BIOMARKERS

original reports abstract

The Prevalence and Prognosis of Microsatellite Instability-High/Mismatch Repair-Deficient Colorectal Adenocarcinomas in the United States

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PURPOSE Microsatellite instability (MSI) and DNA mismatch repair (MMR) status is an indispensable biomarker in the management of colorectal cancers. We therefore examined the epidemiology of MSI-high/MMR-deficient colorectal cancers in the United States.

METHODS Adults presenting with colorectal adenocarcinoma in 2018-2019 were identified from the US National Cancer Database. Attributes associated with MSI-high/MMR-deficiency were identified using multivariable logistic regression and reported using average adjusted probabilities ($\%_{AAP}$) and 99.9% CIs. As a secondary aim, the survival associated with MSI/MMR status was assessed.

RESULTS Among 101,259 colorectal adenocarcinomas in 2018-2019, 82.0% were microsatellite stable/MMR-proficient, 3.8% MSI-low, and 14.2% MSI-high/MMR-deficient—including 16.6%, 19.9%, 12.4%, and 7.3% of stage I, II, III, and IV cancers, respectively. In locoregional cancers, MSI-high/MMR-deficiency was associated with a bimodal age distribution, female sex, right-sided colonic origin, wild-type *KRAS*, and a prior diagnosis of cancer (all $P < .001$). By race/ethnicity, colorectal adenocarcinomas were MSI-high/MMR-deficient in $16.9\%_{AAP}$ of non-Hispanic White (99.9% CI, 16.5 to 17.4) patients, compared with $11.3\%_{AAP}$ of non-Hispanic Black (99.9% CI, 10.3 to 12.4), $12.4\%_{AAP}$ of Asian/Pacific Islander (99.9% CI, 10.5 to 14.3), and $15.1\%_{AAP}$ of Hispanic (99.9% CI, 13.4 to 16.7) patients (all $P < .001$). Histologically, MSI-high/MMR-deficiency was associated with increasing grade, from $11.3\%_{AAP}$ of well-differentiated tumors (99.9% CI, 10.2 to 12.4) to $28.4\%_{AAP}$ of poorly differentiated cases (99.9% CI, 27.1 to 29.8; $P < .001$). Compared with conventional histology ($15.2\%_{AAP}$, 99.9% CI, 14.8 to 15.6), medullary ($41.1\%_{AAP}$, 99.9% CI, 33.0 to 49.3; $P < .001$) and mucinous ($24.6\%_{AAP}$, 99.9% CI, 22.8 to 26.3; $P < .001$) subtypes—but not signet-ring cell histology ($15.5\%_{AAP}$, 99.9% CI, 11.6 to 19.4; $P = .79$)—were more frequently MSI-high/MMR-deficient when adjusting for clinicopathologic features including grade.

CONCLUSION Our findings establish the epidemiology, features, and prognostic implications of MSI-high/MMR-deficiency among colorectal adenocarcinoma patients in the United States.

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INTRODUCTION

DNA mismatch repair (MMR) deficiency commonly arises because of a loss of MMR protein function, which is caused by germline and/or somatic mutations (including copy-number loss) of MMR genes (namely *MLH1*, *MSH2*, *MSH6*, or *PMS2*) or somatic hypermethylation of the *MLH1* promoter. MMR deficiency leads to an accumulation of unrepaired errors in short repetitive DNA microsatellites (ie, high-level microsatellite instability [MSI]).[1] MSI-high/MMR deficiency status has emerged as a potent predictive biomarker for response to programmed cell death-1 (PDCD1; ie, PD-1) checkpoint inhibitors in a range of cancer types.[2,3]

The clinical value of MSI/MMR testing is exemplified in colorectal adenocarcinoma, where, in addition to serving as an indispensable predictive biomarker for first-line or second-line PDCD1 (PD-1) checkpoint inhibitors in the metastatic setting, MSI/MMR status also plays a critical role in the initial screening for Lynch syndrome and appears to identify stage II patients who may not benefit from fluorouracil-based adjuvant chemotherapy.[4-7] Therefore, we examined the molecular pathologic epidemiology of MSI-high/MMR-deficient colorectal adenocarcinomas across the United States, and, secondarily, the prognostic implications of MSI/MMR status.

METHODS

Patient Population

The data source for this retrospective cohort study was the National Cancer Database (NCDB), a nationwide

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Microsatellite instability and DNA mismatch repair (MSI/MMR) status is an important predictive biomarker of response to immune checkpoint inhibitors in patients with colorectal cancer. This study, therefore, examined the molecular pathologic epidemiology and prognostic implications of MSI-high/MMR-deficient colorectal adenocarcinomas across the United States.

Knowledge Generated

In this US national cohort, 16% of newly diagnosed colorectal adenocarcinomas were MSI-high/MMR-deficient, with the highest prevalence among stage I-II tumors. In addition to confirming several well-described associations between colorectal cancer attributes and MSI-high/MMR-deficiency—such as female sex, bimodal age distribution, right-sided colonic origin, poorly differentiated histology, and medullary and mucinous subtypes—MSI/MMR status also varied by patients' race/ethnicity, with MSI-high/MMR deficiency less likely among non-Hispanic Black, Asian/Pacific Islander, and Hispanic patients with colorectal cancer. Well-differentiated and signet-ring cell histologies were not independently associated with MSI-high/MMR deficiency.

Relevance

These findings establish the national-level epidemiology, features, and prognostic implications of MMR-deficiency/MSI-high among patients with colorectal adenocarcinoma in the United States.

observational database containing ≥ 71% of newly diagnosed colorectal cancers in the United States.[8] Patients who presented with a histologically confirmed invasive colorectal adenocarcinoma in 2018 and 2019 (the latest year of available NCDB data and the first year with data reported for the NCDB's new MSI/MMR data item, and the latest year of available NCDB data, respectively) were identified using International Classification of Diseases-O-3 histologic codes (adenocarcinoma 8140/3, mucinous adenocarcinoma 8480/3, signet-ring cell carcinoma 8490/3, or medullary carcinoma 8510/3) and primary colorectal site codes (C18.0, C18.2-18.9, C19.9, and C20.9). Patients were excluded if they lacked MSI/MMR testing results or lacked complete staging data.

Study Variables

Starting for patients diagnosed in 2018, a new colorectal site–specific data item was implemented by cancer registries for reporting both MSI and MMR status: MSI (NAACCR item no. 3890), which defines microsatellite stable and/or MMR intact (no loss of nuclear expression of MMR proteins) as code 0, MSI-low as code 1, and MSI-high and/or MMR deficiency (loss of nuclear expression of ≥ 1 MMR proteins) as code 2. MSI/MMR not assessed, unknown if assessed, or indeterminate results were all defined as code 9. The NCDB did not report details about the specific MSI/MMR testing modality (eg, immunohistochemistry *v* polymerase chain reaction–based methods *v* next-generation sequencing panels; use of mononucleotide markers only *v* mononucleotide and dinucleotide markers; *MLH1* promoter methylation; etc) or strategy (*eg,* whether immunohistochemistry and/or molecular testing was used), nor were the details reported regarding whether MMR deficiency was sporadic or germline.

Patient and tumor factors of interest were patient age, sex, race/ethnicity, and tumor features including location, sidedness, *KRAS* mutational status (reported as either wild-type, codon 12/13/61 mutated, codon 146 mutated, other codon mutated, and mutated but codons not specified), pretreatment carcinoembryonic antigen (CEACAM5, ie, CEA) levels, history of prior cancer, and American Joint Committee on Cancer (AJCC) eighth edition pathologic stage group. Right-sided colon was defined as cecum, ascending colon, hepatic flexure, or transverse colon, whereas left-sided was defined as splenic flexure, descending colon, sigmoid, or rectosigmoid junction. Histologic features included subtype (adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, or medullary carcinoma), grade, lymphovascular invasion, and perineural invasion. For analyses of stage IV cancers, metastatic site involvement (liver, lung, bone, brain, distant lymph node, and other visceral organs or carcinomatosis) was also included as separate binary variables.

Statistical Analysis

The associations between patient and tumor factors and MSI/MMR status (categorized as either MSI-high/MMR-deficient or microsatellite stable/MSI-low/MMR-proficient) were evaluated separately for patients with locoregional (stage I-III) and metastatic (stage IV) colorectal adenocarcinomas using multivariable logistic regression and reported with corresponding 99.9% CIs. In addition to reporting effect sizes using odds ratios, we also used the multivariable logistic regression models to estimate the average adjusted predicted probability ($\%_{AAP}$; ie, average predicted margin) associated with being MSI-high/MMR-deficient for any given clinicopathologic feature—so as to help with interpretation of the effect sizes associated with

each feature.[9] To reduce false positives, two-sided *P* values < .001 were stipulated as statistically significant.

The prognostic roles of MSI-high/MMR-deficient versus MSI-low versus microsatellite stable/MMR-proficient statuses were explored in a secondary analysis, in which overall survival (OS) was estimated via Kaplan-Meier techniques from the date of initial diagnosis to the date of death or last contact, and adjusted for patient, tumor, and first-line treatment characteristics using multivariable Cox proportional hazards regression analysis. A less-conservative two-sided alpha level of .05 was used for the exploratory secondary analysis, with Bonferroni method to correct for multiplicity of testing: the association between MSI/MMR status and OS was tested for each of four stages, corresponding to a significant *P* value threshold of .006 per test. All analyses were conducted using Stata (v17.1, StataCorp). The NCDB excludes OS data for patients diagnosed in the final year of the released database, so OS data were not yet available for patients diagnosed in 2019. This study was approved by the Mass General Brigham institutional review board (no. 2019P000950) as exempt and performed in accordance with the Declaration of Helsinki. The NCDB Participant User Files contain deidentified national data for which consenting was not applicable.

Ethics Approval and Consent to Participate

This study was not considered human subjects research and was approved by the Mass General Brigham institutional review board (no. 2019P000950) and performed in accordance with the Declaration of Helsinki. The NCDB Participant User Files contain deidentified national data for which consenting was not applicable.

RESULTS

In 2018-2019, 101,259 patients with colorectal adenocarcinoma met study criteria, of whom 82% were reported as microsatellite stable/MMR-proficient (n = 83,051), 3.8% as MSI-low (n = 3,884), and 14.2% as MSI-high/MMR-deficient (n = 14,324). MSI-high/MMR deficiency was detected in 16.6% of stage I, 19.9% of stage II, 12.4% of stage III, and 7.3% of stage IV cancers.

Attributes of MSI-High/MMR Deficiency in Locoregional (stage I-III) Colorectal Adenocarcinomas

Among patients with locoregional cancers (n = 79,556), women were more likely to have MSI-high/MMR-deficient tumors (18.2%$_{AAP}$, 99.9% CI, 17.6 to 18.8; $P < .001$) compared with men (13.8%$_{AAP}$, 99.9% CI, 13.2 to 14.3; Table 1). By age, MSI-high/MMR deficiency demonstrated a bimodal pattern: peaking at 30.6%$_{AAP}$ in < 30-year-olds (99.9% CI, 23.3 to 37.9), falling to 12.4%$_{AAP}$ in 50-59-year-olds (99.9% CI, 11.5 to 13.4), and rising to 19.6%$_{AAP}$ in ≥ 80-year-olds (99.9% CI, 18.7 to 20.5). Additionally, patients who were of non-Hispanic Black (11.3%$_{AAP}$, 99.9% CI, 10.3 to 12.4; $P < .001$), Asian/Pacific Islander (12.4%$_{AAP}$, 99.9% CI, 10.5 to 14.3; $P < .001$), or Hispanic (15.1%$_{AAP}$, 99.9% CI, 13.4 to 16.7; $P < .001$) race/ethnicities less frequently had MSI-high/MMR-deficient cancers than non-Hispanic White patients (16.9%$_{AAP}$, 99.9% CI, 16.5 to 17.4; referent). A history of a prior cancer diagnosis was also associated with MSI-high/MMR-deficient cancer (19.3%$_{AAP}$, 99.9% CI, 18.4 to 20.3; *v* 15.2%$_{AAP}$ without, 99.9% CI, 14.7 to 15.6; $P < .001$).

In terms of histologic features, increasing grade was independently associated with increasing likelihood of MSI-high/MMR deficiency: whereas 11.3%$_{AAP}$ of well-differentiated (99.9% CI, 10.2 to 12.4; $P < .001$) and 13.7%$_{AAP}$ of moderately differentiated (99.9% CI, 13.2 to 14.2; referent) cancers were MSI-high/MMR-deficient, 28.4%$_{AAP}$ of poorly differentiated cases were (99.9% CI, 27.1 to 29.8; $P < .001$). This association with increasing grade persisted when only those cases with conventional histology were included in the regression model (data not shown). Additionally, although lymphovascular invasion was not associated with MSI/MMR status, perineural invasion was inversely associated with MSI-high/MMR deficiency (13.4%$_{AAP}$, 99.9% CI, 12.2 to 14.5; *v* 16.3%$_{AAP}$ for no perineural invasion, 99.9% CI, 15.9 to 16.8; $P < .001$). MSI-high/MMR-deficient status was also more commonly associated with the medullary (41.1%$_{AAP}$, 99.9% CI, 33.0 to 49.3; $P < .001$) and mucinous (24.6%$_{AAP}$, 99.9% CI, 22.8 to 26.3; $P < .001$) histologic subtypes of colorectal adenocarcinoma, compared with 15.2%$_{AAP}$ of conventional histology (99.9% CI, 14.8 to 15.6; referent) and 15.5%$_{AAP}$ of signet-ring cell histology (99.9% CI, 11.6 to 19.4; $P = .79$). Because signet-ring cell histology overwhelmingly is poorly differentiated, the regression analysis was repeated excluding grade, in which the association between signet-ring cell histology and MSI-high/MMR deficiency strengthened (23.4%$_{AAP}$, 99.9% CI, 18.2 to 28.5; $P < .001$ compared with conventional histology).

A higher prevalence of MSI-high/MMR-deficient tumors was observed on the right side of the colon, peaking at 25.5%$_{AAP}$ of ascending colon tumors (99.9% CI, 24.3 to 26.7) and bottoming at 7.6%$_{AAP}$ of sigmoid colon tumors (99.9% CI, 6.8 to 8.3) and 5.4%$_{AAP}$ of rectosigmoid junction tumors (99.9% CI, 4.3 to 6.5). Rectal tumors exhibited the lowest prevalence of MSI-high/MMR deficiency (5.5%$_{AAP}$, 99.9% CI, 4.7 to 6.2). By AJCC eighth edition stage groups, stage III cancers were less likely to be MSI-high/MMR-deficient (*eg,* 12.8%$_{AAP}$ of stage IIIC, 99.9% CI, 11.6 to 14.0) than either stage I (18.1%$_{AAP}$, 99.9% CI, 17.2 to 19.0) or stage II (eg, 20.4%$_{AAP}$ of stage IIC, 99.9% CI, 17.8 to 22.9) cancers. Furthermore, among the 13.3% (n = 10,580) of cases with reported *KRAS* molecular status, *KRAS* codon 12/13/61 mutated cancers (10.9%$_{AAP}$, 99.9% CI, 8.6 to 13.2; $P < .001$)—but not codon 146 mutated (15.4%$_{AAP}$, 4.0 to 26.8; $P = .38$)—were less commonly MSI-high/MMR-deficient compared with *KRAS* wild-type cancers (18.7%$_{AAP}$, 99.9% CI, 17.2 to 20.1).

TABLE 1. Attributes of MSI-H/MMRd Cancers in Locoregional (Stage I-III) Colorectal Adenocarcinoma

Variable	MSS/MSI-L/MMRp No.	MSI-H/MMRd No.	OR of Being MSI-H/MMRd	99.9% CI	*P*	AAP% of Being MSI-H/MMRd	99.9% CI
Overall	66,812	12,744				16.0	15.6 to 16.4
Age at diagnosis, years							
< 30	285	102	3.27	2.13 to 5.03	**< .001**	30.6	23.3 to 37.9
30-39	1,752	347	1.99	1.59 to 2.49	**< .001**	22.7	19.6 to 25.8
40-49	5,998	690	1.15	0.98 to 1.35	.004	15.5	13.9 to 17.1
50-59	14,423	1,395	0.85	0.76 to 0.96	**< .001**	12.4	11.5 to 13.4
60-69	18,219	2,642	Referent			14.0	13.2 to 14.8
70-79	15,691	3,663	1.22	1.11 to 1.35	**< .001**	16.2	15.4 to 17
≥ 80	10,444	3,905	1.60	1.45 to 1.77	**< .001**	19.6	18.7 to 20.5
Sex							
Male	36,603	5,153	Referent			13.8	13.2 to 14.3
Female	30,209	7,591	1.47	1.37 to 1.58	**< .001**	18.2	17.6 to 18.8
Race/ethnicity							
White, non-Hispanic	50,053	10,581	Referent			16.9	16.5 to 17.4
Black, non-Hispanic	7,513	917	0.58	0.51 to 0.66	**< .001**	11.3	10.3 to 12.4
Asian/Pacific Islander	3,093	337	0.65	0.53 to 0.8	**< .001**	12.4	10.5 to 14.3
Hispanic	4,440	670	0.85	0.73 to 0.99	**< .001**	15.1	13.4 to 16.7
Other	1,224	168	0.82	0.61 to 1.1	.03	14.7	11.6 to 17.8
NA	489	71	0.75	0.48 to 1.18	.04	13.8	9.2 to 18.4
Primary site							
C18.0 cecum	10,027	3,151	Referent			21.7	20.6 to 22.9
C18.2 ascending colon	9,458	3,806	1.26	1.14 to 1.39	**< .001**	25.5	24.3 to 26.7
C18.3 hepatic flexure	2,152	868	1.24	1.06 to 1.46	**< .001**	25.3	22.9 to 27.8
C18.4 transverse colon	4,780	1,714	1.16	1.02 to 1.3	**< .001**	24.1	22.4 to 25.8
C18.5 splenic flexure	1,587	337	0.79	0.63 to 0.98	**< .001**	18.3	15.4 to 21.1
C18.6 descending colon	3,067	578	0.71	0.6 to 0.85	**< .001**	16.9	14.9 to 18.9
C18.7 sigmoid colon	14,144	947	0.27	0.24 to 0.31	**< .001**	7.6	6.8 to 8.3
C18.8 overlapping lesion	670	224	1.09	0.82 to 1.43	.33	23.1	18.7 to 27.5
C18.9 colon, NOS	582	137	0.79	0.57 to 1.11	.02	18.4	13.9 to 22.9
C19.9 rectosigmoid junction	4,993	226	0.18	0.15 to 0.23	**< .001**	5.4	4.3 to 6.5
C20.9 rectum, NOS	15,352	756	0.19	0.16 to 0.22	**< .001**	5.5	4.7 to 6.2
Histologic subtype							
Adenocarcinoma	63,029	10,851	Referent			15.2	14.8 to 15.6
Mucinous adenocarcinoma	3,291	1,457	2.04	1.81 to 2.3	**< .001**	24.6	22.8 to 26.3
Signet-ring cell carcinoma	403	158	1.03	0.73 to 1.45	.79	15.5	11.6 to 19.4
Medullary adenocarcinoma	89	278	5.27	3.44 to 8.09	**< .001**	41.1	33 to 49.3
Histologic grade							
Well differentiated	6,386	967	0.78	0.69 to 0.89	**< .001**	11.3	10.2 to 12.4
Moderately differentiated	41,451	7,043	Referent			13.7	13.2 to 14.2
Poorly differentiated	6,475	3,652	2.91	2.66 to 3.2	**< .001**	28.4	27.1 to 29.8
NA	12,500	1,082	1.35	1.16 to 1.57	**< .001**	17.1	15.4 to 18.9
Lymphovascular invasion							
No	42,087	8,499	Referent			16.2	15.7 to 16.7
Yes	15,527	3,109	0.96	0.87 to 1.05	.12	15.7	14.8 to 16.6
NA	9,198	1,136	0.93	0.81 to 1.07	.09	15.4	14.1 to 16.8

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TABLE 1. Attributes of MSI-H/MMRd Cancers in Locoregional (Stage I-III) Colorectal Adenocarcinoma (Continued)

Variable	MSS/MSI-L/MMRp No.	MSI-H/MMRd No.	OR of Being MSI-H/MMRd	99.9% CI	*P*	AAP% of Being MSI-H/MMRd	99.9% CI
Perineural invasion							
No	51,731	10,722	Referent			16.3	15.9 to 16.8
Yes	8,715	1,271	0.76	0.67 to 0.86	**< .001**	13.4	12.2 to 14.5
NA	6,366	751	1.09	0.93 to 1.29	.07	17.4	15.5 to 19.2
AJCC eighth edition stage group							
I	15,153	3,007	1.00	0.91 to 1.1	.87	18.1	17.2 to 19
IIA	18,417	4,487	Referent			18.0	17.3 to 18.8
IIB	2,435	630	0.91	0.77 to 1.09	.09	16.9	15 to 18.9
IIC	1,604	476	1.20	0.98 to 1.47	.003	20.4	17.8 to 22.9
IIIA	3,576	412	0.66	0.54 to 0.8	**< .001**	13.4	11.5 to 15.2
IIIB	19,225	2,609	0.62	0.56 to 0.69	**< .001**	12.8	12.1 to 13.6
IIIC	6,402	1,123	0.62	0.54 to 0.72	**< .001**	12.8	11.6 to 14
Pretreatment CEA level							
Within normal limits	28,174	5,395	Referent			16.3	15.6 to 16.9
Elevated	17,827	3,393	1.04	0.95 to 1.13	.18	16.7	15.9 to 17.5
NA	20,811	3,956	0.91	0.84 to 0.99	**< .001**	15.2	14.5 to 15.9
KRAS status							
Wild-type	5,414	1,286	Referent			18.7	17.2 to 20.1
Mutant, codon 12/13/61	1,648	177	0.48	0.35 to 0.64	**< .001**	10.9	8.6 to 13.2
Mutant, codon 146	78	14	0.76	0.27 to 2.14	.38	15.4	4 to 26.8
Mutant, other codon	180	21	0.49	0.22 to 1.11	.004	11.1	4.1 to 18.1
Mutant, codon not specified	1,533	229	0.65	0.5 to 0.86	**< .001**	13.8	11.3 to 16.4
NA	57,959	11,017	0.80	0.71 to 0.9	**< .001**	16.0	15.5 to 16.4
Prior diagnosis of cancer							
No	56,145	9,475	Referent			15.2	14.7 to 15.6
Yes	10,654	3,265	1.41	1.3 to 1.54	**< .001**	19.3	18.4 to 20.3
Year of diagnosis							
2018	31,532	5,883	Referent			15.7	15.1 to 16.3
2019	35,280	6,861	1.05	0.98 to 1.13	.01	16.3	15.8 to 16.8

NOTE. Complete data for multivariable analysis were available for 79,539 patients.

Bold entries indicate significant *P* value.

Abbreviations: %AAP, average adjusted predicted probability; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; MMR, mismatch repair; MSI-H/MMRd, MSI-high/MMR-deficient; MSS/MSI-L/MMRp, microsatellite stable/MSI-low/MMR-proficient; NA, not available; NOS, not otherwise specified; OR, odds ratio.

Attributes of MSI-High/MMR Deficiency in Distantly Metastatic (stage IV) Colorectal Adenocarcinomas

Among the n = 21,703 patients who presented with stage IV colorectal adenocarcinoma, 7.3%$_{AAP}$ had MSI-high/MMR-deficient cancers. Unlike locoregional tumors, however, the MSI-high/MMR deficiency levels varied only minimally by patient features (Table 2). The associations that were observed among locoregional tumors between MSI/MMR status and primary tumor site, histologic subtype, *KRAS* status, and prior diagnosis of cancer were also found in stage IV patients. In terms of metastatic sites, stage IV cases with liver involvement were less likely to be MSI-high/MMR-deficient (6.1%$_{AAP}$, 99.9% CI, 5.4 to 6.8, *v* 9.6%$_{AAP}$ without, 99.9% CI, 8.4 to 10.9; $P < .001$), whereas those with distant lymph node involvement were more likely to be MSI-high/MMR-deficient (9.3%$_{AAP}$, 99.9% CI, 7.6 to 11.1; *v* 6.9%$_{AAP}$ without, 99.9% CI, 6.3 to 7.5; $P < .001$). MSI/MMR status was not otherwise associated with bone or brain metastatic involvement.

Secondary Analysis of the Prognostic Implications of MSI/MMR Status for Colorectal Adenocarcinoma

As a secondary analysis, we examined the prognosis associated with MSI/MMR status for patients diagnosed in 2018 (OS data for patients diagnosed in 2019 were not yet

TABLE 2. Predictors of MSI-H/MMRd Tumors in Patients With Stage IV Colorectal Adenocarcinoma

Variable	MSS/MSI-L/MMRp No.	MSI-H/MMRd No.	OR of Being MSI-H/MMRd	99.9% CI	*P*	AAP% of Being MSI-H/MMRd	99.9% CI
Overall	20,123	1,580				7.3	6.7 to 7.9
Age at diagnosis, years							
< 30	175	16	1.32	0.51 to 3.39	.33	8.4	1.8 to 15
30-39	898	79	1.54	0.99 to 2.42	.001	9.6	6.3 to 12.8
40-49	2,633	156	1.04	0.74 to 1.46	.74	6.8	5.1 to 8.5
50-59	4,781	247	0.88	0.66 to 1.18	.15	5.9	4.7 to 7.1
60-69	5,555	384	Referent			6.6	5.6 to 7.7
70-79	3,860	355	1.13	0.86 to 1.48	.13	7.4	6.1 to 8.6
≥ 80	2,221	343	1.60	1.21 to 2.13	**< .001**	9.9	8.1 to 11.6
Sex							
Male	11,321	745	Referent			6.8	6 to 7.6
Female	8,802	835	1.18	0.98 to 1.41	.004	7.8	7 to 8.7
Race/ethnicity							
White, non-Hispanic	14,475	1,206	Referent			7.5	6.8 to 8.1
Black, non-Hispanic	2,816	195	0.93	0.7 to 1.23	.40	7.0	5.5 to 8.6
Asian/Pacific Islander	849	37	0.59	0.33 to 1.05	.003	4.7	2.3 to 7.1
Hispanic	1,471	104	1.02	0.7 to 1.47	.88	7.6	5.3 to 9.8
Other	384	26	0.80	0.39 to 1.61	.29	6.1	2.4 to 9.8
NA	128	12	1.06	0.37 to 3.07	.85	7.9	0.8 to 14.9
Primary site							
C18.0 cecum	3,185	337	Referent			8.5	7 to 10
C18.2 ascending colon	2,265	351	1.43	1.08 to 1.9	**< .001**	11.5	9.6 to 13.5
C18.3 hepatic flexure	582	94	1.65	1.07 to 2.54	**< .001**	13.0	8.9 to 17.1
C18.4 transverse colon	1,178	196	1.53	1.09 to 2.14	**< .001**	12.2	9.4 to 15
C18.5 splenic flexure	440	45	1.14	0.64 to 2.01	.47	9.5	5.1 to 13.8
C18.6 descending colon	876	62	0.84	0.52 to 1.37	.24	7.3	4.5 to 10.2
C18.7 sigmoid colon	4,701	196	0.50	0.36 to 0.69	**< .001**	4.6	3.5 to 5.6
C18.8 overlapping lesion	287	37	1.18	0.62 to 2.24	.39	9.8	4.7 to 14.9
C18.9 colon, NOS	874	67	0.85	0.52 to 1.39	.28	7.4	4.5 to 10.3
C19.9 rectosigmoid junction	1,729	69	0.49	0.3 to 0.78	**< .001**	4.5	2.8 to 6.2
C20.9 rectum, NOS	4,006	126	0.37	0.25 to 0.55	**< .001**	3.5	2.4 to 4.5

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TABLE 2. Predictors of MSI-H/MMRd Tumors in Patients With Stage IV Colorectal Adenocarcinoma (Continued)

Variable	MSS/MSI-L/MMRp No.	MSI-H/MMRd No.	OR of Being MSI-H/MMRd	99.9% CI	*P*	AAP% of Being MSI-H/MMRd	99.9% CI
Histologic subtype							
Adenocarcinoma	18,912	1,357	Referent			7.0	6.4 to 7.6
Mucinous adenocarcinoma	919	147	1.56	1.11 to 2.17	**< .001**	10.2	7.5 to 12.8
Signet-ring cell carcinoma	286	45	0.95	0.52 to 1.71	.763	6.7	3.3 to 10.1
Medullary adenocarcinoma	< 10	31	23.48	5.05 to 109.12	**< .001**	55.1	22.1 to 88.1
Histologic grade							
Well differentiated	459	38	1.20	0.66 to 2.2	.313	6.5	3.2 to 9.9
Moderately differentiated	5,934	383	Referent			5.5	4.5 to 6.5
Poorly differentiated	2,158	458	2.41	1.84 to 3.14	**< .001**	11.8	9.7 to 13.8
NA	11,572	701	1.29	0.96 to 1.75	.005	7.0	5.9 to 8
Lymphovascular invasion							
No	3,996	327	Referent			7.6	6.1 to 9.1
Yes	5,804	608	1.02	0.78 to 1.33	.83	7.7	6.4 to 9
NA	10,323	645	0.88	0.63 to 1.23	.21	6.8	5.7 to 7.9
Perineural invasion							
No	6,765	661	Referent			7.6	6.5 to 8.7
Yes	3,956	328	0.79	0.61 to 1.02	.003	6.2	5 to 7.5
NA	9,402	591	0.99	0.72 to 1.37	.95	7.6	6.2 to 9
AJCC eighth edition stage group							
IVA	11,440	853	Referent			7.7	6.8 to 8.6
IVB	4,626	294	0.88	0.67 to 1.17	.14	6.9	5.5 to 8.3
IVC	4,057	433	0.88	0.66 to 1.16	.12	6.8	5.6 to 8.1
Pretreatment CEA level							
Within normal limits	2,713	311	Referent			8.6	7 to 10.1
Elevated	13,262	919	0.81	0.63 to 1.03	.004	7.1	6.4 to 7.9
NA	4,148	350	0.75	0.57 to 1.01	.001	6.8	5.6 to 7.9
KRAS status							
Wild-type	5,987	460	Referent			7.4	6.3 to 8.5
Mutant, codon 12/13/61	2,518	100	0.53	0.36 to 0.78	**< .001**	4.2	2.9 to 5.6
Mutant, codon 146	103	< 10	0.61	0.11 to 3.36	.34	4.8	to 2.5 to 12
Mutant, other codon	288	14	0.70	0.27 to 1.76	.20	5.4	1 to 9.7
Mutant, codon not specified	2,809	162	0.84	0.6 to 1.16	.07	6.3	4.8 to 7.9
NA	8,418	840	1.15	0.93 to 1.42	.03	8.3	7.4 to 9.2

(Continued on following page)

TABLE 2. Predictors of MSI-H/MMRd Tumors in Patients With Stage IV Colorectal Adenocarcinoma (Continued)

Variable	MSS/MSI-L/MMRp No.	MSI-H/MMRd No.	OR of Being MSI-H/MMRd	99.9% CI	*P*	AAP% of Being MSI-H/MMRd	99.9% CI
Prior diagnosis of cancer							
No	17,545	1,255	Referent			7.0	6.4 to 7.6
Yes	2,572	323	1.32	1.04 to 1.68	**< .001**	8.9	7.3 to 10.5
Bone metastasis							
No	19,008	1,498	Referent			7.2	6.7 to 7.8
Yes	990	78	1.17	0.75 to 1.82	.24	8.3	5.3 to 11.3
Brain metastasis							
No	19,755	1,549	Referent			7.3	6.7 to 7.8
Yes	210	21	1.34	0.59 to 3.04	.24	9.3	3 to 15.5
Liver metastasis							
No	5,546	730	Referent			9.6	8.4 to 10.9
Yes	14,487	844	0.59	0.47 to 0.73	**< .001**	6.1	5.4 to 6.8
Lung metastasis							
No	14,988	1,314	Referent			7.6	6.9 to 8.2
Yes	4,900	255	0.78	0.6 to 1.01	.002	6.1	4.9 to 7.4
Distant LN metastasis							
No	17,030	1,249	Referent			6.9	6.3 to 7.5
Yes	2,874	310	1.42	1.11 to 1.83	**< .001**	9.3	7.6 to 11.1
Other site metastasis							
No	14,902	1,013	Referent			7.2	6.5 to 8
Other visceral organ	4,754	532	1.05	0.81 to 1.36	.55	7.5	6.3 to 8.8
Carcinomatosis	294	25	0.73	0.34 to 1.56	.17	5.5	1.9 to 9
Year of diagnosis							
2018	9,389	761	Referent			7.5	6.6 to 8.3
2019	10,734	819	0.95	0.79 to 1.14	.34	7.1	6.4 to 7.9

NOTE. Complete data for multivariable analysis were available for 21,063 patients. Per NCDB requirements, cells < 10 are suppressed.

Bold entries indicate significant *P* value.

Abbreviations: %AAP, average adjusted predicted probability; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; MMR, mismatch repair; MSI-H/MMRd, MSI-high/MMR-deficient; MSS/MSI-L/MMRp, microsatellite stable/MSI-low/MMR-proficient; NA, not available; NCDB, National Cancer Database; NOS, not otherwise specified; OR, odds ratio.

reported by the NCDB). We evaluated the OS associated with MSI-high/MMR-deficient cancers, compared with MSI-low and microsatellite stable/MMR-proficient cancers. For locoregional cases, the survival analysis was adjusted for patients' age, primary site, histologic subtype, stage group, and primary therapy (ie, surgery, chemotherapy for stage II-III, and radiotherapy for stage III; n = 36,090; Appendix Table A1) and, for stage IV cases (n = 8,940), further adjusted for metastatic sites, resection of non-primary sites, and first-line immunotherapy, given that some stage IV patients may have been receiving first-line immune checkpoint inhibitors in the context of clinical trials or in an off-label manner (Appendix Table A2). Of note, the NCDB does not report data for therapy received in the second-line or subsequent-line setting, including immune checkpoint inhibitors. MSI-high/MMR-deficient status was independently associated with improved OS compared with MSS/MMR-proficient cancers in stage IV patients (hazard ratio [HR], 0.72; 95% 99.9% CI, 0.64 to 0.81; $P < .001$). Among locoregional cancers, the adjusted HR associated with MSI-high/MMR-deficient status was 0.78 (95% 99.9% CI, 0.64 to 0.96; $P = .02$) for stage I, 0.92 (95% 99.9% CI, 0.81 to 1.04; $P = .19$) for stage II, and 0.90 (95% 99.9% CI, 0.71 to 1.01; $P = .07$) for stage III, which did not reach corrected significance for secondary analysis (ie, $P < .006$). Furthermore, a significant difference in OS between MSI-low and MSS/MMR-proficient cancers was not observed at any stage follow correction for multiple testing, although MSI-low stage IV cancers demonstrated an adjusted HR of 0.83 (95% 99.9% CI, 0.70 to 0.98) compared with MSS/MMR-proficient cancers.

DISCUSSION

Herein, we examined the relationships between colorectal adenocarcinoma patients' clinicopathologic features and their MSI/MMR status across the United States. Overall, 14% of colorectal adenocarcinomas were MSI-high/MMR-deficient and 4% were MSI-low, which is in line with prior estimates from institutional series. Our findings recapitulated many of the well-described features of MSI-high/MMR-deficient tumors, including a predilection for the right side of the colon, higher-grade histology, wild-type *KRAS*, earlier stages, and female patients.[1] Using multivariable logistic regression, we provide estimates for the prevalence of MSI-high/MMR-deficiency associated with each of these attributes. In survival analyses accounting for patients' treatments, MSI-high/MMR-deficient cancers independently displayed a more favorable prognosis compared with MSS/MMR-proficient cancers in stage IV disease—although, owing to the limitations of the NCDB, these survival results were confounded by receipt of immune checkpoint inhibitor therapy in the ≥ second line, which was US Food and Drug Administration–approved in 2017 for patients with MSI-high/MMR-deficient metastatic colorectal cancer who had progressed following chemotherapy. Consequently, it is likely that a majority of MSI-high/MMR-deficient stage IV colorectal cancers in our analysis had received PD-1 inhibitor therapy in the ≥ second line. As additional years of data become available, it will become important to assess how the natural history of MSI-high/MMR-deficient disease changes over the years.

MSI-high/MMR-deficient colorectal cancers displayed a bimodal age distribution, which corresponds with the well-characterized observation that early-onset MSI-high colorectal cancers frequently are due to germline MMR mutations (ie, Lynch syndrome; approximately 30% of cases), whereas late-onset MSI-high cancers are predominantly sporadic (approximately 70% of cases) and associated with CpG island methylator phenotype in older women.[1] We have previously shown that older patients with colorectal cancer in the United States were less likely to receive MSI testing and our findings herein underscore the need to consider MSI/MMR testing even among elderly patients, who experience an increased incidence of sporadic MSI-high/MMR-deficient tumors.[10]

There have been limited molecular epidemiology data with regards to MSI/MMR status by racial/ethnicity status, with some institutional series suggesting a lower incidence of MSI-high/MMR deficiency among colorectal adenocarcinomas in Black non-Hispanic patients and others reporting no differences.[11,12] However, in the national data, MSI/MMR status clearly varied independently by race/ethnicity, with colorectal adenocarcinomas in Black non-Hispanic, Asian/Pacific Islander, and Hispanic patients all less likely to be MSI-high/MMR-deficient than in White non-Hispanic patients. Although we previously identified MSI testing disparities by patients' socioeconomic status in the United States, differences specifically because of patients' race/ethnicity were not observed.[10] These findings underscore the importance of incorporating patients' race/ethnicity in future research into the genetic mechanisms of MSI-high/MMR deficiency.

In terms of histologic features, poorly differentiated cancers were more than twice as likely to be MSI-high/MMR-deficient as their well-differentiated or moderately differentiated counterparts. It has been suggested that well-differentiated cancers may be more likely to be MSI-high/MMR-deficient than moderately differentiated cancers, but our results portray the opposite—when adjusting for clinicopathologic features, well-differentiated cases were least likely to be MSI-high/MMR-deficient. These findings persisted when evaluating only those cases with conventional histology (data not shown). Furthermore, as previously described,[13,14] medullary and mucinous subtypes were more frequently associated with MSI-high/MMR deficiency than conventional histology. Of note, although signet-ring cell histology has been reported in institutional series to be associated with MSI-high/MMR deficiency,[15] we did not find that to be the case nationally when considering the patients' other clinicopathologic attributes. Importantly, cases with signet-ring cell histology were predominantly reported as being poorly

differentiated. We therefore repeated the multivariable regression model excluding grade and found that the association between signet-ring cell histology and MSI-high/MMR deficiency significantly strengthened. By comparison, medullary and mucinous histologies remained significantly associated with increased MSI-high/MMR-deficiency, irrespective of adjustment for grade.

A distinct characteristic of MSI-high/MMR-deficient colorectal cancer that has been widely observed clinically is its penchant for local growth and invasion—reflected in the national data by a prevalence that peaked in stage I-II cancers (up to 20% of stage IIC cases) and fell to 7% of stage IV cancers.[1,14] This finding is likely related to the remarkably elevated neoantigen load of MSI-high/MMR-deficient tumors, which may elicit robust local and systemic antitumoral immune responses that both help eliminate tumor cells that leave the primary and that correlate with a favorable prognosis.[16,17] Among stage IV cases, there was a higher MSI-high/MMR-deficiency proportion in our cohort than previously published, potentially reflecting that the NCDB would only capture cases that presented as stage IV disease and not metastatic cases that had previously presented at earlier stages.

Because of the nature of NCDB data, there were several important limitations that constrained our analyses. For example, the NCDB did not permit the analysis of incidence. In addition to a lack of details about MSI/MMR testing methodology, for MSI-high/MMR-deficient cases, there were no further molecular details encoded regarding which MMR gene is mutated, nor about the *MLH1* promoter methylation, CIMP, or *BRAF* mutational statuses of tumors. Data regarding *BRAF* and *NRAS* mutational status in colorectal cancers began to be collected by US cancer registries in 2021, but will generally not be publicly available until approximately 3 years following initial collection, nor did the NCDB report data regarding mixed histologic patterns, tumor-infiltrating lymphocytes, serrated precursor lesions, or other histopathologic features in these tumors. Furthermore, the NCDB did not collect data about somatic tumor panels, germline data, or family history of colorectal cancer. The NCDB only reports treatment data from a patient's initial treatment course, and so does not capture immunotherapy (ie, immune checkpoint inhibitors) administered beyond the first-line setting—which is an important confounder for the analysis of MSI/MMR prognosis in stage IV patients. Moreover, the NCDB categorizes all immunotherapeutic agents and monoclonal antibodies (eg, cetuximab and bevacizumab) into a binary immunotherapy variable, without identifying specific agents or doses. For outcomes, only all-cause OS was reported by the NCDB, precluding the evaluation of additional outcomes such as disease-free survival and postrelapse survival for patients with metachronous stage IV disease. Additionally, the number of prognostic variables reported by the NCDB for patients with stage IV disease was limited.

In conclusion, in a US national cohort, 16% of newly diagnosed colorectal adenocarcinomas were MSI-high/MMR-deficient, with the highest prevalence among stage I-II tumors. In addition to confirming several well-described associations between colorectal cancer attributes and MSI-high/MMR-deficiency—such as female sex, bimodal age distribution, right-sided colonic origin, poorly differentiated histology, and medullary and mucinous subtypes—we found that MSI/MMR status also varied by patients' race/ethnicity, with lower MSI-high/MMR deficiency prevalence among non-Hispanic Black, Asian/Pacific Islander, and Hispanic patients. In contrast to some institutional series, well-differentiated and signet-ring cell histologies were not independently associated with MSI-high/MMR-deficiency when adjusting for other clinicopathologic features.

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DATA SHARING STATEMENT

In accordance with the NCDB data use agreement, data are available by application to the NCDB.

AUTHOR CONTRIBUTIONS

Conception and design: J. Bryan Iorgulescu
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Overall Survival by MSI/MMR Status Among Patients With Stage I-III Colorectal Adenocarcinoma Using Multivariable Cox Regression

	Stage I (n = 8,412)			Stage II (n = 12,787)			Stage III (n = 14,891)		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
MSI/MMR status									
MSS/MMR-proficient	Referent			Referent			Referent		
MSI-low	0.91	0.63 to 1.33	.63	0.85	0.67 to 1.09	.20	0.81	0.67 to 0.99	.04
MSI-high/MMR-deficient	0.78	0.64 to 0.96	.02	0.92	0.81 to 1.04	.19	0.90	0.81 to 1.01	.07
Age at diagnosis, years									
< 30		NA		0.28	0.04 to 2		0.96	0.49 to 1.86	
30-39	0.59	0.14 to 2.41		0.44	0.2 to 0.94		0.66	0.47 to 0.92	
40-49	0.69	0.33 to 1.46		0.64	0.45 to 0.93		0.71	0.57 to 0.88	
50-59	Referent			Referent			Referent		
60-69	1.77	1.27 to 2.46		1.34	1.09 to 1.65		1.31	1.14 to 1.51	
70-79	3.40	2.49 to 4.63		2.18	1.79 to 2.65		2.09	1.82 to 2.39	
≥ 80	8.57	6.33 to 11.6		3.91	3.23 to 4.73		2.76	2.39 to 3.19	
Primary site									
C18.0 cecum	Referent			Referent			Referent		
C18.2 ascending colon	1.07	0.84 to 1.37		1.05	0.89 to 1.23		0.95	0.84 to 1.08	
C18.3 hepatic flexure	1.10	0.72 to 1.67		1.08	0.84 to 1.39		0.93	0.75 to 1.15	
C18.4 transverse colon	1.14	0.84 to 1.54		1.09	0.9 to 1.33		1.00	0.85 to 1.16	
C18.5 splenic flexure	1.35	0.79 to 2.31		1.10	0.81 to 1.5		0.75	0.57 to 0.99	
C18.6 descending colon	1.38	0.94 to 2.01		1.38	1.09 to 1.75		1.01	0.83 to 1.24	
C18.7 sigmoid colon	1.00	0.77 to 1.3		1.19	1 to 1.41		0.77	0.67 to 0.88	
C18.8 overlapping lesion	0.75	0.28 to 2.04		1.44	0.96 to 2.18		1.16	0.84 to 1.6	
C18.9 colon, NOS	1.73	0.91 to 3.3		1.94	1.27 to 2.98		1.34	0.95 to 1.91	
C19.9 rectosigmoid junction	0.98	0.65 to 1.46		1.30	1.01 to 1.68		0.77	0.63 to 0.93	
C20.9 rectum, NOS	0.82	0.61 to 1.08		1.45	1.18 to 1.79		0.84	0.7 to 1.01	
Histologic subtype									
Adenocarcinoma	Referent			Referent			Referent		
Mucinous adenocarcinoma	0.98	0.69 to 1.4		0.92	0.77 to 1.11		1.31	1.14 to 1.5	
Signet-ring cell carcinoma	3.73	1.76 to 7.88		1.39	0.79 to 2.46		2.37	1.88 to 2.99	
Medullary carcinoma	0.29	0.04 to 2.09		1.47	0.96 to 2.23		1.14	0.7 to 1.84	
Primary site surgery									
Excisional biopsy	Referent			Referent			Referent		
Surgical resection	0.47	0.37 to 0.59		0.31	0.25 to 0.38		0.32	0.27 to 0.38	
Chemotherapy (ref none)[a]	NA			0.55	0.48 to 0.64		0.31	0.28 to 0.34	
Radiotherapy (ref none)[a]	NA			NA			1.00	0.84 to 1.19	
AJCC8 stage group									
I	Referent			NA			NA		
IIA	NA			Referent			NA		
IIB	NA			1.75	1.52 to 2.02		NA		
IIC	NA			2.26	1.93 to 2.65		NA		
IIIA	NA			NA			Referent		

(Continued on following page)

TABLE A1. Overall Survival by MSI/MMR Status Among Patients With Stage I-III Colorectal Adenocarcinoma Using Multivariable Cox Regression (Continued)

	Stage I (n = 8,412)			Stage II (n = 12,787)			Stage III (n = 14,891)		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
IIIB	NA			NA			1.44	1.24 to 1.67	
IIIC	NA			NA			3.16	2.7 to 3.7	

NOTE. Cox regression included patients who underwent primary site surgery and were histopathologically diagnosed in 2018 with a colorectal adenocarcinoma. Patients diagnosed at the reporting institution but entirely treated elsewhere were excluded.

Abbreviations: HR, hazard ratio; MMR, mismatch repair; MSI, microsatellite instability; NA, not applicable.

[a]Chemotherapy and chemoradiotherapy were indicated for stage II and stage III cancers, respectively.

TABLE A2. Overall Survival by MSI/MMR Status Among Patients With Stage IV Colorectal Adenocarcinoma Using Multivariable Cox Regression

	Stage IV (n = 8,940)		
Variable	**HR**	**95% CI**	***P***
MSI/MMR status			
MSS/MMR-proficient	Referent		
MSI-low	0.83	0.7 to 0.98	.03
MSI-high/MMR-deficient	0.72	0.64 to 0.81	< .001
Age at diagnosis, years			
< 30	1.19	0.86 to 1.63	
30-39	0.86	0.72 to 1.02	
40-49	0.98	0.88 to 1.1	
50-59	Referent		
60-69	1.18	1.08 to 1.28	
70-79	1.48	1.35 to 1.62	
≥ 80	1.82	1.64 to 2.01	
Primary site			
C18.0 cecum	Referent		
C18.2 ascending colon	0.92	0.83 to 1.03	
C18.3 hepatic flexure	0.93	0.78 to 1.1	
C18.4 transverse colon	0.96	0.85 to 1.09	
C18.5 splenic flexure	0.72	0.58 to 0.89	
c18.6 descending colon	0.79	0.67 to 0.92	
C18.7 sigmoid colon	0.72	0.66 to 0.8	
C18.8 overlapping lesion	0.99	0.79 to 1.24	
C18.9 colon, NOS	1.12	0.96 to 1.3	
C19.9 rectosigmoid junction	0.68	0.6 to 0.78	
C20.9 rectum, NOS	0.67	0.6 to 0.75	
Histologic subtype			
Adenocarcinoma	Referent		
Mucinous adenocarcinoma	1.09	0.96 to 1.24	
Signet-ring cell carcinoma	1.55	1.27 to 1.9	
Medullary carcinoma	1.00	0.55 to 1.83	
Primary site surgery			
None	1.01	0.92 to 1.11	
Excisional biopsy	Referent		
Surgical resection	0.48	0.45 to 0.52	
Chemotherapy (ref no)	0.30	0.28 to 0.33	
Radiotherapy (ref no)	0.79	0.71 to 0.88	
Immunotherapy (ref no)	0.80	0.74 to 0.85	
Resection of nonprimary site			
No	Referent		
Yes	0.71	0.66 to 0.78	
Metastatic site(s)			
Bone metastasis			
No	Referent		
Yes	1.63	1.45 to 1.84	
Brain metastasis			
No	Referent		
Yes	2.40	1.91 to 3.02	
Liver metastasis			
No	Referent		
Yes	1.42	1.32 to 1.52	
Lung metastasis			
No	Referent		
Yes	1.14	1.06 to 1.22	
Distant nodal metastasis			
No	Referent		
Yes	1.25	1.16 to 1.36	
Other site metastasis			
No	Referent		
Other visceral organ	1.49	1.38 to 1.6	
Carcinomatosis	1.83	1.47 to 2.27	

NOTE. Multivariable Cox regression included patients who were diagnosed in 2018 with a histopathologically confirmed colorectal adenocarcinoma. Patients diagnosed at the reporting institution but entirely treated elsewhere were excluded.

Abbreviations: HR, hazard ratio; MMR, mismatch repair; MSI, microsatellite instability; NA, not applicable.

