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Original Research

Microsatellite instability (MSI) in endometrial cancer; frequency and prognostic significance

Microsatellite instability (msi) by immunohistochemistry in endometrial cancer

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Abstract
Aim: In our study, we aimed to evaluate the frequency of MSI in endometrial cancer and its relationship with prognostic parameters and inflammatory indexes.
Material and Methods: MLH1, MSH2, MSH6, and PMS2 mutations were evaluated immunohistochemically in paraffin blocks of 74 patients diagnosed with endometrial cancer. If no staining was detected in any of these proteins, the tumor was considered microsatellite instable (MSI). Demographic and pathological data of the patients were obtained from the file records.
Results: MSI was detected in 21 (28.3%) of 74 patients; expression loss of MLH-1/PMS-2 (18.9%) in 14, PMS-2 (4.03%) in 3, MSH-2 (2.7%) in 2, MSH-6/PMS-2 (1.3%) in 1 and loss of expression of MSH-2/PMS-2 (1.3%) was observed in 1 of them. There was no significant difference between MSS and MSI groups in terms of age, grade, lymph node, stage, LVI, histological subtype. The 5-year survival rates were 73% in the MSS group and 46% in the MSI group, but this difference was not statistically significant (p=0.760).
Discussion: In conclusion, in this study, it was determined that MSI status did not affect the prognosis in endometrial cancers. With the widespread use of immunotherapies, the predictive role of knowledge of the MSI status in endometrial cancer comes to the forefront rather than its prognostic value. In addition, knowledge of the MSI status has gained importance in the new molecular classification of endometrial cancer.

Keywords
Microsatellite Instability (MSI), Endometrial Carcinoma, Prognosis

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Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries. It is the fourth most common cancer in women after breast, lung, and colorectal cancers. Despite its high incidence, mortality rates are low. Mortality rates are 4.1 per 100,000 women and 2.5% in cancer-related deaths [1].

Known risk factors for endometrial carcinoma are obesity, unopposed estrogen, chronic anovulation, diabetes, nulliparity, early menarche, late menopause, tamoxifen use, family history, and genetic predisposition [2].

There is no recommended screening test for endometrial carcinoma in asymptomatic patients. However, in patients with abnormal thickness increase, irregularity, and cystic degeneration in the endometrium on ultrasonography, an endometrial biopsy can help make the diagnosis. Abnormal uterine bleeding is present in 75-90% of patients diagnosed with endometrial cancer [3] .

Microsatellites are DNA base sequences consisting of 2-4 nucleotides and repeated 3-100 times sequentially. As the number of repeats increases, likelihood errors in the form of insertions or deletions during DNA replication increases. In a normal cell, these errors are recognized by MMR genes (Mismatch Repair Genes) and repaired. In one of the genes encoding proteins involved in mismatch repair (MLH1,MSH2, MSH6, PMS1, PMS2, MLH3, EXO1), any mutation or the development of epigenetic change causes dysfunction in related proteins [4]. In neoplastic lesions that develop due to the disruption of this mechanism, the number of microsatellite repeats in tumor tissues is different from that in normal tissues. This phenomenon is called Microsatellite instability (MSI) and is a marker of a DNA repair error that can lead to the accumulation of mutations in cells. MSI is closely associated with the carcinogenicity of hereditary tumors such as Lynch syndrome and was first identified in 1993 in sporadic and familial colon cancer. It is currently used as a secondary screening test for patients with suspected Lynch syndrome [5,6].

MSI is observed in 90% of colorectal cancers and 75% of endometrial cancers in Hereditary Nonpolyposis Colorectal Cancer (HNPCC) (7). MSI is observed in 12% of sporadic colorectal cancers and 25-30% of sporadic endometrial cancers [8] .

One of the clinical implications of the MSI test is in predicting the efficacy of anti-PDL1 therapy in MSI-associated endometrial cancers. The role of immunotherapy in many PDL1-expressing cancers is increasing. Clinical studies have shown that MSI-associated endometrial cancers respond better to anti-PDL1 therapy than microsatellite stable endometrial cancers. In the treatment of MSI-H endometrial cancers, the option of immunotherapy has taken its place in the treatment guidelines [9]. Therefore, routine evaluation of MSI status has become important.

However, the relationship between MSI status and prognosis is still unclear. Therefore, we planned to investigate the incidence of MSI and its relationship with prognosis and clinicopathological factors in patients with endometrial cancer followed in our clinic.

Material and Methods

The files of 150 patients diagnosed with endometrial carcinoma who applied to Afyonkarahisar Health Sciences University Medical Faculty Department of Medical Oncology between 01.01.2008 and 01.10.2020 were evaluated retrospectively. Patients who were older than 18 years of age, diagnosed with pathologically confirmed endometrial cancer, had sufficient file information and had regular follow-up data were included in the study. Seventy-six patients were excluded from the; because their pathological diagnosis was endometrial sarcoma, carcinosarcoma, or mixed histology, 5 patients due to insufficient follow-up data, and 6 patients because pathology blocks were not available in our center. The remaining 74 patients were included in the study. Information such as demographic data, tumor grade, lymph node status, tumor size of the patients was obtained retrospectively through file scanning or medical records in the hospital information system. The patient's risk factors and treatments, relapse dates, last control dates or exitus dates were recorded.

Paraffin blocks of tumor tissue of the patients included in the study for MSI analysis were obtained from the archive of the Department of Pathology. Sections 1-1.5 mm thick were taken from the paraffin blocks with a microtome knife and placed on adhesive slides. Deparaffinization was performed at 60 °C for 30 minutes. A dewax solution was applied at 72 °C. Washing was done with alcohol. ER-2 solution was applied for 12 minutes. Bond Wash washing solution at 35 °C, then distilled water, Hematoxylin-eosin for 5 minutes, distilled water and finally washing water were applied, respectively.

Evaluation of all immunohistochemical stainings was carried out in accordance with the literature, using the method of Gark et al [10]. Accordingly, normal endometrial glandular structures, stromal cells, and lymphocytes were used as internal positive controls. Hyperplasia areas were excluded from the evaluation. The presence or absence of staining was detected in tumor cell nuclei. Any presence of nuclear staining was considered positive and evaluated as microsatellite stability (MSS). Total staining loss in tumor cell nuclei was evaluated as negative and considered as microsatellite instability (Figure 1).

Statistical analysis

Descriptive statistics for categorical variables are given with frequency and percentage values. In the comparisons between groups, an independent sample t-test was used for data conforming to normal distribution, and the Mann-Whitney U test was used for data not conforming to a normal distribution. Comparison of categorical variables between groups was determined using the Pearson Chi-square test, survival times and factors affecting survival time were determined using the Kaplan-Meier method. The log-rank test was used when comparing the survival times between groups. IBM SPSS 22.0 was used for statistical analysis, $p<0.05$ was considered statistically significant.

Ethical Approval

The study was started after the approval of the ethics committee with the decision numbered 2020/1 dated 03.01.2020 of the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University Faculty of Medicine.

Results

The median age of the diagnosed patients was 61±9.5 (37-85) years. Thirty (40.5%) of the patients were stage I, 21 (28.4%) were stage II, 14 (18.9%) were stage III, and 9 (12.2%) were stage IV. Pathological subtypes of the patients were endometrioid adenocarcinoma in 85.1% (62), serous carcinoma in 10.8% (8), and other histological subtypes in 4.3% (3), respectively. Of the patients, 16 (21.6%) had grade 1, 35 (47.3%) grade 2, and 23 (31.1%) grade 3 tumors. At the time of analysis, 15 (20.2%) of the cases were exitus, only 2 (2.7%) of the cases relapsed. The clinical and demographic data of the study group are summarized in Table 1.

Microsatellite instability was detected in 21 (28.3%) of 74 patients. Of these patients, 14 had MLH-1/PMS-2 (18.9%), 3 had PMS-2 (4.03%), 2 had MSH-2 (2.7%), 1 had MSH- 6/PMS-2(1.3%), 1 had loss of expression of MSH-2/PMS-2 (1.3%). Fifty-three patients with no loss of expression in any MSI marker were considered MSS.

There was no difference between the MSI and MSS groups in terms of age and lymph node metastasis (p=0.190). Lymph node metastases were detected in 13 (17.8%) patients with MSI, while 7 (9.6%) did not have lymph node metastases. Myometrial invasion rates were different between MSI and MSS groups. While 95.2% of the patients in the MSI group had myo-

Table 1. Baseline clinical characteristics of patients.

	Results* (n=74)
Age, years	61.0 ± 9.0
Smoking, n (%)	1 (1.4)
Menopausal status, n (%)	
Premenopausal	11 (14.9)
Postmenopausal	63 (85.1)
Histological type, n (%)	
Endometrioid adenocarcinoma	62 (85.1)
Serous carcinoma	8 (10.8)
Others	3 (4.1)
Histological grade, n (%)	
Grade 1	16 (21.6)
Grade 2	35 (47.3)
Grade 3	23 (31.1)
Stage, n (%)	
1	30 (40.5)
2	21 (28.4)
3	14 (18.9)
4	9 (12.2)
Lymph node metastasis, n (%)	
Yes	39 (52.7)
No	35 (47.3)
Lymphovascular space invasion, n (%)	
Yes	17 (23.0)
No	39 (52.7)
Missing data	18 (24.3)
Myometrial invasion, n (%)	
No	15 (20.3)
Yes	59 (79.7)
Recurrence, n (%)	
No	71 (95.9)
Yes	2 (2.7)

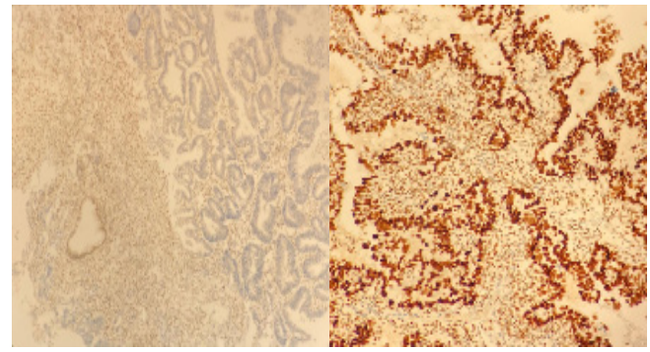


Figure 1. A: Total loss of tumor cells in PMS-2 immunohistochemical study, strong positive reaction in normal endometrial gland nuclei and lymphocytes (x100). B: Strong nuclear positive reaction (x200) in both tumor cell nuclei and stromal elements and lymphocytes in the PMS-2 immunohistochemical study

Table 2. Comparison of groups according to MSI status

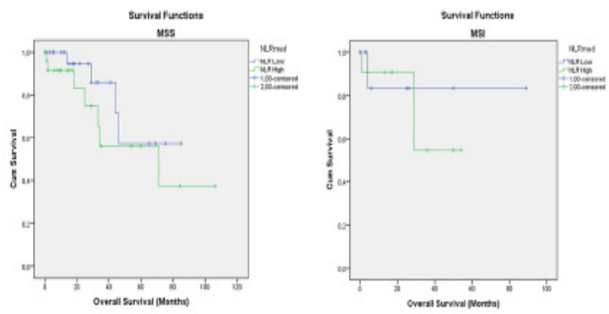
	MSI (n=21)	MSS (n=53)	P value
Age, years	61 ± 9.5	60 ± 10.4	0.939
Menopausal status, n (%)			
Premenopausal	3 (14.3)	8 (15.1)	0.621
Postmenopausal	18 (85.7)	45 (84.9)	
Histological type, n (%)			
Endometrioid adenocarcinoma	21 (100)	42 (79.2)	0.077
Serous carcinoma	0	8 (15.1)	
Others	0	3 (5.7)	
Histological grade, n (%)			
Grade 1	2 (9.5)	14 (26.4)	0.121
Grade 2	13 (61.9)	22 (41.5)	
Grade 3	6 (28.6)	17 (32.1)	
Stage, n (%)			
1	6 (28.6)	24 (45.3)	0.180
2	9 (42.9)	12 (22.6)	
3	5 (23.8)	9 (17.0)	
4	1 (4.8)	8 (15.1)	
Distant metastasis, n (%)			
yes, n (%)	6 (28.6)	12 (23.1)	0.415
no, n (%)	15 (71.6)	40 (76.9)	
Lymph node metastasis, n (%)			
yes, n (%)	14 (66.7)	25 (47.2)	0.104
no, n (%)	7 (33.3)	28 (52.8)	
Lymphovascular space invasion,			
yes, n (%)	4 (22.2)	13 (34.2)	0.278
no, n (%)	14 (77.8)	25 (65.8)	
Myometrial invasion, n (%)			
yes, n (%)	20 (95.2)	39 (73.6)	0.031
no, n (%)	1 (4.8)	14 (26.4)	
CA 125	23.5 (11.3-103.3)	19.5 (13.3-57.3)	0.442
Mortality, yes, n (%)	4 (19)	11 (20.8)	0.573
NLR, n (%)			
Low, n (%)	10 (47.6)	27 (50.9)	0.500
High, n (%)	11 (52.4)	26 (49.1)	
SII, n (%)			
Low, n (%)	12 (57.1)	25 (47.2)	0.303
High, n (%)	9 (42.9)	28 (52.8)	

metrial invasion, this rate was 73.6% in the MSS group and was statistically significant (p=0.031).

Both groups were found to be similar in terms of histological grade (p=0.230). It was determined that 2 (2.7%) of the patients with MSI were grade 1, 12 (16.4%) were grade 2, and 6 (8.2%) were grade 3. A summary of the evaluations made in terms of prognostic factors among the groups according to MSI status is given in Table 2.

The relationship between MSI and MSS patient groups and inflammation parameters was also evaluated in the study. NLR (neutrophil-lymphocyte ratio), SII (systemic immune inflammation index) parameters were used for inflammation parameters. Since no significant value could be obtained by ROC analysis for NLR and SII cut-off values, the median value was accepted as the cut-off value. When those below and above the median value in terms of NLR and SII were compared according to their MSI status, no statistically significant difference was observed (p=0.500 and p=0.303), respectively. Again, when the survival rates below and above the NLR and SII cut-off values were compared between the MSI and MSS groups, no significant difference was found between the groups (p=0.269 and p=0.164, respectively) (Figure 2). The median overall survival in the entire study group was 17 months, and disease-free survival was 18.5 months. The 5-year survival rate was 73% in the MSS group, and 46% in the MSI group, and this difference was not statistically significant (p=0.760) (Figure 3).

A)



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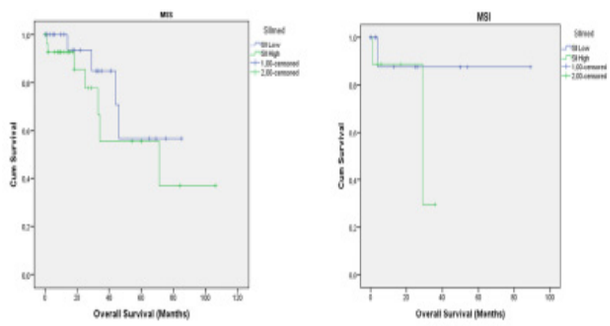

Figure 2. A) Kaplan-Meier survival curves for NLR in the MSS and MSI patients groups. (p=0,269) B) Kaplan-Meier survival curves for SII in the MSS and MSI patients groups. (p=0,164)

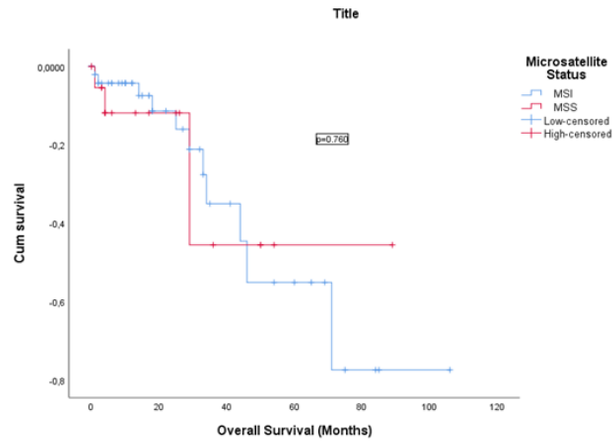

Figure 3. Overall survival analysis according to Microsatellite Instability Status

Discussion

In our study, in which we evaluated the relationship between MSI status and prognostic factors in sporadic endometrial cancer, we found that there was no statistically significant difference in prognosis in MSI tumors compared to those with MSS tumors. In terms of 5-year survival rates, although survival seems to be shorter in MSI tumors than in MSS tumors (5-year OS 73% vs 43%), this difference was not statistically significant.

No statistically significant difference was found between MSI and MSS groups in terms of prognostic factors such as age, stage, grade, LVI, lymph node metastasis, and distant metastasis. The rate of myometrial invasion in MSI tumors was statistically significantly higher than in MSS tumors.

MSI is observed in hereditary non-colorectal polyposis coli (HNPCC) associated cancer syndromes, 90-95% of colorectal cancers, and 65-75% of endometrial cancers [11]. The discovery that the presence of MSI has a prognostic effect in colorectal cancers paved the way for its investigation in gynecological malignancies as well. However, there is no clear data on the prognostic significance of MSI status in endometrial cancer and the study results are confusing. The rate of MSI in endometrial cancer in sporadic cases is 25-30% [8]. Similarly, the rate of MSI was found to be 28.3% in our study. When we look at the studies on this subject in the world, it is seen that the rate of MSI is very variable. In a study conducted in the USA, the rate of MSI was found to be 20% in sporadic endometrial cancers [12]. In a study conducted in Pakistan, it was found to be 44% [13]. It is thought that the reasons for the different results may be related to the evaluation of small study groups quantitatively, retrospective analyzes, the use of different marker panels for MSI detection, not taking into account the effect of histological type, and racial characteristics.

In our study, the highest loss of MLH-1/PMS-2 expression (66%) was observed in patients with MSI. Similar to our study, in the study by Hashmi et al., the highest loss of MLH1/PMS-2 expression was observed (60%) in patients with MSI [13]. The presence of MSI in uterine sarcomas was less than 5% [14]. Considering this situation, cases with pathology subtype sarcoma were not included in our study.

In a large series of 1024 cases in the gynecology/oncology group,

MMR defects were found to be associated with poor prognostic factors such as advanced stage (p=0.001), myometrial invasion (<0.001) (15). In the study by Sahinturk et al., 26.3% of MSI cases were stage I, 31.6% were stage II, 42.1% were stage III, and this relationship was statistically significant (p = 0.014) [16]. In our study, although myometrial invasion was statistically significantly higher in the group with MSI (p=0.008), there was no statistical difference in terms of disease stage (p=0.202). Here, it was seen that myometrial invasion may be associated with MSI. However, it can be thought that detection of the disease at an early stage may limit its effect on prognosis.

In the study by Arabi H et al., no statistically significant difference was found in survival (p=0.700) between patients with MSI and MSS, similar to the results of our study [17]. In the study by Kanopiene et al., MSI status was associated with better survival, early cancer stage, higher tumor differentiation, and endometrioid histology [18]. The Kaplan-Meier survival analysis did not show a statistically significant difference between patients with MSI-H and MSS tumors (p=0.400). In our study, there was no statistical difference in the overall survival analysis between cases with MSI tumors and MSS tumors (p=0.760), and this result was consistent with the literature.

Today, it is known that MSI is a marker that predicts the use of immunotherapies. Based on our study results, we think that MSI status may be a marker for Lynch syndrome screening and selection of patients for whom immunotherapies can be used, rather than prognosis.

The effect of systemic inflammation on cancer development has attracted great attention in recent years. Analysis of hematological inflammatory markers and their potential as prognostic factors have been investigated in various malignant tumors. In the study by Holub et al., pretreatment inflammatory markers (NLR ≥ 2.2, SII ≥ 1100) were found to be associated with worse survival outcomes in high-risk endometrial cancer patients who were surgically staged as FIGO I-III and treated with adjuvant EBRT (post-operative external radiotherapy) [19]. In our study, we evaluated the relationship between MSI status and inflammation parameters. However, we found the distribution of NLR and SII values in MSI and MSS subgroups to be similar (p=1,000 and p=0.600, respectively).

The prognostic value of the presence of MSI in endometrial cancer is still unclear. In our study, the effect of the presence of MSI on the prognosis could not be demonstrated. In our study, although there was a statistically significant difference between the presence of myometrial invasion and MSI (p=0.008), it was found that there was no effect on survival in accordance with the literature.

However, there are some limitations to our study. Our study is a retrospective study with a small number of patients and a short follow-up period. Another limitation is the lack of knowledge of other molecular factors that may have an impact on the prognosis of patients, such as P53, loss of PTEN, and POLE mutation.

Conclusion

In this study, it was determined that MSI status did not affect the prognosis in endometrial cancers. In order to have a clear understanding of the prognostic value of MSI in endometrial cancer, prospective, well-designed studies involving a large number of patients and examining other prognostic molecular markers other than MSI are needed. With the widespread use of immunotherapies, the predictive role of knowing the MSI status in endometrial cancer comes to the forefront rather than its prognostic value. In addition, knowledge of MSI status has gained importance in the new molecular classification of endometrial cancer.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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