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Relationship between Microsatellite Status and Other Prognostic Factors in Patients with Colon Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. Author OE designed the study and wrote the first draft of the manuscript, Author SC wrote the protocol, author FA managed the literature searches, author ÜM performed the statistical analysis, author CY managed the analyses of the study, author AEÜ made final checks and corrections. All authors read and approved the final manuscript.

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ABSTRACT

It is reported that 0.5-13 % of all colorectal cancers are hereditary. Many mutations that cause genomic instability have been described lately in this cancers; the most famous one is yet microsatellite instability pathway. Investigating the presence of these mutations is important in tailoring patients' treatment and predicting prognosis.

Aims: We evaluated the association between micro satellite status and other pathologic prognostic factors like grade, tumor size, lymph node metastasis, lymphovascular invasion and perineural invasion in patients who underwent curative colon resection for colorectal cancers (CRC) in our clinic in the past five years.

Study Design: A total of 205 sequential patients who were older than 18 and had curative colon resection for CRC in Ankara University Surgical Oncology Unit and been tested for microsatellite instability (MSI) were analyzed on behalf of the facultys' database.

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Methodology: Pathology results had been determined and tumor localizations, lymph node metastasis status, grade, lymphovascular and perineural invasion status were evaluated. Information about MSI status and defected genes were obtained from detailed pathology reports. Patients were divided into two groups as MSI and MSS.
Results: No significant difference was found between two the groups in the context of microsatellite instability status. Lymphovascular invasion had been seen higher in high frequency microsatellite instability (MSH-H) compared to low frequency microsatellite instability (MSH-L) group (76.4% vs 53.1%, *P* =.02). There was no statistical difference in perineural invasion between the two groups (*P* = 0.102). Signet ring cell status between the groups we found a higher rate of signet ring cells and consequently a higher grade in MSH-H group (17.6% vs 10.6%, *P* = 0.042).
Conclusion: In conclusion, although many important points have been identified in our study, more studies are needed to compare the evaluation of MSI in colon cancer with other prognostic factors and to investigate its effect on the course of the disease.

Keywords: Colon cancer; micro satellite status; prognosis; mutations.

1. INTRODUCTİON

It was reported that 0.5-13 % of all CRC are hereditary [1]. However, it is a known that gene mutations has also an association with sporadic colorectal cancers. Although many mutations that cause genomic instability have been described lately; the most famous one is yet MSI pathway. Structural pathologies in DNA mismatch repairing (MMR) system refers to microsatellite instability which can be seen in 15% of all sporadic colon cancers. Abnormal MMR genes fail to correct the mistakes that are left behind by replicative polymerases or remove insertion and deletion loops (IDL) and this causes an increased mutation load in genome [2]. The mistake in MMR system origins mostly from hypermethylation of MLH1 DNA repair gene. 20% of these mistakes are sporadic. Whereas 3% of the mare a part of Lynch syndrome which is an autosomal dominant germline mutation of a MMR gene [3]. MSI can be detected by polymerase chain reaction or MMR absence can be identified immunohistochemically. To assess MSI in tissues, a panel that contains four different mononucleotide repeat markers called MLH1, MSH2, MSH6 and PMS2 is used. Three different tumor phenotypes are described for sporadic CRCs. These are microsatellite stability (MSS), MSI-L and MSI-H. MSS is described as absence of instability markers whereas instability in one marker or less than 30% of the markers is called MSI-L and instability in more than 30% of the markers is called MSI-H. Nowadays multiple centers support MSI tests for Lynch Syndrome screening. Despite the common opinion, these tumors have good outcomes but also they have resistance to standard chemotherapy regimens that contain 5 fluoruracil which is a substantial drug of CRC treatment [4]. The impact of additional drugs like oxaliplatin and irinotecan are also lower [5,6]. It is known that these tumors respond well to immunotherapies especially like anti-PD-1/PD-L1 [7,8]. These important differences in CRC management and prognosis supports that it is crucial to investigate for MSI or MMR genes routinely in CRC patients.

In our study we evaluated the association between microsatellite status and other pathologic prognostic factors like grade, tumor size, lymph node metastasis, lymphovascular invasion and perineural invasion in patientswho underwent curative colon resection for CRC in our clinic in the past five years.

2. PATIENTS AND METHODS

2.1 Patient Selection

A total of 205 sequential patients who were older than 18 and had curative colon resection for CRC in Ankara University Surgical Oncology Unit and been tested for MSI were analyzed on behalf of the facultys' database. Fourteen patients are excluded due to lack of clinical information. The patients who were stage 4, took preoperative simultaneous or neoadjuvant chemotherapy and had recurrent tumors were excluded. Patients who had been suspected to have Lynch Syndrome, who had synchronous colon cancer, hereditary polyposis or familial adenomatous polyposis were excluded. The remaining 158 patients who match the criteria are included. Patients' medical history records had been reviewed and demographic data was collected. Pathology results had been determined and tumor localizations, lymph node metastasis status, grade, lymphovascular and perineural invasion status were evaluated. Operation notes

had been checked to verify tumor localizations. Information about MSI status and defected genes were obtained from detailed pathology reports. Patients are divided into two groups as MSI and MSS.

2.2 Surgical Procedure

All the surgical procedures which were mainly the standard procedure for colorectal cancers including the unblock resection of the colon segment including the tumor, with complete regional lymph node dissection by open or laparoscopic approach were performed by the same surgical team. To analyze the MSI status, genomic DNA were collected from the tumor tissue in the paraffin blocks for PCR enlarging. No evidence of instability in the markers were accepted as MSS whereas instability in one marker was defined as MSI-L and instability in two or more markers was defined as MSI-H. Tumors which were located between caecum and 1/3 distal part of transverse colon were classified as proximal colon cancers, 1/3 distal part of transverse colon and descending colon as distal colon cancers and tumors which were located in sigmoid colon or rectum as rectosigmoid colon cancer.

2.3 Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 10.0. For analyzing the association and the statistical differences between MSI and other prognostic factors Mann-Whitney test was used. To evaluate categoric variables Fisher exactorchi-square tests were used. P values less than 0,05 were considered as statistically significant.

3. RESULTS

MSI-H colorectal cancer was found in 17 out of 158 patients (10.7%), (Table 1). There was no association between age or gender and microsatellite status. 52.9% of the MSI-H patients had proximal colon cancer whereas in MSS and MSI-I group 25.5% of the tumors were localized proximally, which is a statistically significant difference (*P* = 0.02).

Table 1. Demographic, clinical and pathological features of 158 colorectal cancer patients who underwent surgical resection with a comparison between MSI-H patients and MSS, MSI-L patients

		MSI-H	MSS, MSI-L	*P* value*
MMR gene status		**17**	**141**	
Age	>70	7 (41.1%)	89 (63.1%)	0.26
	<70	10 (58.8%)	52 (36.8%)	
Gender	Female	6 (35.2%)	67 (47.5%)	0.58
	Male	11 (64.7%)	74 (52.4%)	
Tumor location	Proksimal	9 (52.9%)	36(25.5%)	0.02
	Distal	3 (17.6%)	34(24.1%)	
	Rektosigmoid	5(29.4%)	71(50.3%)	
Stage	I	2 (11.7%)	30 (21.2%)	
	II	9 (52.9%)	42 (29.7%)	
	III	6 (35.2%)	69 (48.9%)	
Grade	I	1 (5.8%)	15 (10.6%)	<0.001
	II	12 (70.5%)	121 (85.8%)	
	III	4 (23.5%)	5 (3.5%)	
Signet Cell	>50%	3 (17.6%)	15 (10.6%)	0.04
T stage	1-2	2 (11.7%)	50 (35.4%)	<0.001
	3-4	15 (88.2%)	91 (64.5%)	
N stage	0	10 (58.8%)	68 (48.2%)	0.26
	1	4 (23.5%)	44 (31.2%)	
	2	3 (17.6%)	29 (20.5%)	
Tumor size	>4 cm	15(88.2%)	102(72.3%)	0.09
	<4 cm	2(11.7%)	39(27.6%)	
Lymphovascular invasion	Pozitif	13(76.4%)	75(53.1%)	0.02
Perineural invasion	Pozitif	11(64.7%)	58(41.1%)	0.11

**MSI-H=microsatellite instability high, MSI-L=microsatellite instability low, MSS=microsatellite stable.*
**Chi-square test*

MSI-H patients had mostly stage 2 cancer and then respectively stage 3 and stage 1. MSS and MSI-L patients had mostly stage 3 cancer and respectively stage 2 and stage 1. Advanced T stage (88.2% vs 64.5%, *P* <0.001), and poor differentiation (23.5% vs 3.5%, *P* <0.001) were significantly higher in MSI-H group. Nodal staging of the two groups were similar where the majority of the patients had N0 disease and then N1 and N2 respectively. The patients were divided in to two groups according to tumor size. First group includes the patients which had a tumor size above 4 cm and the other group had a tumor size below 4 cm. This division was based on a study which reported that in colorectal cancers, tumor size cut-off value which affects the prognosis was 4 cm [9]. No significant difference was found between two groups in the context of microsatellite instability status. Lymphovascular invasion had been seen higher in MSH-H group (76.4% vs 53.1%, *P* =0.02). There was no statistical difference in perineural invasion between two groups (*P* =0.11). When we looked for the signet ring cell status between the groups we found a higher rate of signet ring cells and consequently a higher grade in MSH-H group (17,6% vs 10,6%, *P* = 0.04).

4. DISCUSSION

CRC's which have microsatellite instabilities have different clinical and pathological features as well as different responses to chemotherapeutic agents. MSI is positive in more than 90% of the Lynch Syndrome patients but only 15% of the patients with sporadic CRC have MSI [10]. Although MSI rate is low in sporadic CRC's, there is still a great number of patients when the prevalence is considered [11]. The mechanism of pathogenesis is the methylation of promoter regions of some DNA MMR genes such as hMLH1. There is a close relationship between DNA methylation and age, there fore MSI positive sporadic CRC's are mostly seen in elderly patients. Patients with Lynch Syndrome can easily be distinguished from the others by detecting MSI in young population with colorectal cancer [12]. In our study there was no statistical difference in the age of diagnosis between MSI and MSS groups (*P*= 0.26). This finding is concordant to other studies [13,14]. We found no gender difference between groups. Proximal cancers were usually associated with DNA mismatch repairing defects, hypermethylation and MSI whereas in distal cancers allele loss and chromosomal instability were revealed more. And also in hereditary non-polyposis colorectal cancer syndrome in other words Lynch syndrome, proximal colon cancers are seen more. In 2/3 of Lynch syndrome patients and more than 90 % of MSI positive sporadic CRC patients; the lesion is localized proximally. In our study ascending colon tumors were statistically higher in MSI group than MSS group (*P*= 0.26). MSI tumors are usually tend to be poor differentiated [15,16]; and signet ring cell configuration and mucinous component rates are high [14]. Our results are also similar; we found that MSI group had significantly more patients with high grade and signet ring cell tumors than MSS group. Tumors below 4 cm had been detected more in MSI-H group. In a study which analyzes the cut-off level of tumor size which affects prognosis; tumors larger than 4 cm is found to be associated with poor prognosis. Although this result is concordant to good prognosis of MSI-H tumors, according to the asymmetry in population of groups, we do not accept this result as a significant difference. Also we did not find a relationship between MSI status and >4 cm tumor size (*P*= 0,09). Buckowitz et al. (2005) reported in their study that MSI increases host immunity that prevents metastasis by a lymphocytic infiltration reaction like in Crohn's disease [17]. It is thought that lymphocytic reaction increases local immunity and helps there action against cancer by representing more antigen. In our study, besides the lymphocytic response to the tumor we found a significantly higher rate of lymphovascular invasion in MSI-H group (*P* =0.02). However, we found no statistical difference in perineural invasion between groups (*P*= 0,10). In literature a relationship is shown between MSI-H and high lymph node positivity, low lymph node ratio and poor differentiation [13]. Unlike this result we did not see an association between lymph node staging and MSI status. When we compared microsatellite instability between the three nodal stage groups we could not find a statistical difference (*P* =0.32).

Our study was a single-centered retrospective study therefore it has a probability of electionbias. Additionally our study includes few MSI-H patients therefore further studies including more patients with MSI-H are needed. Another limitation of this study is the absence of a propensity score match to prevent bias in patients' clinicopathological features. Propensity score match would have been in significant therefore could not have been done because of the asymmetry in population of the groups and the limitation of the MSI-H group with 17 patients.

5. CONCLUSION

In this study, in which we examined the relationship between MSI status in CRCs and other prognostic factors, we found that it was closely related with tumor grade and T stage. From this result, we deduce that survival studies examining the effect of this relationship on prognosis are needed.

CONSENT

Written informed consent was obtained from all the patients.

ETHICAL APPROVAL

This study is planned after the approval of Ankara University Medical Faculty Ethical Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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