)

Variables	n (%)
Age at diognosis. mean±SD (range.yr)	60.11±9.54 (38-87)
BMI. mean±SD (range. kg/m²)	32.35±6.32 (21.48-53.33)
DM	78 (39.6)
Hypertension	99 (50.3)
FIGO Stage	
I	3 (1.5)
IA	57 (28.9)
IB	15 (7.6)
II	2 (1)
IIA	3 (1.5)
IIB	8 (4.1)
III	1 (0.5)
IIIA1	3 (1.5)
IIIB	1 (0.5)
IIIC	3 (1.5)
IV	1 (0.5)
IVB	1 (0.5)
Lymph node (LN) metastasis	
No	181 (91.9)
Yes	16 (8.1)
MMR status	
MMR-proficient	130 (66.0)
MMR-deficient	67 (34.0)
MMR protein loss (n=67)	
MLH1	2 (3.0)
MLH1/PMS2	49 (73.1)
MLH1/MSH6/PMS2	1 (1.5)
PMS2	3 (4.5)
MSH2/MSH6	9 (13.4)
MLH1/MSH2/MSH6/PMS2	1 (1.5)
MSH6	2 (3.0)

Data are expressed as mean±SD or number (percentage) where appropriate.

MMRd was identified in 67 patients (34.0%). The predominant pattern of protein loss was MLH1/PMS2 (73.1%), followed by MSH2/MSH6 (13.4%). Baseline clinicopathologic features, including age (p=0.083), grade (p=0.149), FIGO stage (p=0.172), depth of myometrial invasion (p=0.295), and LVSI (p=0.474), did not differ significantly between MMRp and MMRd groups. However, lymph node metastasis was significantly more frequent in MMRd tumors (13.4%) compared to MMRp tumors (5.4%) (p=0.05) (Table 2).

Multivariate logistic regression analysis identified depth of invasion >50% (RR=0.427, 95% CI: 0.270–0.673, p=0.003), grade 3 (RR=0.177, 95% CI: 0.084–0.374, p<0.001), and MMR deficiency (RR=0.570, 95% CI: 0.352–

0.922, p=0.050) as independent predictors of LN metastasis. For LVSI, only depth of invasion >50% (RR=0.446, 95% CI: 0.293–0.680, p=0.001) and grade 3 (RR=0.221, 95% CI: 0.102–0.478, p<0.001) were independently associated; MMR status was not a significant predictor (p=0.474) (Table 3).

Table 2. Clinicopathologic variables according to MMR status in endometrioid type EC (n=197)

Variables	MMR-p N=130	MMR-d N=67	p-value
Age at diagnosis. mean±SD	59.26±9.67	61.75±9.12	0.083
Grade*			
1	67 (51.5)	25 (37.3)	0.149
2	51 (39.3)	29 (43.3)	
3	11 (8.5)	10 (14.9)	
FIGO Stage**			
I	3 (2.3)	0	0.172
IA	44 (33.8)	13 (19.4)	
IB	11 (8.5)	4 (6.0)	
II	1 (0.8)	1 (1.5)	
IIA	1 (0.8)	2 (3.0)	
IIB	7 (5.4)	1 (1.5)	
III	0	1 (1.5)	
IIIA1	2 (1.5)	1 (1.5)	
IIIB	1 (0.8)	0	
IIIC	2 (1.5)	1 (1.5)	
IV	1 (0.8)	0	
IVB	0	1 (1.5)	
Depth of invasion			
< 1/2	88 (67.7)	39 (58.2)	0.295
>1/2	31 (23.8)	23 (34.3)	
LVSI			
Negative	110 (84.61)	54 (80.6)	0.474
Positive	20 (15.39)	13 (19.4)	
LN metastasis			
Negative	123 (94.6)	58 (86.6)	0.05
Positive	7 (5.4)	9 (13.4)	
Estrogen receptor			
Negative	0	2 (3.0)	0.102
Positive	106 (81.5)	56 (83.6)	
Progesterone receptor			
Negative	3 (2.3)	1 (1.5)	0.815
Positive	(8.5)	55 (82.1)	

p value of <0.05 indicates a significant difference.

Kaplan-Meier analysis revealed no statistically significant difference in OS or PFS between MMRp and MMRd groups. Median follow-up time was 36 months.

Discussion

This study provides clinically meaningful insights into the association between MMR protein expression and clinicopathologic outcomes in EC. Our findings reinforce the relevance of MMR status in refining preoperative risk stratification and guiding surgical management.

Table 3. Multivariate analysis of risk factors for lymph node metastasis and lymphovascular space invasion in patients

Variables	RR	95%CI	p
Lymphovascular space invasion			
Depth of invasion > 1/2	0.446	0.293-0.680	0.001
Grade 3	0.221	0.102-0.478	0.000
MMR-d	0.836	0.519-1.346	0.474
LN metastasis			
Depth of invasion > 1/2	0.427	0.270-0.673	0.003
Grade 3	0.177	0.084-0.374	0.000
MMR-d	0.570	0.352-0.922	0.050

A p value of <0.05 indicates a significant difference.

MMRd was identified in 34.0% of patients, aligning with previously reported rates ranging from 20% to 40%. The predominant pattern of loss was MLH1/PMS2 (73.1%), consistent with literature identifying this as the most common MMR deficiency, typically driven by MLH1 promoter hypermethylation. Loss of MSH2/MSH6, observed in 13.4% of our MMRd cases, is more commonly associated with Lynch syndrome.

Consistent with the findings of de Freitas et al., our study revealed no statistically significant differences between MMRd and MMRp endometrioid endometrial carcinoma cases with respect to patient age, tumor grade, FIGO stage, depth of myometrial invasion, or the presence of LVSI (15). These results diverge from prior studies that have reported significant associations between MMR deficiency and adverse histopathologic features, including high-grade tumors, advanced-stage disease, and increased LVSI rates (10,11). Such discrepancies may be explained by heterogeneity in study populations, variations in LVSI assessment methodologies, or insufficient statistical power in single-institution cohorts compared to large-scale meta-analyses.

A principal finding of this study is the significantly higher frequency of LN metastasis in MMRd tumors compared to MMRp tumors. Importantly, MMRd remained an independent predictor of nodal involvement after adjusting for other risk factors, including deep myometrial invasion and high-grade histology. These results are consistent with findings by Riedinger al. who reported an association between MMRd and presence of nodal metastasis (6). The potential biological mechanisms underlying the association between MMR deficiency and LN metastasis are complex and warrant further investigation. MMR deficiency leads to genomic instability and a high mutation rate, which could potentially drive the acquisition of mutations that promote tumor

invasion and metastasis (16,17). It is also possible that the altered tumor microenvironment in MMR-d tumors, characterized by increased immune infiltration, may paradoxically contribute to metastasis in some cases, although the precise interplay between MMR status, immune response, and metastatic potential remains to be fully elucidated (18,19). Given the prognostic importance of LN involvement, MMR status may serve as a useful preoperative marker to guide decisions regarding the extent of lymphadenectomy, particularly in patients with equivocal uterine risk features.

Regarding survival outcomes, no significant difference in OS or PFS was observed between MMRd and MMRp groups. This aligns with several studies reporting no prognostic impact of MMR status on survival (3,15,20). However, the literature remains inconsistent. Some investigations have linked MMRd, particularly tumors with MLH1 promoter hypermethylation, to poorer outcomes, whereas others report improved survival in MMRd cohorts, potentially attributable to heightened immunogenicity and increased responsiveness to therapy (11,12,21-24). These findings should be interpreted with caution given a key limitation of our study. The absence of comprehensive molecular classification. The MMRp group likely comprises a biologically diverse set of tumors, including POLE-ultramutated (favorable prognosis), p53-abnormal (poor prognosis), and NSMP (intermediate prognosis) subtypes. This molecular heterogeneity may obscure true survival differences between MMRd and its most appropriate comparator group, particularly NSMP. Future studies incorporating POLE sequencing and p53 immunohistochemistry are essential to allow for precise molecular stratification and more definitive prognostic assessment.

Strengths of this study include the use of standardized IHC-based MMR assessment, and a well-characterized patient cohort. However, several limitations warrant consideration. The retrospective design introduces the potential for selection bias. Lack of MLH1 promoter methylation testing and POLE sequencing limits our ability to distinguish sporadic from hereditary MMRd and to fully stratify patients according to TCGA subtypes. Additionally, the modest sample size may reduce statistical power for detecting subtle survival differences or performing robust subgroup analyses. The follow-up duration may also be insufficient to capture long-term outcome disparities.

The clinical implications of our findings suggest that MMR status, a standard component of EC evaluation, may serve as a valuable biomarker for preoperative risk stratification of LN metastasis. Incorporating MMR status into surgical planning could inform the extent of nodal assessment, such as determining the appropriateness of sentinel lymph node mapping versus comprehensive lymphadenectomy, particularly in patients with equivocal or low-risk uterine features. Prospective, multicenter studies with fully molecularly annotated cohorts are essential to validate these observations and to investigate whether MMR status may also guide adjuvant treatment strategies in node-positive disease.

Conclusion

This study identifies MMRd as an independent predictor of LN metastasis in EEC, underscoring its potential utility in preoperative risk stratification and surgical decision-making. While no significant differences in survival outcomes were observed, these findings highlight the need for integrative molecular profiling to optimize prognostication and treatment strategies in EEC.

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Conflict of interest statement

There is no conflict of interest.

Ethics Committee Approval

Kartal City Hospital Ethics Committee/ date: 25/06/2025/ Decision No: 2025/010.99/17/34.

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