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ORIGINAL RESEARCH

Mismatch repair status in endometrial cancer: detection with immunohistochemical markers and its relationship with clinical outcome

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Abstract

Background: Over the past decade, molecular classification in endometrial cancer has provided valuable insights into its pathogenesis, prognosis, and implications for adjuvant therapy. However, the prognostic impact of mismatch repair deficiency in endometrioid endometrial cancer (EEC) remains uncertain. The goal of this study is to determine the clinicopathological significance of mismatch repair (MMR) protein defects in EEC. **Methods**: A total of 100 patients diagnosed with EEC between 2002 and 2017 were retrospectively reviewed. Immunohistochemical analysis was performed to assess the expression of MMR proteins, including *MutL Homolog 1* (*MLH1*), *MutS Homolog 2* (*MSH-2*), *MutS Homolog 6* (*MSH-6*), and *PostMeiotic Segregation increased 2* (*PMS-2*). Associations between MMR status, clinicopathologic features, and survival outcomes were analyzed. **Results**: Twenty-nine samples (29%) had at least one loss of MMR protein expression which was categorized as MMR-deficient. There was a significant relation of lymphovascular space invasion (LVSI) in MMR-deficient (MMRd) group compared to MMR-proficient group (MMRp) (55.2% *vs.* 28.2%, $p = 0.020$). However, MMRd tumors were not associated with recurrence, lymph node involvement, administration of adjuvant therapy, overall and progression-free survival. **Conclusions**: MMR-deficient tumors were more frequently associated with lymphovascular space invasion. The marked association suggests a potentially more aggressive clinical phenotype, despite the absence of significant differences in survival outcomes in this cohort. Further prospective, multi-institutional studies are warranted to clarify the prognostic and therapeutic implications of MMR status in EEC.

Keywords

Endometrioid cancer; Mismatch repair; Immunohistochemistry; Survival; Prognostic factors

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy, with its incidence steadily increasing in developed countries [1]. The majority of patients diagnosed with EC are postmenopausal with a median age at diagnosis of 60 years [2]. Endometrioid endometrial cancer (EEC) is the most prevalent histologic subtypes, accounting for 75–80% of all ECs [3]. The majority of cases diagnosed with EEC are presented as stage I or II, with a 5-year survival rate of around 90%, reflecting a favorable prognosis [4]. Nevertheless, recurrence occurs in a subset of patients with early-stage disease; in a large multicenter cohort of 2974 patients with stage I–II endometrial cancer reporting a recurrence rate of 6.4%, and significantly poorer overall survival among patients who developed recurrence [5]. The prognosis is less favorable in advanced-stage EEC, with a 5-year overall survival rate of 70.4%, and a median progression-free survival of 43 months reported among patients with stage III–IV disease [6].

The standard care for endometrial cancer typically involves surgery, including total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment [7]. The conventional approach to prognostic stratification is based on clinicopathologic parameters (*e.g.*, histotype, grade, stage), which are also used to define the therapeutic strategy [8]. A significant diagnostic challenge lies in differentiating patients with early-stage EC who have low-risk disease and a limited likelihood of recurrence from those with high-risk disease who require adjuvant therapy [9]. Consequently, numerous studies have been conducted to identify new prognostic biomarkers that enable the early identification of patients at high risk of recurrence [10].

The majority of endometrial cancer cases are sporadic. Nevertheless, a small subset of hereditary cases arises from

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germline mutations, predominantly affecting the mismatch repair (MMR) genes [11]. Microsatellite instability (MSI) results from functional inactivation of MMR genes and is characteristic of patients harboring germline mutations associated with Lynch syndrome [12]. Since 2018, the National Comprehensive Cancer Network (NCCN) guidelines have recommended universal testing of all ECs for MSI/MMR-deficient tumors [13]. MSI has been detected in approximately 20–40% of all ECs [14]. A significant number of oncology centers utilize immunohistochemistry (IHC) for MSI/MMR testing, as it is cost-effective and exhibits high sensitivity, specificity, and reproducibility [14, 15]. According to the European Society for Medical Oncology (ESMO) guidelines, MMR-IHC testing is recommended for all patients with EC, regardless of histologic subtype [16]. Furthermore, with the advent and regulatory approval of immuno-oncologic therapies for tumors exhibiting MSI-high or MMR-deficient (MMRd) phenotypes, the identification of these biomarkers has become increasingly important as predictive and therapeutic indicators [17]. However, the prognostic significance of MMR deficiency remains controversial [17]. Several studies have reported improved survival outcomes in MSI-high tumors compared with microsatellite-stable tumors receiving the same adjuvant therapy [18], whereas others have shown no difference or even poorer outcomes in MSI-high cases [19–21].

The primary objective of the present study is to comprehensively evaluate the relationship between MMR status and clinicopathological variables, with a particular focus on their impact on survival and recurrence outcomes in patients with EEC.

2. Materials and methods

2.1 Study design

The Institutional Research Ethics Committee of Ege University Faculty of Medicine approved before its initiation (approval number: 22-7T/45). A cohort of patients diagnosed with endometrial cancer was identified and treated in the Division of Gynecological Oncology at Ege University Faculty of Medicine between 2002 and 2017. This study included a total of 100 primary EEC patients who had results from MMR testing.

During the preoperative evaluation period, patients with clinically uterine-confined EEC were selected for primary surgical management. None of the patients received neoadjuvant radiotherapy or chemotherapy. Cases with mixed or non-endometrioid histologic types, endometrial hyperplasia, abnormal p53 (p53-abn) expression, absence of lymph node assessment at surgery, or incomplete medical records were excluded. No patients included in this study exhibited synchronous malignancies.

All patients underwent comprehensive surgical staging, including total hysterectomy and bilateral salpingo-oophorectomy, with or without lymph node dissection, followed by adjuvant radiotherapy and/or chemoradiotherapy as clinically indicated. Demographic, clinical, surgical, pathological, and follow-up data were retrospectively retrieved from the hospital's electronic medical records.

The staging of the disease was determined in accordance with the 2009 revisions to the International Federation of Gynaecology and Obstetrics (FIGO) guidelines [22]. For patients with early-stage EEC exhibiting high-risk features, standard adjuvant therapy consisted of vaginal brachytherapy or pelvic radiotherapy [13]. In contrast, patients with advanced-stage EEC received combined chemotherapy and radiotherapy, with the paclitaxel-carboplatin regimen serving as the preferred chemotherapy protocol [13].

Post-treatment surveillance included physical examination, tumor marker assessment, vaginal cytology, and ultrasonography, performed every three months for the first two years, every six months for the subsequent three years, and annually thereafter. As required, Positron emission tomography/computed tomography (PET-CT) or CT imaging, and/or biopsy, were performed as clinically indicated to confirm disease recurrence. Overall survival (OS) was defined as the interval between the date of surgery and either December 2022 or the date of death from any cause, whichever occurred first. Progression-free survival (PFS) was defined as the time from the date of surgery or completion of adjuvant therapy to the earliest date of disease progression, recurrence, or death from any cause. The follow-up of vital status concluded on 30 December 2022.

The patients were stratified based on the loss of nuclear expression of MMR proteins using the IHC method, along with various prognostic factors including age, menopausal status, stage, grade, tumor diameter, cervical involvement, adnexal involvement, presence of lymphovascular space invasion (LVSI), recurrence, depth of deep myometrial infiltration (MI), lymph node (LN) metastasis, and need for adjuvant treatment. The effects of these parameters on survival outcomes were also analyzed.

2.2 Immunohistochemistry

No comprehensive molecular classification was performed for the cases; only p53 and MMR-IHC analyses were conducted. The haematoxylin and eosin (H&E) stained slides were re-evaluated by an expert pathologist (GS) for detecting MMR status. Tissue microarray (TMA) blocks were prepared from formalin-fixed, paraffin-embedded tumor samples, and 4 μm-thick sections were immunohistochemically stained using antibodies against *MutL Homolog 1* (*MLH-1*), *MutS Homolog 2* (*MSH-2*), *MutS Homolog 6* (*MSH-6*), and *PostMeiotic Segregation increased 2* (*PMS-2*) (Fig. 1) [23]. Loss of protein expression for *MLH-1*, *MSH-2*, *MSH-6*, or *PMS-2* was defined as staining in fewer than 5% of tumor cell nuclei, provided that internal positive controls (normal lymphocytes and/or stromal cells) demonstrated retained nuclear staining [24]. Tumor samples were divided into two groups. (1) MMR-deficient (MMRd) was defined as the loss of at least one of four MMR proteins was lost. (2) MMR-proficient (MMRp) was defined as intact expression of all four MMR proteins in tumors. The monoclonal antibodies used for IHC detection of MMR proteins during routine pathological assessment are shown in Table 1.

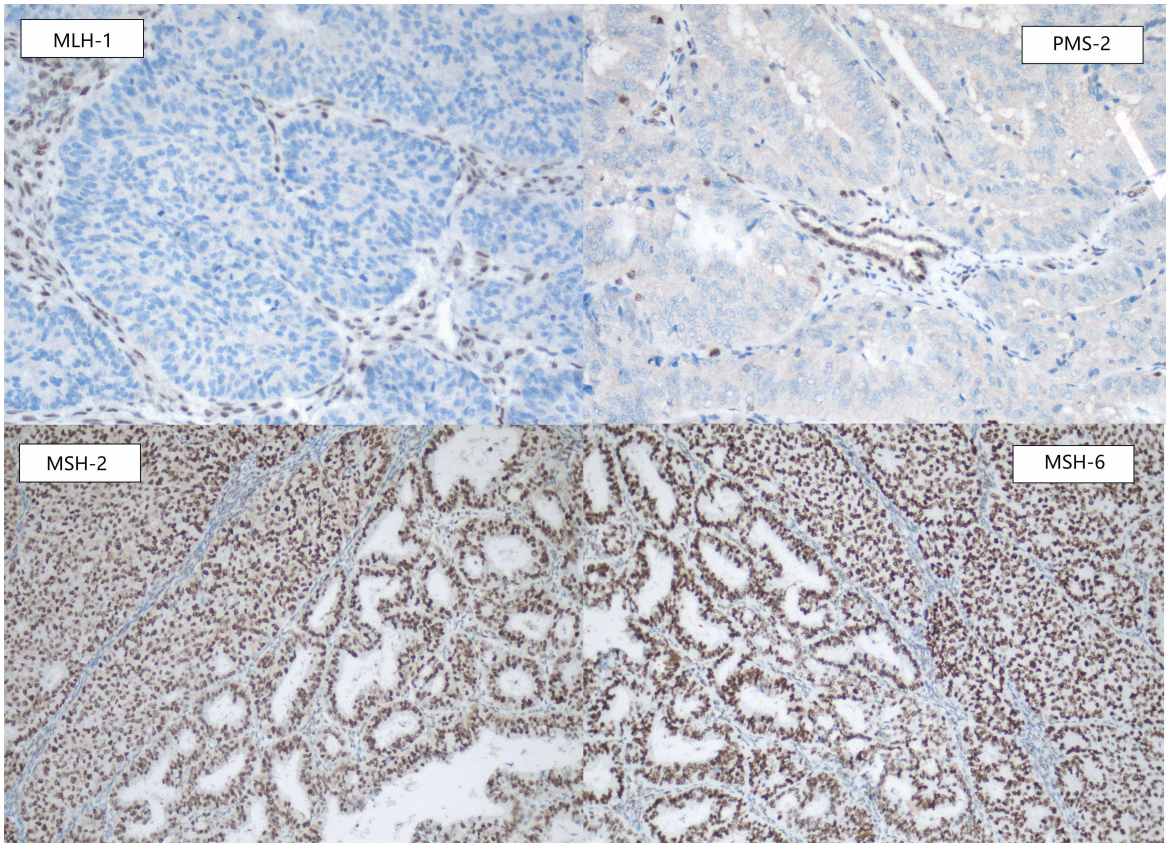

FIGURE 1. Immunohistochemical staining demonstrating loss of *MLH-1* and *PMS-2* expression, with retained nuclear expression of *MSH-2* and *MSH-6* (×200). Detection of all 4 MMR proteins was performed on serial sections obtained from the same tumor tissue. *MLH-1*: *MutL Homolog 1*; *MSH-2*: *MutS Homolog 2*; *MSH-6*: *MutS Homolog 6*; *PMS-2*: *PostMeiotic Segregation increased 2*.

TABLE 1. Monoclonal antibodies for mismatch repair proteins.

Antibody	Clone	Dilution	Company
MLH-1	m1	ready-to-use solution	Ventana
PMS-2	G219-1129	ready-to-use solution	Ventana
MSH-2	sp93	ready-to-use solution	Ventana
MSH-6	A16-4	ready-to-use solution	Ventana

MLH-1: MutL Homolog 1; MSH-2: MutS Homolog 2; MSH-6: MutS Homolog 6; PMS-2: PostMeiotic Segregation increased 2.

2.3 Statistical analysis

The Kolmogorov-Smirnov test was applied to evaluate the normality of distribution for quantitative variables. A comparison was conducted between independent groups using a *t*-test for variables distributed normally and a Mann-Whitney U test for non-normally distributed variables. The relationship between MMR status and clinicopathologic data was assessed using chi-square analysis. Kaplan-Meier survival analyses were conducted to estimate overall and progression-free survival, and differences between survival curves were evaluated using the log-rank test. Categorical variables were presented with numbers and percentages, while continuous variables were expressed as absolute numbers, mean ± standard deviation, median and range. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM Corp., Chicago, IL, USA). The values of $p < 0.05$ were considered to be statistically significant.

3. Results

A total of 100 patients with EEC were included in this study. Overall, MMRp was detected in 71 patients (71%), while loss of at least one MMR protein was observed in 29 patients (29%) (Table 2). Among the 29 MMRd cases, the most common pattern of protein loss was concurrent loss of *MLH-1* and *PMS-2* in 23 cases (79.3%), followed by loss of *MSH-2* and *MSH-6* in 2 cases (6.8%), isolated loss of *MSH-6* in 2 cases (6.8%), combined loss of *MLH-1*, *PMS-2*, and *MSH-6* in 1 case (3.4%), and loss of all four MMR proteins in 1 case (3.4%). No cases exhibited isolated loss of *PMS-2* expression.

The relationship between MMR protein status and clinicopathologic parameters was shown in Table 3. At diagnosis, the mean age was 57.7 years for MMRd group and 58.3 for MMRp group ($p = 0.775$). Four patients in MMRd group and ten patients in MMRp group had family history for any cancers

TABLE 2. Expression of MMR protein status in endometrioid-type endometrial cancers.

MMR protein status	N (%)
Total	100 (100.0%)
MMR-proficient	71 (71.0%)
MMR deficiency	29 (29.0%)
MLH-1 + *PMS-2*	23 (79.3%)
MSH-2 + *MSH-6*	2 (6.8%)
MSH-6 only	2 (6.8%)
PMS-2 only	0 (0.0%)
MLH-1 + *PMS-2* + *MSH-2* + *MSH-6*	1 (3.4%)
MLH-1 + *PMS-2* + *MSH-6*	1 (3.4%)

MMR: mismatch repair; MLH-1: MutL Homolog 1; MSH-2: MutS Homolog 2; MSH-6: MutS Homolog 6; PMS-2: PostMeiotic Segregation increased 2.

TABLE 3. Clinicopathologic characteristics of patients according to MMR status.

Parameter	N (%)	MMRd N (%)	MMRp N (%)	*p* value
	Total = 100	Total = 29	Total = 71	
Age, yr				
Mean	58.1	57.7 (range, 54.8–60.6)	58.3 (range, 56.1–60.4)	0.775
SD	8.6	7.5	9.1	
Menopausal status				
Premenopause	17 (17.0%)	5 (17.2%)	12 (16.9%)	1.000
Postmenopause	83 (83.0%)	24 (82.8%)	59 (83.1%)	
Family history for any cancer				
Yes	14 (14.0%)	4 (13.8%)	10 (14.1%)	1.000
No	86 (86.0%)	25 (86.2%)	61 (85.9%)	
Grade				
I	28 (28.0%)	8 (27.6%)	20 (28.2%)	
II	57 (57.0%)	14 (48.3%)	43 (60.6%)	0.244
III	15 (15.0%)	7 (24.1%)	8 (11.3%)	
FIGO Stage				
I	77 (77.0%)	25 (86.2%)	52 (73.2%)	
II	14 (14.0%)	3 (10.3%)	11 (15.5%)	0.616
III	8 (8.0%)	1 (3.4%)	7 (9.9%)	
IV	1 (1.0%)	0 (0.0%)	1 (1.4%)	
Tumor size (mm)	31 (range, 15–90)	35 (range, 15–90)	30 (range, 5–80)	0.653
Deep MI				
Yes	39 (39.0%)	4 (13.8%)	35 (49.3%)	**0.002**
No	61 (61.0%)	25 (86.2%)	36 (50.7%)	
LVSI				
Yes	36 (36.0%)	16 (55.2%)	20 (28.2%)	**0.020**
No	64 (64.0%)	13 (44.8%)	51 (71.8%)	
Adnexal involvement				
Yes	2 (2.0%)	0 (0%)	2 (2.8%)	1.000
No	98 (98.0%)	29 (100%)	69 (97.2%)	

TABLE 3. Continued.

Parameter	N (%)	MMRd N (%)	MMRp N (%)	*p* value
	Total = 100	Total = 29	Total = 71	
LN status				
Positive	5 (5.0%)	1 (3.4%)	4 (5.6%)	
Negative	76 (76.0%)	26 (89.7%)	50 (70.4%)	0.093
Not described	19 (19.0%)	2 (6.9%)	17 (23.6%)	
Adjuvant therapy				
Yes	97 (97.0%)	28 (96.6%)	69 (97.2%)	1.000
No	3 (3.0%)	1 (3.4%)	2 (2.8%)	
Recurrence				
Yes	15 (15.0%)	2 (6.9%)	13 (18.3%)	0.219
No	85 (85.0%)	27 (93.1%)	58 (81.7%)	
Mortality				
Yes	15 (15.0%)	2 (6.9%)	13 (18.3%)	0.219
No	85 (85.0%)	27 (93.1%)	58 (81.7%)	
OS months (median)	-	117 (range, 30–173)	130 (range, 18–209)	0.154
PFS months (median)	-	112 (range, 14–170)	122 (range, 1–208)	0.423

OS: overall survival; PFS: progression-free survival; LVSI: lymphovascular space invasion; MMRd: mismatch repair deficient; MMRp: mismatch repair proficient; MI: myometrial infiltration; LN: lymph node; SD: standard deviation; FIGO: International Federation of Gynecology and Obstetrics. Bold numbers indicate significance.

(p = 1.000). Deep MI was found higher in MMRp group compared to MMRd group (49.3% *vs.* 13.8%, p = 0.002). On the other hand, patients with MMRd tumors tend to have had more frequent LVSI (55.2% *vs.* 28.2%, p = 0.020).

However, no statistically significant differences were observed between the two groups in terms of FIGO stage, tumor grade, tumor size, adnexal involvement, or LN metastasis ($p > 0.05$ for all comparisons). A total of 97 patients received adjuvant treatment, including chemotherapy and radiotherapy or radiotherapy only; however, this result had no statistically significant for both groups (MMRd: n = 28, (96.6%) *vs.* MMRp: n = 69, (97.2%); p = 1.000). At the last follow-up, 15 recurrences and 15 deaths were recorded across the entire cohort, with no statistically significant difference in recurrence or mortality between MMRd and MMRp groups (p = 0.219).

The relationships between MMR protein status and survival outcomes were evaluated, as presented in Fig. 2. The median OS was 117 months in the MMR-deficient group and 130 months in the MMR-proficient group, with corresponding 5-year OS rates of 93% in both groups. The median PFS was 112 months for patients with MMRd tumors and 122 months for those with MMRp tumors. Neither OS nor PFS was significantly affected by MMR protein loss (p = 0.154 and p = 0.423, respectively).

In the subgroup analysis limited to patients with FIGO stage I–II disease (n = 91), deep MI was significantly more frequent in the MMR-proficient group than in the MMR-deficient group (29/64 (45.3%) *vs.* 4/27 (14.8%); p = 0.008). No significant differences were observed for other clinicopathologic parameters ($p > 0.05$ for all comparisons).

4. Discussion

In the present study, the MMR protein status was retrospectively assessed using IHC, and its effects on the clinicopathologic features of 100 patients with EEC were examined. Our results demonstrated that MMRd was found in 29% of all patients and MMRd was significantly associated with LVSI (p = 0.020). However, there were no effects on survival outcomes.

Despite the generally favorable prognosis of patients with EEC, approximately 20% present with high-risk disease, which is associated with an increased likelihood of recurrence [10]. Consistent with these reports, the present study identified a high-risk subgroup comprising 24% of cases. The defining features of high-risk EC include high tumor grade, advanced stage, and/or non-endometrioid histology [25]. In recent years, the molecular characterization of EC has developed. Defects in the DNA-MMR system represent one of the most frequent molecular alterations observed in EEC [26, 27]. Tumors with these defects can be easily identified by analysing MSI or loss of MMR protein expression [26, 27].

In the current study, the frequency of MMR-deficient tumors was comparable to previous findings, with MMRd identified in 29% of cases, aligning with the 20–40% range reported in earlier studies [28–30]. Among the characteristic expression

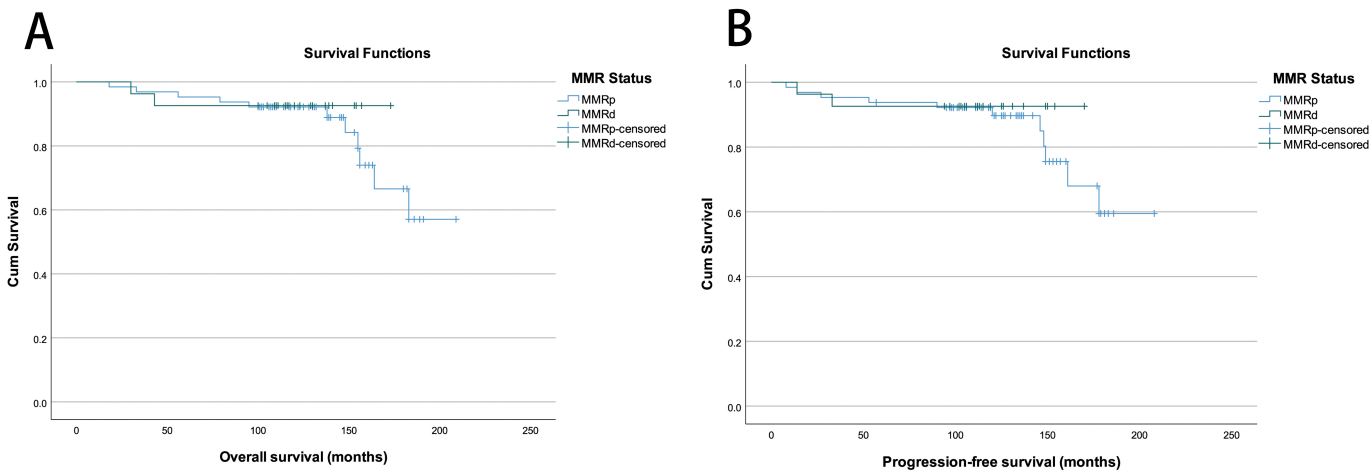

FIGURE 2. Overall survival (A) and progression-free survival (B) according to MMR protein status. MMR: mismatch repair; MMRp: mismatch repair proficient; MMRd: mismatch repair deficient.

patterns of MMR deficiency, concurrent loss of *MLH-1* and *PMS-2* is the most prevalent, accounting for approximately 60–70% of cases, followed by combined *MSH-2/MSH-6* loss (20–25%), isolated *MSH-6* loss (5–10%), and isolated *PMS-2* loss (~5%) [17, 30, 31].

Comparing clinicopathological parameters between MMR-proficient and MMR-deficient tumors revealed that MMRd was significantly associated with the presence of LVSI. Similarly, Kim *et al*. [17] evaluated 163 patients with EEC and reported that MMRd tumors were significantly more likely to exhibit LVSI, which was also correlated with an increased risk of LN metastasis. Consistently, the NRG Oncology/Gynecologic Oncology Group, along with two additional studies, demonstrated a significant association between MMR deficiency and advanced FIGO stage, higher tumor grade, LVSI, and deep MI [20, 32, 33]. In a separate cohort of 206 EC patients, MMRd tumors were likewise associated with LVSI and deep MI and were more likely to have received adjuvant therapy; however, MMR status did not correlate with LN metastasis [34]. In 2021, the Hong Kong study investigated 238 patients with FIGO 2009 EEC and was found that MMRd in EEC was associated with older age, greater tumor size, stage II and high-grade disease, as well as increased need of adjuvant pelvic radiotherapy [35]. In contrast, several studies have reported conflicting findings or no significant differences in prognostic factors based on MMR protein expression. For instance, Ruiz *et al*. [36] observed no association between MMRd and age, grade, stage, LVSI, and MI in 212 EEC patients. Similarly, Black *et al*. [37] and Arabi *et al*. [38] found no correlation with age, race and LVSI; but deep MI and advanced stage were significantly higher in MMRd patients. In line with these reports, the current study found no significant associations between MMR status and variables such as age, stage, grade, adnexal involvement, MI, or tumor size. Although LVSI was more frequently observed in MMRd tumors, the rate of LN metastasis was comparable between groups, and the use of adjuvant therapy did not differ significantly. Decisions regarding adjuvant treatment were made by a multidisciplinary tumor board and individualized for each patient, based on an integrated assessment of prognostic factors including tumor size, grade, MMR status, patient age, LN status, depth of myometrial invasion, and FIGO stage.

A comparative analysis of recurrence and mortality rates between MSI-positive and MSI-negative groups, as reported by Zighelboim *et al*. [21], revealed no statistically significant difference that aligns with the results of our study. Conversely, Cosgrove *et al*. [33] reported that recurrence rates were similar between MSI-positive and MSI-negative patients in early-stage EEC; however, a higher recurrence rate was observed in MSI-positive patients with advanced-stage disease. Moreover, the need for adjuvant therapy was greater among MSI-positive patients, even in the early-stage cohort. In a similar context, Lee *et al*. [35] found that patients with MMRd tumors experienced higher recurrence rates despite a greater likelihood of receiving adjuvant pelvic radiotherapy.

In the current study, we found no significant association between MMRd and survival outcomes in patients with EEC. These findings are in agreement with a previous study of 212 EEC patients by Ruiz *et al*. [36], which also reported no significant relationship between MMRd and survival. Similarly, two additional studies demonstrate no association between MMR protein status and OS, and PFS [21, 39]. In contrast, a previous meta-analysis suggested that MMRd was associated with poorer PFS and OS; however, the differences did not reach statistical significance [19]. Kim *et al*. [17] demonstrated that PFS was significantly shorter in patients with MMRd tumors, this result was attributed to the higher incidence of lymph node metastasis, which was identified as one of the independent risk factors. Conversely, Kato *et al*. [40] found that MMRd tumors were significantly associated with early-stage disease and low-grade (grade I–II) histology and concluded that MMRd could serve as a favorable prognostic marker for OS.

The retrospective design of this study, its single-institution setting, and the relatively small number of patients with MMR-deficient tumors represent key limitations. Additionally, the inclusion of cases with advanced-stage disease and the fact that the study sample spanned a somewhat older diagnostic period (2002–2017) may have influenced the generalizability of the findings. Despite these limitations, the study's strength lies in its ability to demonstrate a significant association between

MMR deficiency and LVSI, without a corresponding increase in LN metastasis.

5. Conclusions

In summary, our findings indicate that MMRd tumors, defined as the loss of at least one MMR protein by immunohistochemistry are significantly associated with LVSI, while showing a reduced incidence of deep MI, and no apparent impact on prognosis or survival outcomes. These results suggest the possibility of distinct biological pathways of tumor progression in MMRd endometrial cancers. The strong association between MMR deficiency and LVSI highlights a potentially aggressive tumor subset, which may benefit from intensified adjuvant therapy and could represent an ideal target population for future immunotherapy trials. These findings underscore the importance of integrating molecular classification, particularly MMR status, with traditional pathological features such as LVSI in order to enhance risk stratification models. Nonetheless, the prognostic value of MSI or MMR deficiency in EEC remains inconclusive, as evidenced by conflicting results across prior studies. Ongoing and future research may enable more accurate risk assessment and support the development of individualized treatment strategies based on both molecular and clinicopathological parameters.

AVAILABILITY OF DATA AND MATERIALS

The data underpinning the finding of this study can be obtained from the corresponding author, LA, upon a reasonable request.

AUTHOR CONTRIBUTIONS

MCT—project administration, supervision. LA—writing–review & editing, validation. TS—writing–original draft, investigation, data curation. GS—conceptualization, methodology. GK—resources, investigation, formal analysis. İH—writing–review & editing, visualization. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the institutional Ethics Committee of Ege University Faculty of Medicine (approval number: 22-7T/45). Consents were obtained from all participants included in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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