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Association of Microsatellite Instability with Pro-inflammatory Markers and Survival in Patients with Endometrial Cancer

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ABSTRACT

Objective: Endometrial cancer is the most common gynaecological cancer and the fourth most common malignancy after breast, lung and colorectal cancer in developed countries. The aim of this study was to investigate the relationship between microsatellite status and simple pro-inflammatory markers and their effect on survival outcomes in patients diagnosed with endometrial cancer.

Material and Methods: We retrospectively reviewed patients with a pathological diagnosis of endometrial cancer who were referred to our clinic between March 2019 and December 2023. Of these patients, 165 were included in our study.

Results: In patients with endometrium cancer, 114 patients had microsatellite stable (MSS) tumors, while mismatch repair deficient (dMMR) tumors were present in 30.91% of the entire cohort. No statistically significant difference was observed between the microsatellite groups according to serum inflammatory markers. When the survival of MSS and dMMR patients was analysed, no statistically significant difference was observed between both groups (p=0.875).

Conclusion: Our study found a higher rate of endometrioid subtype in dMMR tumours. There was no correlation between microsatellite status and serum inflammatory markers. Microsatellite status was not found to be associated with survival in endometrial cancer.

Keywords: Endometrial neoplasms; microsatellite instability; survival

INTRODUCTION

After cervical cancer, endometrial cancer is the most common gynaecological malignancy worldwide.[1] It is the most common gynaecological cancer and the fourth most common malignancy after breast, lung, and colorectal cancer in developed countries such as the United States of America.[2] More than 95% of endometrial cancers are adenocarcinomas originating from the endometrial epithelium, and mesenchymal malignancies originating from the muscle or stroma are observed less frequently.[3]

In a healthy cell, mutations rarely occur during deoxyribonucleic acid (DNA) replication. However, these are repaired by DNA repair systems. In the case of mutations in genes encoding DNA repair systems, mismatched DNA sequences known as microsatellites accumulate and genomic instability occurs. As a result, cancer formation is triggered.[4]

Microsatellite instability (MSI) is detected at different rates in many cancer types. Endometrial cancer is another cancer type that is notable following colorectal cancer among high MSI tumours. Tumours with deficient mismatch repair (dMMR) constitute 25-30% of endometrial cancers.[5] Detection of MSI is important because it has both prognostic significance and predictive value for the possible use of immune checkpoint inhibitor therapies according to current standards.[6]

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In addition to genetic alterations, the role of inflammation in carcinogenesis is well recognised. Simple blood parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and large unstained cell (LUC) have been investigated as pro-inflammatory markers and prognostic factors in many cancer types and have been confirmed to be both prognostic and predictive markers for systemic therapy in many malignancies.[7,8]

In a previous study conducted in colorectal cancer patients with high microsatellite instability (MSI-H), it was shown that patients with high inflammation parameters were more resistant to immunotherapy and had a worse prognosis.[9] However, to our knowledge, there are not enough studies on this subject in endometrial cancer.

The aim of this study was to investigate the relationship between MSI status and simple pro-inflammatory markers (NLR, PLR, MLE, LUC) and their effect on survival outcomes in patients diagnosed with endometrial cancer.

MATERIAL AND METHODS

We retrospectively reviewed patients with a pathological diagnosis of endometrial cancer, who were referred to our clinic between March 2019 and December 2023. Of these patients, 165, who were over 18 years of age, had MSI status assessed in their pathology and had regular follow-up at our clinic, were included in our study. Patients younger than 18 years, with unclear MSI status and irregular follow-up, were excluded from the study. Patients were retrospectively reviewed for clinical, laboratory, and pathological findings and treatment information.

Patients were staged according to the International Federation of Gynaecology and Obstetrics (FIGO) 2009 staging system. MSI status of the patients, was determined according to the immunohistochemistry pathology results. The time from pathological diagnosis to death from any cause was assessed as overall survival (OS). NLR was calculated by dividing neutrophils by lymphocytes, PLR by dividing platelets by lymphocytes, and MLR by dividing monocytes by lymphocytes. To determine these values, the blood test results of the patients at the time of initial diagnosis were used. Receiver operating characteristic (ROC) analysis was used to calculate cut-off values for inflammatory markers.

Statistical Analysis

IBM SPSS version 25 was used for statistical analysis. To understand normal distribution, a histogram and Shapiro-Wilk tests were used. Comparisons of categorical variables were made using the Fisher's exact test or the chi-square test, and comparisons of continuous variables were made using the Mann-Whitney U test. The mean ± standard deviation was used for numerical variables with a normal distribution, and the median (minimum-maximum) was used for variables with a non-normal distribution. Log-rank test, Cox regression analysis, and Kaplan-Meier survival curves were used to analyse survival. $P<0.05$ was accepted as statistically significant.

The Ethics Committee for Clinical Research at our hospital has decided that informed consent is not required due to the retrospective nature of the study. Ethical approval has been obtained for the study Ankara Bilkent City Hospital Ethics Committee (date: 14.2.2024/no: 24-18). The study was designed in accordance with the principles of the Declaration of Helsinki.

RESULTS

Our study included 165 patients who were diagnosed with endometrial cancer between March 2019 and December 2023, and whose MSI status was studied in their pathologies. The median age of the patients in the study was 64 (28-81) years. The Eastern Cooperative Oncology Group performance status was 0-1 for 86.1% of the patients, while 13.9% were 2-4. When the FIGO stages of the patients were analysed, 53.3% were early stages and 46.6% were advanced stages. Of these patients, 114 (69.09%) were microsatellite stable (MSS) and 51 (30.91%) were dMMR. Baseline clinical and pathological characteristics of the patients are shown in Table 1.

Cut-off values according to ROC analysis result: 0.12 for LUC [area under curve (AUC): 0.526, specificity: 50.4%, sensitivity: 61.5%, p=0.675], 1.45 for LUC percentage in serum (LUC%) (AUC: 0.429, specificity: 47.4%, sensitivity: 42.3%, p = 0.254), 2.72 for NLR (AUC: 0.612, specificity: 55.5%, sensitivity: 57.7%, p=0.071), 153.1 for PLR (AUC: 0.601, specificity: 51.1%, sensitivity: 61.5%, p=0.105) and 0.21 for MLR (AUC: 0.558, specificity: 55.5%, sensitivity: 57.7%, p=0.353). The ROC curve graph is presented in Figure 1.

When MSS and dMMR groups were compared in terms of clinical features such as age, menopausal status, performance status, and pathological features such as grade, p53 positivity, lymphovascular invasion, a significant difference was found only in histopathological subtype (p=0.001). Accordingly, 60.4% of the pathological subtypes of the MSS group patients were endometrioid, while 90.2% of the MSI-H group patients were endometrioid, the remaining patients were non-endometrioid. The comparison between the two groups according to baseline characteristics is shown in Table 2.

Microsatellite groups were compared according to serum inflammatory markers. When LUC, LUC%, NLR, PLR, and MLR

differences were compared between the two groups, no statistically significant difference was observed in terms of serum inflammatory markers Table 3.

Among patients with stage I-II in the MSS group, 10 (18.5%) patients received no adjuvant treatment, 24 (44.4%) patients received only adjuvant brachytherapy (BT) or radiotherapy (RT), and 20 (37.1%) patients received adjuvant chemotherapy (CT) in addition to BT or RT. In the dMMR group, 8 (34.7%) patients received no adjuvant treatment, 10 (43.5%) patients received only adjuvant BT or RT, and 5 (21.8%) patients received adjuvant CT in addition to BT or RT. In both groups, stage III patients received adjuvant CT, RT, and BT. In stage IV patients, one patient in each group could not receive systemic treatment due to performance reasons, while the remaining patients received CT. None of the patients received immunotherapy.

When the survival of MSS and dMMR patients was analyzed, the estimated median survival of MSS patients was 56.84 (22.82-90.86), months, while the median survival of dMMR groups could not be reached by the Kaplan-Meier method. The difference between the two groups was not statistically significant (p=0.875). Survival curves of the patients are shown in Figure 2. Subgroup OS analyses were performed according to MSI status for early stage (stage I-II) and advanced stage (stage III-IV) patients. No difference was found in the OS analysis for early-stage patients (p=0.836) and advanced-stage patients (p=0.862).

TABLE 1: Baseline characteristics of the patients.

Variables	n (%)
Age, years, median	64 (28-81)
<65 years	85 (51.5%)
≥65 years	80 (48.5%)
Menopausal status	
Premenopausal	32 (19.4%)
Postmenopausal	133 (80.6%)
ECOG performance status	
0-1	124 (86.1%)
2-4	41 (24.8%)
FIGO stage	
I-II	88 (53.3%)
III-IV	77 (46.7%)
Histological type	
Endometrioid	113 (69.8%)
Non-endometrioid	49 (30.2%)
Pathological grade	
1-2	83 (61.0%)
3	53 (39.0%)
Lymphovascular invasion	
Yes	102 (30.6%)
No	45 (69.4%)
p53 mutation	
Yes	27 (19.6%)
No	111 (80.4%)
P16 mutation	
Yes	10 (8.2%)
No	112 (91.8%)
MSI status	
MSS	114 (69.09%)
dMMR	51 (30.91%)

dMMR: Mismatch repair deficient; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; MSI: Microsatellite instability; MSS: Microsatellite stable.

TABLE 2: The features of microsatellite groups.

Variables	MSS (n=114)	dMMR (n=51)	p-value
Age, years			
<65 years	59 (51.8%)	26 (51.0%)	0.927
≥65 years	55 (48.2%)	25 (49.0%)	
Menopausal status			
Premenopausal	25 (21.9%)	7 (13.7%)	0.218
Postmenopausal	89 (78.1%)	44 (86.3%)	
ECOG performance status			
0-1	87 (76.3%)	37 (72.5%)	0.605
2-4	27 (23.7%)	14 (27.5%)	
FIGO stage			
I-II	60 (52.6%)	28 (54.9%)	0.787
III-IV	54 (47.4%)	23 (45.1%)	
Histological type			
Endometrioid	67 (60.4%)	46 (90.2%)	**0.001**
Non-endometrioid	44 (39.6%)	5 (9.8%)	
Pathological grade			
1-2	53 (60.9%)	30 (61.2%)	0.972
3	34 (30.1%)	19 (38.8%)	
Lymphovascular invasion			
Yes	68 (68.7%)	34 (70.8%)	0.791
No	31 (31.3%)	14 (29.2%)	
p53 mutation			
Yes	22 (23.2%)	5 (11.6%)	0.114
No	73 (76.8%)	38 (88.4%)	
P16 mutation			
Yes	7 (8.3%)	3 (7.9%)	0.935
No	77 (91.7%)	35 (92.1%)	

dMMR: Mismatch repair deficient; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; MSS: Microsatellite stable.

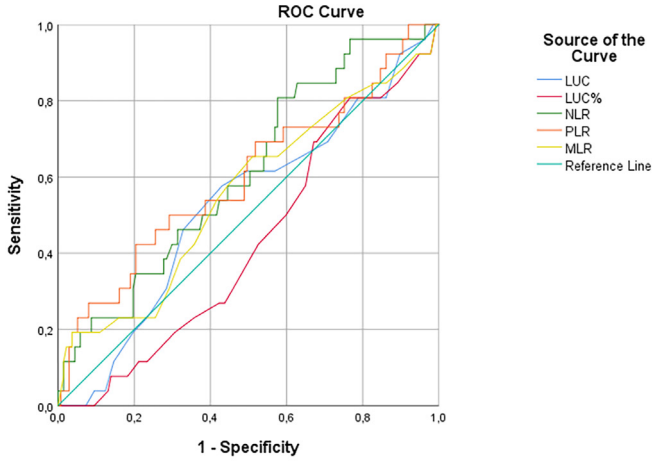

FIGURE 1: ROC curve to determine cut-offs for serum inflammatory markers.

LUC: Large unstained cell; LUC%: LUC percent in serum; MLR: Monocyte-lymphocyte ratio; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; ROC: Receiver operating characteristic

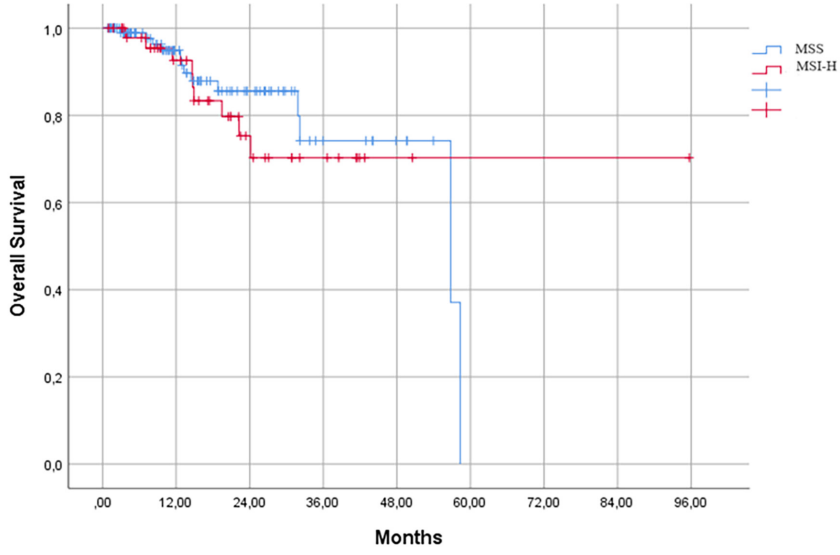

FIGURE 2: Overall survival rates of microsatellite groups.

MSS: Microsatellite stable; MSI-H: High microsatellite instability

TABLE 3: Association of serum inflammation markers with microsatellite groups.

Variables	dMMR, median	MSS, median	p-value
LUC	0.12 (0.04-0.34)	0.11 (0.04-0.031)	0.484
LUC%	1.50 (0.60-4.00)	1.40 (0.30-3.30)	0.208
NLR	2.58 (0.44-14.52)	2.72 (1.01-13.05)	0.748
PLR	162.22 (53.40-512.90)	151.14 (38.46-400.00)	0.225
MLR	0.19 (0.09-0.52)	0.22 (0.08-0.50)	0.638

dMMR: Mismatch repair deficient; LUC: Large unstained cell; LUC%: LUC percent in serum; MLR: Monocyte-lymphocyte ratio; MSS: Microsatellite stable; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio.

DISCUSSION

As a result of our study, no difference was found in serum inflammatory markers between MSS and dMMR groups in endometrial cancer. No significant difference in survival was observed between the microsatellite groups. We were not able to demonstrate a survival benefit in dMMR EC, possibly due to the heterogeneous study population, a limited sample size, and no IO use in dMMR patients at progression.

In recent years, with the increasing use of immunotherapy in cancer treatment, the microsatellite status of tumours has become much more prominent. The effectiveness of

immunotherapy in MSI-H tumours has made the study of microsatellite status in pathology almost mandatory in many cancer types.[10] In endometrial cancer, it has been observed that immunotherapy is very effective in MSI-H patients, and as a result, MSI status has started to be examined in patient pathology.[11,12] There are studies showing that approximately 30% of patients with endometrial cancer have MSI-H.[13] In our study, we observed that 31.1% of the patients were MSI-H, in accordance with the literature. There are studies in the literature showing that tumour subtypes may change in endometrial cancer according to MSI status. In the study by Fountzilas et al.[14], MSI-H tumours were predominantly of the endometrioid subtype, whereas in the study by Nagle et al.[15], MSI-H tumours were predominantly of the non-endometrioid subtype. In our study, it was observed that dMMR tumours were more likely to have endometrioid subtype than MSS tumours.

There are many studies reporting that inflammatory markers such as NLR, PLR, MLR, LUC, are associated with prognosis in many cancer types.[16-18] We are not aware of any studies in the literature that have correlated MSI status with serum inflammation levels in patients with endometrium cancer. In our study, no difference was observed between MSI status and inflammatory markers.

Fountzilas et al.[14] found better survival in MSI-H patients. A poorer prognosis for MSI-H tumours was found by Cosgrove et al.[19] and Nagle et al.[15] Studies also exist showing that MSI status does not affect survival. In our study, we observed that MSI status did not affect survival.[20,21]

As a result of our study, a higher rate of endometrioid subtype was observed in dMMR tumours. There was no correlation between MSI status and serum inflammatory markers. MSI status was not found to be associated with survival in endometrial cancer.

Study Limitations

The limitations of our study include its retrospective design, the heterogeneous nature of the patients who had varying performance status and were at different stages, and the inability to access all information for all patients due to the retrospective design. The clinical stages of the patients at the time of diagnosis and the treatments they receive are slightly different from each other.

CONCLUSION

In our study, no correlation was found between serum inflammation markers and microsatellite status in endometrial cancer. Microsatellite status did not affect the prognosis in endometrial cancer. Further studies on this subject are needed.

Ethics

Ethics Committee Approval: Ethical approval has been obtained for the study Ankara Bilkent City Hospital Ethics Committee (date: 14.2.2024/no: 24-18).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Concept: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Design: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Data Collection or Processing: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Analysis or Interpretation: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Literature Search: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Writing: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Critical Review: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A.

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