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RESEARCH ARTICLE

Effect of Mismatch Repair and Human Epidermal Growth Receptor 2 Expression on Prognosis in Colon Adenocarcinoma

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ABSTRACT

Aim: Colon adenocarcinomas are common worldwide and are among the most common causes of cancer-related deaths despite recent advances. In our study, we aimed to investigate the effect of the expression of human epidermal growth receptor 2 (HER2) and mismatch repair (MMR), which are used in the treatment of other solid organ tumors, on prognosis in colon adenocarcinoma.

Method: HER2 and MMR expressions were examined by immunohistochemical examination by identifying colon adenocarcinoma diagnosed and treated in our center between 2010 and 2019. Clinicopathological features and disease-free survival (DFS) were compared with the expressions.

Results: The mean DFS was 49.71 months in patients with HER2 score 3 and 104.45 months in patients with microsatellite instability. A HER2 score of 3 in patients with colon adenocarcinoma increases the mortality risk 3.36 times in multivariate analysis. Microsatellite instability was not associated with clinicopathological features and prognosis.

Conclusion: HER2 was found to be an independent prognostic factor in patients with colon adenocarcinoma.

Keywords: Colon adenocarcinoma, human epidermal growth receptor 2, mismatch repair, microsatellite instability, prognosis

Introduction

Colon cancer is among the top five most common organ tumors.[1] Despite its molecular characteristics, tumor stage remains the gold standard in terms of prognosis.[2] Colon cancer is a prevalent form of tumor worldwide, and while molecular characteristics are important in predicting prognosis, tumor stage remains the primary determinant.[1,2] Tumors can be classified as either microsatellite stable (MSS) or microsatellite instable (MSI), depending on the status of the mismatch repair (MMR) system. Deficiency in the MMR system is caused by inactivation of genes responsible for MMR, namely MLH1, MSH2, MSH6, and PMS2. MMR immunohistochemical staining results were compatible with the genetic results. MSI tumors can be further categorized as MSI with or without germline mutations in DNA.[3] The frequency of MSI tumors is approximately 15% (12% are sporadic, and 3% are inherited).[4] MSI tumors have been reported at a rate of 24% in advanced metastatic tumors.[5,6] Patients with MSI colon cancer have histological and molecular features, such as high lymph node involvement and poorly differentiated colon cancer.[7] However, patients with MSI tumors are more sensitive to immune checkpoint inhibitors than are patients with low microsatellite instability in colon cancer.[8] However, it should be noted that the prognosis may be heterogeneous in patients with MSI tumors. This is especially important in stage 2 patients, and this group of patients with a poor outcome may require adjuvant chemotherapy to prevent relapse after surgery.[5]

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Studies have shown that overexpression of human epidermal growth receptor 2 (HER2) in colon cancer may be associated with lower disease-free survival (DFS) and overall survival (OS).[9-11] HER2 is a tyrosine kinase-related epidermal growth factor receptor (EGFR) located on 17q12.[12] Efforts have been made to target HER2 with trastuzumab for the treatment of gastric and breast cancers, and this approach has shown effectiveness. Consequently, there have been drug-targeting efforts in colorectal cancers.[11-13] HER2 has been incorporated into the treatment of patients with metastatic colon cancer with appropriate HER2 status.[15] Additionally, the relationship between HER2 and clinicopathological prognostic factors is contradictory.[9,14] These conflicting findings suggest that the role of HER2 in colon cancer requires further investigation.

In this study, the relationship between MMR and HER2 status, clinicopathological findings, and survival in patients with colon adenocarcinoma is retrospectively examined in light of literature information.

Materials and Method

Patients diagnosed with colon cancer and followed up in the oncology clinic between 2010 and 2019 were identified from the pathology department and hospital records. The study was conducted in cases with surgical resection material.Approval for the study was obtained from the Hittite University Clinical Research Ethics Committee (approval number: 2023-168, dated: 26.12.2023).

A total of 146 patients diagnosed with colon adenocarcinoma were identified based on pathology records. Confidentiality of patient information was ensured.

Histologic Study

The histopathological features of 146 patients were examined by two expert pathologists (BY and YB) who were blinded to the patients' clinical information. The examination was conducted using the tumor node metastasis 8th classification.[16] The study focused on a specific group of patients and did not include those diagnosed with other rare types, such as neuroendocrine carcinoma or pure mucinous carcinoma. Tumors of type pT1 were not detected, and since there were not enough patients in the pT2 and pT3 groups, pT2-3 and pT4 were grouped to be able to work statistically. Furthermore, patients whose materials could not be accessed and those with no tissue left for examination (n=24) were also excluded. Patients who received neoadjuvant treatment were excluded from the study. All patients could receive surgical treatment. Formalin-fixed paraffin-embedded tumor tissues from 122 patients with adenocarcinoma meeting the study criteria were sectioned serially at 4-micron thickness for hematoxylin-eosin, MMR (MLH1, MSH2, MSH6, PMS2), and HER2 analysis (Figure 1).

Clinicopathological data, sex, patient age at diagnosis, tumor location, diameter, depth (pT), lymph node metastasis, organ metastasis, tumor grade, angiolymphatic invasion, perineural invasion, and clinical stage were determined. DFS time and the number of deaths were recorded until the study termination date (June 2023).

Stage and tumor depth ratios were grouped separately according to the distribution of the cases, and the differences in the ratios between HER2 scores, MMR status, and prognosis were analyzed according to the size of the ratios in the cross-table.

Immunohistochemical Study

The following immunohistochemical staining was performed using the Dako platform (Dako Omnis closed system immunohistochemical staining device), in accordance with the manufacturer's instructions. The following Dako platform clones were used: Clone A048529 for HER2, Clone FE11 for MSH2, Clone ES05 for MLH1, Clone EP49 for MSH6, and Clone EP51 for PMS2. A previously detected positive tumor tissue was selected as the HER2 control. MMR colon tumor tissue samples were selected as MMR-positive controls. Since the immunohistochemical method was used in the study, MMR examinations were grouped as MSI/MSS. The slides underwent evaluation using a Nikon Eclipse Ni microscope. Tumor areas were examined sequentially at low-to-high magnification. The artifacts and necrotic areas were not evaluated.

Statistical Analysis

A statistical analysis was conducted using IBM SPSS Statistics version 22 software (SPSS Inc., Chicago, IL, USA). The mortality effects were examined using Cox regression analysis. The Kolmogorov-Smirnov test was used for the normality analysis of variables. When the dependent variable was quantitative,

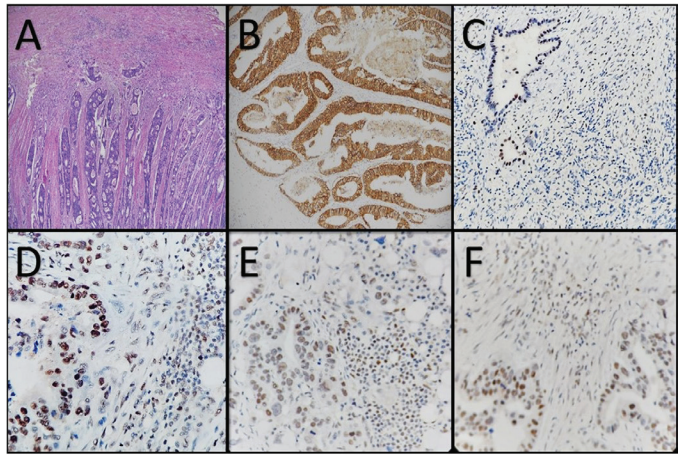

Figure 1. Colorectal cancer H&E staining and mismatch repair immunohistochemistry staining; A-Colon adenocarcinoma H&E, 10X, B-HER2 score 3 staining, 20X, C-PMS2 positive staining, 40X, D-MLH1 positive staining, 40X, E-MSH2 positive staining, 40X, F-MSH6 positive staining, 40X
HER2: Human epidermal growth receptor 2, H&E: Hematoxylin and eosin

two independent groups were compared using the Mann-Whitney U test, and more than two independent groups were compared using the Kruskal-Wallis test. If the variables were distributed normally, median values were determined using Kaplan-Meier survival analysis. Descriptive statistics were performed using Kaplan-Meier analyses and evaluated with log-rank tests. The chi-squared independence test was used to investigate whether the two qualitative variables influenced each other. A p-value of <0.05 was considered significant.

Results

Table 1 shows the descriptive statistics for the clinicopathological characteristics.

The expression rates of MLH1, MSH2, MSH6, and PMS2 in MMR cases were 84%, 97.5%, 91.8%, and 89.3%, respectively. The HER2 expression rate was 5.7%.

The MMR status did not affect survival or other prognostic factors. The mean life expectancy for those with MSI tumors was 104.45 [95% confidence interval (CI): 80.43-128.46] months, while that for those without MSS tumors was 92.78 (95% CI: 81.73-103.83) months. There was no statistically significant difference in survival rates between patients with and without MSI tumors (log-rank =0.295, p=0.587).

At pathological stage 3, a statistically significant difference was observed between HER2 rates and DFS time rates (p=0.025) (Figure 2). There was no statistically significant difference between the HER2 rates and survival rates at clinical stages 2, 3, and 4 (p>0.05). Similarly, no statistically significant difference was observed between the HER2 rates and survival rates at pathological stage 4 (p>0.05).

There was no statistically significant difference between the HER2 rates and survival rates when clinical and pathological stages 3 and 4 were combined with clinical stage 2 (p>0.05) (Table 2). However, a statistically significant difference was found between the HER2 rates and survival time rates when combined pathological stages 3 and 4 were compared (p=0.034); (Table 2).

In the univariate model, none of the variables was statistically significant (p>0.05). These variables included sex, localization, tumor diameter, histological grade, lymphovascular invasion, perineural invasion, lymph node metastasis (N1), tumor depth, and MSI status.

The results of the univariate model indicated that certain factors were statistically significant, including age (<65 vs. >65 years), lymph node metastasis (N2), distant metastasis, and HER2 expression (p=0.033, p=0.029, p=0.004, and p=0.021, respectively). The corresponding hazard ratios (HRs) (95% CI) for age, lymph node metastasis (N2), distant metastasis, and HER2 scores (3/0) were 1,030 (1,002-1,058), 3,506 (1,569-7,837), 2,636 (1,351-5,143), and 3,023 (1,180-7,742), respectively.

Table 1. Statistical distributions of clinicopathological features

		Mean ± SD (min.-max.)
Age		67.71±12.54 (25-93)
Sex	Male	72 (59%)
	Female	50 (41%)
Tumor diameter		5 (2-15)
Tumor localization	Right colon	59 (48.4%)
	Left colon	63 (51.6%)
Tumor grade	Good	29 (23.8%)
	Moderately	86 (70.5%)
	Poorly	7 (5.7%)
Lymphovascular invasion	No	61 (50%)
	Yes	61 (50%)
Perineural invasion	No	63 (51.6%)
	Yes	59 (48.4%)
Number of metastatic lymph nodes		0 (0-16)
Clinic stage	2	67 (54.9%)
	3	34 (27.9%)
	4	21 (17.2%)
pT2-3, pT4	pT2-3	95 (77.9%)
	pT4	27 (22.1%)
pN	0	68 (55.7%)
	1	45 (36.9%)
	2	9 (7.4%)
pM	0	101 (82.8%)
	1	21 (17.2%)
MMR	MSI	20 (16.4%)
	MSS	102 (83.6%)
HER2	0	115 (94.3%)
	3	7 (5.7%)
DFS	Alive	83 (68%)
	Ex	39 (32%)

min.-max.: Minimum-maximum, MMR: Mismatch repair, HER2: Human epidermal growth receptor 2, DFS: Disease-free survival

Non-significant variables in the univariate model were excluded from the multivariate model. Lymph node metastasis (N2) was not statistically significant (p>0.05) in the multivariate model. However, age, distant metastasis, and HER2 expression were statistically significant (p=0.001, p=0.032, and p=0.019, respectively) in the multivariate model. The HR (95% CI) for

age, distant metastasis, and HER2 (3/0) scores were found to be statistically significant. This study suggests that age is positively associated with mortality risk, as DFS times decrease with age. Patients with M-stage disease had a significantly higher mortality risk than those without M-stage disease. Moreover, patients with a HER2 score of 3 had a higher mortality risk than those with a score of 0.

The mean survival of those with a HER2 score of 0 was 98.81 (88.32-109.3) months (95% CI), and those with a HER2 score of 3 had a mean survival of 49.71 (9.88-89.54) months (95% CI), with a statistically significant difference in survival between HER2 rates (log-rank =5,955, p=0.015) (Table 3).

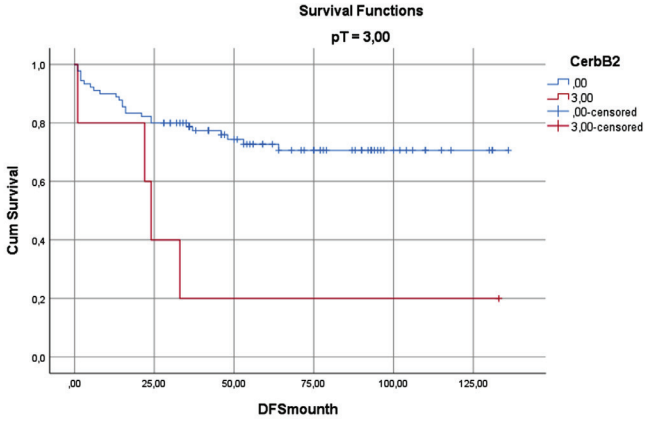

Figure 2. Kaplan-Meier curves of disease-free survival in HER2-positive and HER2-negative patients with pathologic stage 3
HER2: Human epidermal growth receptor 2

Discussion

In colon cancers, the average 5-year survival rate is approximately 65%, and in the presence of distant metastasis, the prognosis decreases to 13%.[17] As in solid organ tumors, patient-specific treatments and immunotherapy are used to improve the prognosis of colon cancer. In this study, we aimed to investigate the effect of HER2 and MMR expressions on prognosis in patients with colon adenocarcinoma diagnosed and treated in our clinic in light of literature information.

In the last 10 years, survival times in metastatic colon cancers have increased from 10 to 20 months as a result of alternative treatments and immunotherapy.[18] Microsatellite instability is detected in 15% of metastatic colon cancers, and 3% is associated with Lynch syndrome.[4,19,20] In our study, the rate of MSI cancer was 20%, which is close to the rates reported in the literature. The MSI status is currently used in patients with colon cancer for neoadjuvant treatment resistance and immunotherapy.[13] Current guidelines for MSI cancer recommend that it be studied in all patients and do not mention its prognostic impact.[21] In solid tumors, pembrolizumab (immunotherapy) was first approved for patients with MSI cancer.[22] Currently, the use of pembrolizumab in patients with MSI tumors is a subgroup that benefits from treatment.[23] Although studies have reported that MSI tumors have better prognostic factors and earlier stages,[13,23] no statistical significance was found in terms of survival in most studies.[18,24,25] In studies comparing MSI and MSS colon cancers, MSI cancers were found to have high mutation and neoantigen load, frequent immune cell infiltration, high response to

Table 2. Comparisons between survival time rates and c-erbB2 rates for clinic stage 2, 3, and 4 and pathologic stage 3 and 4 conditions

				DFS time		p-value
				Alive	Ex	
Clinic stage	2	HER2	0	48 (98%)	15 (83.3%)	0.056[b]
			3	1 (2%)	3 (16.7%)	
	3 ve 4	HER2	0	33 (97.1%)	19 (90.5%)	0.551[b]
			3	1 (2.9%)	2 (9.5%)	
Pathological stage	pT3 ve pT4	HER2	0	81 (97.6%)	34 (87.2%)	0.034[b]
			3	2 (2.4%)	5 (12.8%)	

[a]Chi-squared test, [b]Fisher's exact test

Table 3. Results of univariate and multivariate Cox regression analysis of the effect of HER2 and MSI on mortality

		Univariate		Multivariate	
		p-values	HR (CI 95%)	p-values	HR (CI 95%)
MMR	MSS/MSI	0.590	-	-	-
HER2	3/0	0.021	3,023 (1,180-7,742)	0.019	3,368 (1,217-9,320)

HR: Hazard ratio, CI: Confidence interval, Cox regression: Backward Wald, MMR: Mismatch repair, HER2: Human epidermal growth receptor 2

immunotherapy, and better survival.[5,13,22] The characteristics of MSI tumors are associated with proximal localization, advanced T stage, N0, and stage 2-3 tumors.[18,22] Survival was longer in MSI tumors than in MMS tumors, although the difference was not statistically significant.[7,18,24] However, the effects of immunotherapy on colorectal tumors have not yet been clarified. Kang et al.[7] reported a mean 5-year survival of 95.8 months in MSI cancer, 74.5 months in MSS cancer, and a mean follow-up of 37.5 months. In our study, the mean follow-up period was 47 months, and the mean survival time in patients with MSI cancer was 104.45 months. According to Afrăsânie et al.,[18] stage 2-3 MSI cancer is a good prognostic factor, but the prognosis is not significant in metastatic disease. In our study, no statistically significant relationship was found between clinicopathological parameters and prognosis and MSI status.

Study Limitations

The effect of the limitations in the number of patients on our results should be considered.

Meta-analysis studies on colon cancer have shown that the incidence of HER2 is highly variable, ranging from 0.5% to 49%.[9,25,26] In a study by Dienstmann et al.[19] on metastatic colon cancers, the rate of HER2 was 2%. In the present study, HER2 expression was observed at a rate of 5.7%. HER2 has been associated with aggressive tumor behaviors, such as lymphatic metastasis, distant metastasis, perineural invasion, and distal localization; however,[27] in our study, we could not detect a significant relationship between HER2 and clinicopathological findings. Studies have also indicated its association with anti-EGFR resistance.[28,29] Anti-EGFR treatment in patients with metastasis worsens the prognosis and decreases the survival rate of HER2-positive patients. Yonesaka et al.[30] found a poor clinical effect of de novo HER2 amplification in 233 patients treated with cetuximab. In patients with amplified HER versus non-amplified HER2, median progression-free survival and OS decreased by 5 months versus 3 months, and OS was 30.5 months versus 10.2 months.[30] Therefore, knowledge of HER2 expression is necessary to organize the treatment protocol. According to the National Comprehensive Cancer Network® guidelines, the prognostic role of HER2 overexpression has not been supported in studies, and HER2-targeted therapies are still being investigated; testing is recommended in patients with metastatic colon cancer.[21] In large meta-analyses on the relationship between HER2 and survival, no relationship with survival was found.[15] Although there were different results related to survival in different studies, it was found to be a prognostic survival marker in both the univariate and multivariate analyses in our study. Its effect on survival should be investigated in larger studies that compare different treatment protocols.

Conclusion

In our study, HER2 was identified as an independent prognostic factor for patients with colon cancer, regardless of the presence of metastatic disease. Patients with a HER2 score of 3 had a 3,368 times higher risk of death. Additionally, no association was found between the clinicopathological features and survival in patients with MSI cancer. The limited sample size in our study may account for this observation. The fact that we only included patients in our clinic in our study causes selection bias as a limitation. Both HER2 and MSI status appear to be essential in the management of colorectal cancer, especially in advanced patients, and in identifying patients who are eligible for treatment.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Hittite University Clinical Research Ethics Committee (approval number: 2023-168, dated: 26.12.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Y., Y.B., G.G., Concept: B.Y., Y.B., G.G., Design: B.Y., Y.B., G.G., Data Collection or Processing: B.Y., Y.B., K.H., Analysis or Interpretation: B.Y., Y.B., K.H., Literature Search: B.Y., Y.B., K.H., Writing: B.Y., Y.B., E.R.

Conflict of Interest: No conflict of interest was declared by the authors.

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