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The differential impact of microsatellite instability as a marker of prognosis and tumour response between colon cancer and rectal cancer

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ABSTRACT

Background: Microsatellite instability (MSI) is a distinct molecular phenotype of colorectal cancer related to prognosis and tumour response to 5-fluorouracil (5-FU)-based chemotherapy. We investigated the differential impact of MSI between colon and rectal cancers as a marker of prognosis and chemotherapeutic response.

Methods: PCR-based MSI assay was performed on 1125 patients. Six hundred and sixty patients (58.7%) had colon cancer and 465 patients (41.3%) had rectal cancer.

Results: Among 1125 patients, 106 (9.4%) had high-frequency MSI (MSI-H) tumours. MSI-H colon cancers (13%) had distinct phenotypes including young age at diagnosis, family history of colorectal cancer, early Tumor, Node, Metastasis (TNM) stage, proximal location, poor differentiation, and high level of baseline carcinoembryonic antigen (CEA), while MSI-H rectal cancers (4.3%) showed similar clinicopathological characteristics to MSS/MSI-L tumours except for family history of colorectal cancer. MSI-H tumours were strongly correlated with longer disease free survival (DFS) ($P = 0.005$) and overall survival (OS) ($P = 0.009$) than MSS/MSI-L tumours in colon cancer, while these positive correlations were not observed in rectal cancers. The patients with MSS/MSI-L tumours receiving 5-FU-based chemotherapy showed good prognosis ($P = 0.013$), but this positive association was not observed in MSI-H ($P = 0.104$).

Conclusion: These results support the use of MSI status as a marker of prognosis and response to 5-FU-based chemotherapy in patients with colon cancers. Further study is mandatory to evaluate the precise role of MSI in patients with rectal cancers and the effect of 5-FU-based chemotherapy in MSI-H tumours.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in Western countries. In Korea, CRC is the third most common cancer with an estimated 20,558 new cases and 6608 deaths each year.[1] Since 1990's, 5-fluorouracil (FU) plus leucovorin (FL) has been the standard of care for patients with CRC.[2] To date, several chemotherapeutic regimens including FL plus

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oxaliplatin or irinotecan have been applied as treatment for CRC.[3] Despite recent advances of combined chemotherapy, CRC is still the second leading cause of cancer-related mortality in the Unites States.[4]

Pathologic tumour staging of CRC has been a key factor in determining treatment and prognosis, but it is evident that CRC has a significant clinical heterogeneity even within the same pathologic stage.[5] Microsatellite instability (MSI) is one of the most promising molecular markers representing the heterogeneity of CRCs.[6] Most high-frequency MSI (MSI-H) tumours of sporadic CRCs are due to epigenetic inactivation of MLH1 by promoter hypermethylation in a setting of CpG island methylator phenotype (CIMP) with MSH2 and MSH6 accounting for a smaller percentage,[7,8] while Lynch syndrome is caused by germline mutations in MLH1, MSH2, MSH6 and PMS2.[9] Although 85% of sporadic CRCs develop via chromosomal instability pathways, approximately 15–20% are characterised by MSI, and have distinct pathologic and clinical phenotypes.[10] CRCs with high-frequency MSI (MSI-H) are dominantly located in the proximal colon and show poor differentiation, mucinous cell type, peritumoural lymphocytic infiltration and diploid DNA content.[6,11]

Accumulating evidence indicates the role of MSI analysis as a marker of prognosis in CRCs. A number of studies have shown that patients with MSI-H tumours tend to be diagnosed at an early stage, and have longer overall survival than those with microsatellite stable (MSS) tumours.[6,12,13] A meta-analysis estimated the combined hazard ratio (HR) for overall survival associated with MSI was 0.65 (95% confidence interval (CI), 0.59–0.71).[13] In addition, several studies have suggested that sensitivity to chemotherapy is affected by MSI status. Notably, it was reported that tumour response to FL regimen varied according to MSI status. FL adjuvant chemotherapy improved survival among patients with MSS tumours, but there was no benefit for patients with MSI-H tumours.[5] However, this observation was not always consistent, and other studies have reported conflicting data that patients with MSI-H tumours had similar outcomes[14] or even showed better outcomes with 5-FU-based treatment compared to those with MSS tumours.[15,16]

It has been suggested that MSI assay is a useful marker to predict prognosis in patients with CRCs.[17] However, the effect of MSI status on tumour response to 5-FU-based chemotherapy remains controversial. Moreover, the impact of MSI status has not been fully evaluated on rectal cancer, which is known to have a lower frequency of MSI-H tumours than colon cancers.[18] This study was conducted to evaluate the differential impact of MSI status between colon and rectal cancers, and to validate the role of MSI status as a predictor of 5-FU-based chemotherapy.

2. Patients and methods

Between November 2004 and December 2007, 1257 patients with colorectal cancers received surgical resection at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Among the 1257 patients, 132 (10.5%) were excluded in this retrospective study; 27 patients with recurrent tumours, 58 with follow-up loss, 20 with familial polyposis coli, five with ulcerative colitis, and 22 with refusal of MSI assay. Finally, 1125 patients were included in this study. After resection, the patients underwent follow-up without treatment (244 patients), or received chemotherapy (665 patients) or chemoradiotherapy (216 patients) with a standard dose and schedule according to tumour stage, regardless of the MSI status. Follow-up evaluations including CT scans were performed regularly. Age, sex, family history of colorectal cancer, tumour stage, tumour location, tumour grade and chemotherapeutic regimen were retrospectively reviewed. This study was approved by the Institutional Review Boards of Yonsei University College of Medicine.

2.1. Tumour MSI analysis

Before obtaining tissue samples, written informed consent was obtained from all patients. Tissue samples from tumour and normal colonic mucosa were obtained from each patient after resection. DNA extracted from each tumour was amplified by a standard polymerase chain reaction using five Bethesda guidelines panel loci (BAT25, BAT26, MFD15, D2S123 and D5S346).[19] In accordance with the consensus definitions of the National Cancer Institute, tumour samples were classified as displaying high-degree microsatellite instability (MSI-H, instability at 30% or more of the markers tested), low-degree microsatellite instability (MSI-L, instability at less than 30% of the markers tested), and microsatellite stability (MSS, stability at all the marker tested). Because of the similar biological properties between low-frequency MSI (MSI-L) and MSS, these two molecular phenotypes were grouped together in all analyses.[5]

2.2. Statistics

The primary outcomes were overall survival (OS) and disease free survival (DFS). The secondary outcome was tumour response to chemotherapy. Each patient's baseline characteristics were analysed by descriptive statistics. OS was calculated from the time of diagnosis to death or the last follow-up visit, and DFS was calculated from the time of diagnosis until disease recurrence or progression. OS and DFS were analysed using the Kaplan–Meier method, and survival curves were compared using the log-rank method. OS and PFS according to chemotherapeutic regimens were analysed in the subset of patients with stages II–IV tumours. HR and 95% confidence intervals (CIs) for univariate or multivariate models adjusted for age, gender and Tumor, Node, Metastasis (TNM) stage were computed with the use of Cox proportional-hazard regression. A P-value <0.05 was considered statistically significant. All values were presented as mean ± standard deviation (SD), median (range), or percentage (number, percent). All statistical analyses were performed using the software package SPSS 15 for Windows (SPSS Inc., Chicago, Ill).

3. Results

3.1. Patients' characteristics associated with MSI status

The clinicopathological characteristics of the patients are summarised in Table 1. Among the 1125 patients, 660

Table 1 – Baseline characteristics of enrolled patients.

n (%)	All	Microsatellite stable (MSS) and low-frequency MSI (MSI-L)	High-frequency MSI (MSI-H)	*P* value
	1125 (100)	1019 (90.6)	106 (9.4)	
Age, median (range)	61 (26–92)	61 (26–92)	57 (26–78)	0.001
Sex, *n* (%)				0.834
Male	691 (61.4)	627 (61.5)	64 (60.4)	
Female	434 (38.6)	392 (38.5)	42 (39.6)	
Family history of colorectal cancer				0.001
No	1066 (94.8)	974 (95.6)	92 (86.8)	
Yes	59 (5.2)	45 (4.4)	14 (13.2)	
Tumour stage				<0.001
I	178 (15.8)	161 (15.8)	17 (16.0)	
II	383 (34.0)	328 (32.2)	55 (51.9)	
III	404 (36.0)	376 (36.9)	28 (26.4)	
IV	160 (14.2)	154 (15.1)	6 (5.7)	
Tumour type				<0.001
Colon	660 (58.7)	574 (56.3)	86 (81.1)	
Rectum	465 (41.3)	445 (43.7)	20 (18.9)	
Site of tumour				<0.001
Proximal	252 (22.4)	191 (18.7)	61 (57.5)	
Distal	874 (77.6)	829 (81.3)	45 (42.5)	
Tumour grade				<0.001
Well differentiated	147 (13.1)	135 (13.2)	12 (11.3)	
Moderate differentiated	867 (77.1)	801 (78.6)	66 (62.3)	
Poorly differentiated	52 (4.6)	39 (3.8)	13 (12.3)	
Undifferentiated	59 (5.2)	44 (4.4)	15 (14.1)	
Initial CEA, mean ± SD	24.1 ± 8.7	25.9 ± 9.5	7.3 ± 2.7	<0.001

Table 2 – Baseline characteristics of patients with colon cancer.

n (%)	All	MSS and MSI-L	MSI-H	*P* value
	660 (100)	574 (87.0)	86 (13.0)	
Age, median (range)	62 (26–92)	63 (26–92)	58 (31–78)	<0.001
Sex, *n* (%)				0.639
Male	389 (58.9)	336 (58.5)	53 (61.6)	
Female	271 (41.1)	238 (41.5)	33 (38.4)	
Family history of colorectal cancer				0.019
No	623 (94.4)	547 (95.3)	76 (88.4)	
Yes	37 (5.6)	27 (4.7)	10 (11.6)	
Tumour stage				0.001
I	74 (11.2)	63 (11.0)	11 (12.8)	
II	247 (37.4)	200 (34.8)	47 (54.7)	
III	233 (35.3)	211 (36.8)	22 (25.6)	
IV	106 (16.1)	100 (17.4)	6 (7.0)	
Site of tumour				<0.001
Proximal	252 (38.2)	191 (33.3)	61 (70.9)	
Distal	408 (61.8)	383 (66.7)	25 (29.1)	
Tumour grade				<0.001
Well differentiated	83 (12.6)	72 (12.5)	11 (12.8)	
Moderate differentiated	500 (75.8)	451 (78.6)	49 (57.0)	
Poorly differentiated	33 (5.0)	22 (3.8)	11 (12.8)	
Undifferentiated	44 (6.6)	29 (5.1)	15 (17.4)	
Initial CEA, mean (range)	35.9 (0.01–7418.3)	40.1 (0.01–7418.3)	7.9 (0.03–267.9)	<0.001

Table 3 – Baseline characteristics of patients with rectal cancer.

n (%)	All	MSS and MSI-L	MSI-H	P value
	466 (100)	446 (95.7)	20 (4.3)	
Age, median (range)	60 (26–85)	60 (28–85)	57 (26–74)	0.174
Sex, *n* (%)				0.347
Male	302 (64.9)	291 (65.4)	11 (55.0)	
Female	163 (35.1)	154 (34.6)	9 (45.0)	
Family history of colorectal cancer				0.011
No	443 (95.3)	427 (96.0)	16 (80.0)	
Yes	22 (4.7)	18 (4.0)	4 (20.0)	
Tumour stage				0.255
I	104 (22.4)	98 (22.0)	6 (30.0)	
II	136 (29.2)	128 (28.8)	8 (40.0)	
III	171 (36.8)	165 (37.1)	6 (30.0)	
IV	54 (11.6)	54 (12.1)	0 (0)	
Tumour grade				0.444
Well differentiated	64 (13.8)	63 (14.1)	1 (5.0)	
Moderate differentiated	367 (78.9)	350 (78.7)	17 (85.0)	
Poorly differentiated	19 (4.1)	17 (3.8)	2 (10.0)	
Undifferentiated	15 (3.2)	15 (3.4)	0 (0.0)	
Initial CEA, mean (range)	7.5 (0.01–205.1)	7.6 (0.01–205.1)	5.0 (0.04–48.0)	0.853

(58.7%) were colon cancers and 465 (41.3%) were rectal cancers. Patients with TNM stages I, II, III and IV numbered 178 (15.8%), 383 (34.0%), 404 (36.0%) and 160 (14.2%), respectively. One hundred and six patients (9.4%) demonstrated MSI-H, 81 patients (7.2%) had MSI-L and 938 patients (83.4%) had MSS. The median follow-up was 42 months.

Patients with MSI-H were diagnosed at younger age (57 years versus 61 years, $P = 0.001$), and more often had fam-

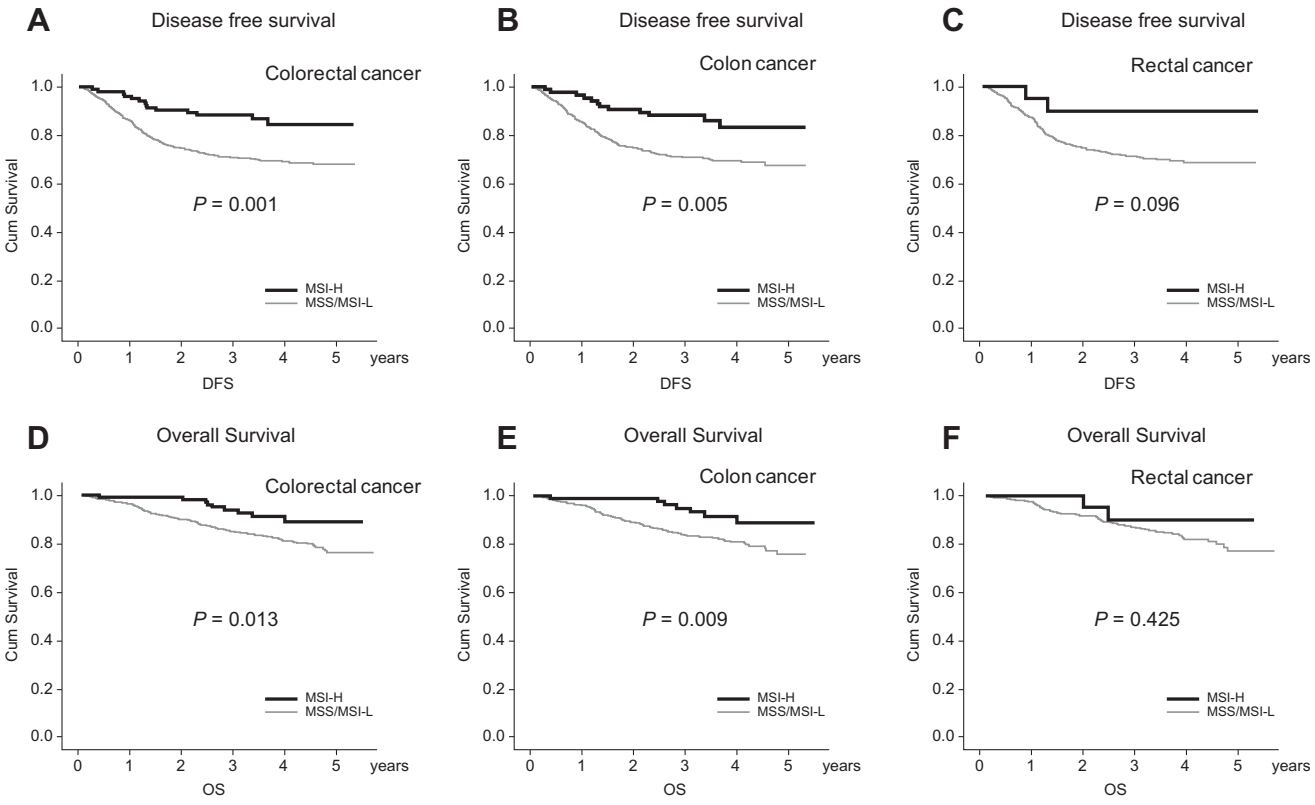

Fig. 1 – Disease free survival of all patients (A), patients with colon cancers (B), and patients with rectal cancers (C) according to microsatellite instability (MSI) status. Overall survival of all patients (D), patients with colon cancers (E) and patients with rectal cancers (F) according to MSI status.

Table 4 – Disease free survival (DFS) and overall survival (OS) by microsatellite instability (MSI) status in univariate and multivariate models adjusted for stage, sex, and age in colorectal cancer.

MMR	No. of patients	DFS						OS					
		3 year rate (%)	Univariate			Multivariate		3 year rate (%)	Univariate			Multivariate	
			Hazard ratio (HR)	95% Confidence interval (CI)	*P*	HR	95% CI	*P*		HR	95% CI	*P*	HR	95% CI	*P*
Overall	1125														
MSI-H	1019	87.6	0.40	0.23–0.68	0.001	0.57	0.32–0.96	0.034	94.1	0.44	0.23–0.86	0.016	0.70	0.35–1.37	0.292
MSS/MSI-L	106	70.9							85.0						
Colon	660														
MSI-H	574	87.0	0.42	0.23–0.75	0.004	0.61	0.33–1.10	0.100	96.3	0.40	0.19–0.86	0.018	0.64	0.29–1.40	0.262
MSS/MSI-L	86	70.7							83.6						
Rectum	465														
MSI-H	445	90.0	0.30	0.07–1.20	0.087	0.48	0.12–1.97	0.311	90.0	0.56	0.14–2.30	0.425	1.07	0.26–4.44	0.924
MSS/MSI-L	20	71.1							86.9						

ily histories of colorectal cancer (13.2% versus 4.4%, $P = 0.001$) than those with MSS/MSI-L. MSI-H was more frequent in colon cancers than in rectal cancers (13.0% versus 4.3%, $P < 0.001$). MSI-H was more likely to be diagnosed at early stage ($P < 0.001$), to be located in the proximal colon ($P < 0.001$) and to have a high tumour grade ($P < 0.001$) than MSS/MSI-L. Initial carcinomebryonic antigen (CEA) level was higher in MSI-H than MSS/MSI-L ($P < 0.001$).

3.2. *Differences in tumour phenotype between MSI-H colon and MSI-H rectal cancer*

The present study showed that MSI-H was less frequent in rectal cancers than in colon cancers. Further analysis was subsequently performed separately in patients with colon and rectal cancers according to MSI. MSI-H colon cancers showed typical characteristics, including young age at diagnosis, family history of colorectal cancer, early TNM stage, proximal location, poor differentiation and high level of initial CEA as compared to MSS/MSI-L colon cancers (Table 2). However, these distinct phenotypes of MSI-H tumours were not observed in rectal cancers (Table 3). Only family history of colorectal cancer was more frequent in MSI-H rectal cancers than MSS/MSI-L (20.0% versus 4.0%, $P = 0.011$).

3.3. *Association of MSI status with prognosis*

To validate the value of MSI status as prognostic marker, PFS and OS were compared between MSI-H and MSS/MSI-L (Fig. 1 and Table 4). MSI-H had longer median DFS than the MSS/MSI-L (58.7 months versus 50.8 months, $P = 0.001$). The HR for DFS in MSI-H versus MSS/MSI-L was 0.40 (95% CI, 0.23–0.68; $P = 0.001$). The OS in patients with MSI-H were also longer than those with MSS/MSI-L (63.5 months versus 60.0 months, $P = 0.013$). The 3-year OS was 94.1% in MSI-H and 85.0% in MSS/MSI-L (HR 0.44; 95% CI, 0.23–0.86; $P = 0.016$). In multivariate models adjusted for stage, gender and age, MSI-H was significantly associated with long DFS compared to MSS/MSI-L (HR 0.57, 95% CI 0.32–0.96; $P = 0.034$).

Since the phenotypes of MSI-H were different between colon and rectal cancers, the meaning of MSI was analysed separately in colon and rectal cancers (Fig. 1 and Table 4). MSI-H colon cancers had longer DFS and OS than MSS/MSI-L (DFS, 58.5 months versus 50.7 months; $P = 0.005$: OS, 63.6 months versus 55.4 months; $P = 0.009$). The HR for DFS and OS in MSI-H versus MSS/MSI-L colon cancers were 0.42 (95% CI, 0.23–0.75; $P = 0.004$) and 0.40 (95% CI, 0.19–0.86; $P = 0.018$). However, MSI-H rectal cancers showed no good prognosis in DFS ($P = 0.096$) and OS ($P = 0.425$) as compared to MSS/MSI-L.

3.4. *MSI status as a predictive marker*

Previous studies demonstrated that chemotherapy with 5-FU had no favourable effects for MSI-H tumours.[5] To evaluate the precise role of MSI status as a predictor, tumour response to 5-FU-based chemotherapy was analysed in patients with colorectal cancers in stages II–IV according to MSI status (Fig. 2). The patients who received 5-FU-based chemotherapy had longer OS than those who did not (59.6 months versus 49.4 months, $P = 0.006$). The patients with MSS/MSI-L

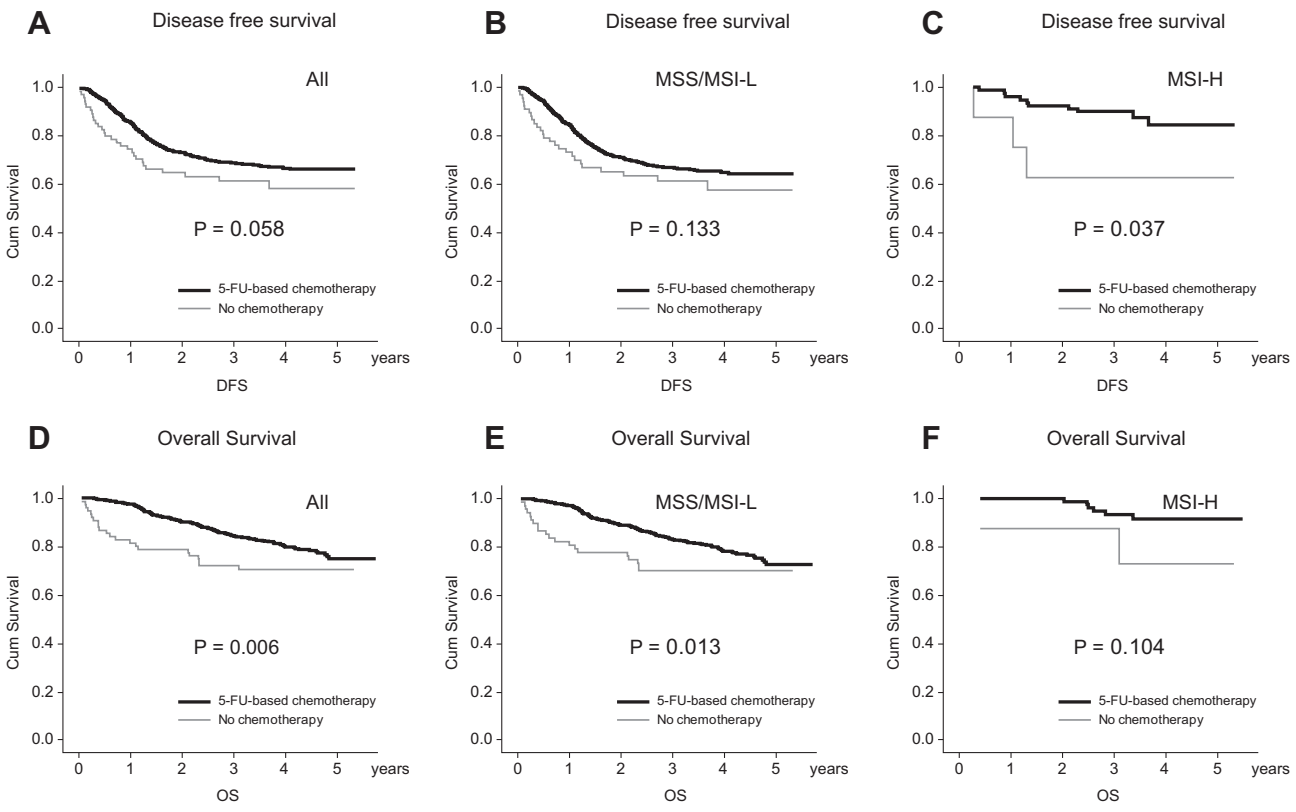

Fig. 2 – Among the patients with stages II–IV colorectal cancer, disease free survival of all patients (A), patients with MSS/MSI-L (B) and patients with high-frequency MSI (MSI-H) (C) according to 5-fluorouracil (5-FU)-based chemotherapy or no chemotherapy. Overall survival of all patients (D), patients with MSS/MSI-L (E) and patients with MSI-H (F) according to 5-FU based chemotherapy or no chemotherapy.

had good prognosis from 5-FU-based chemotherapy (OS, 59.2 months versus 49.0 months, $P = 0.013$). However, 5-FU-based chemotherapy had no favourable effects for patients with MSI-H (OS, 64.1 months versus 53.6 months, $P = 0.104$). 5-FU based chemotherapy had also no favourable effects in stages II–III CRC patients with MSI-H compared to those with MSS/MSI-L (OS, 64.5 months versus 63.2 months, $P = 0.127$). In multivariate model adjusted for stage, sex and age in stages II–IV colorectal cancers, 5-FU-based chemotherapy was significantly associated with longer DFS (HR 0.54, 95% CI 0.36–0.80; $P = 0.002$) and OS (HR 0.39, 95% CI 0.25–0.63; $P < 0.001$) than observation (Table 5). The association of good prognosis and 5-FU-based chemotherapy was statistically significant in MSS/MSI-L tumours (DFS, HR 0.50, 95% CI 0.32–0.76; $P = 0.001$: OS, HR 0.34, 95% CI 0.21–0.57; $P < 0.001$). This positive association was not observed in MSI-H tumours (DFS, HR 0.42, 95% CI 0.10–1.72; $P = 0.225$: OS, HR 0.57, 95% CI 0.09–3.75; $P = 0.556$). However, the effect of 5-FU-based chemotherapy was not fully evaluated in MSI-H tumours because of the low number of cases.

4. Discussion

This retrospective study demonstrated that the clinical and pathological features of MSI-H differ between colon and rectal cancers. MSI-H colon cancers showed distinguished phenotypes, including young age at diagnosis, family history of colorectal cancer, early TNM stage, proximal location, poor differentiation and high level of baseline CEA from MSS/MSI-L colon cancers. However, these characteristics of MSI-H were not observed in rectal cancers. Unlike in colon cancers, the positive prognostic value of MSI-H was not observed in rectal cancers.

The tumourigenesis of colon and rectal cancers is thought to occur through multistep genetic alterations. It seems that the two types of tumour share similar molecular pathways, but also have some differences. The effect of MSI, one of the distinct molecular features in colon tumourigenesis, is ambiguous in rectal cancers. The incidence of MSI-H has been reported to be less than 10% in rectal cancers,[20,21] while 15–20% of colon cancers are MSI-H. Although one study reported 19% of MSI-H rectal cancers with a small sample size of 91 cases,[22] the 4.4% of MSI-H found in the present study is more comparable to other recent studies.[18,21] As to the low frequency of MSI-H in rectal cancers, the present study demonstrates that its phenotype differed from colon cancers. One of the interesting findings from the present study was that positive family history of CRC cancer was more frequent in patients with MSI-H rectal cancer than in those with colon cancers. Previous studies also indicated a strong correlation between family history and MSI-H rectal cancers.[18,23] One study demonstrated that most MSI-H rectal cancers were caused by the loss of MSH2 and MSH6, which is strongly

Table 5 – Disease free survival (DFS) and overall survival (OS) by microsatellite instability (MSI) status and 5-fluorouracil (5-FU) based chemotherapy in univariate and multivariate models adjusted for stage, sex and age in stages II–IV colorectal cancer.

MMR	No. of patients	DFS							OS						
		3 year rate (%)	Univariate			Multivariate			3 year rate (%)	Univariate			Multivariate		
			HR	95% CI	P	HR	95% CI	P		HR	95% CI	P	HR	95% CI	P
Overall	947														
5-FU-based chemotherapy	872	68.7	0.69	0.47–1.02	0.060	0.54	0.36–0.80	0.002	84.7	0.54	0.35–0.84	0.007	0.39	0.25–0.63	<0.001
No	75	63.2							72.0						
MSS/MSI-L	858														
5-FU-based chemotherapy	791	66.6	0.74	0.49–1.10	0.134	0.50	0.32–0.76	0.001	96.7	55.8	0.35–0389	0.14	0.34	0.21–0.57	<0.01
No	67	61.3							70.1						
MSI-H	89														
5-FU-based chemotherapy	81	88.7	0.28	0.08–1.01	0.051	0.42	0.10–1.72	0.225	91.6	0.29	0.06–1.42	0.127	0.57	0.09–3.75	0.556
No	8	62.5							87.5						

suggestive of Lynch syndrome.[18] These results indicate that MSI-H rectal cancers have different clinical and pathological features from colon cancers, and strongly suggest a different subset of hereditary cancer.

It is remarkable that an MSI assay could predict prognosis in patients with CRC. Many studies have emphasised that MSI-H CRCs had a good prognosis compared to MSS/MSI-L CRCs. Recent meta-analysis including 31 eligible studies validated that MSI-H CRCs of stages I–IV had not only better OS with an odds ratio (OR) of 0.6 (95% CI, 0.53–0.69) but also better DFS, with an OR of 0.58 (95% CI, 0.47–0.72), than MSS/MSI-L CRCs, which were comparable to the present study.[24] Although MSI-H rectal cancers had different phenotypes from colon cancers, most studies evaluated the prognostic impact of MSI without comparing the two tumour types. When focusing on rectal cancers, the implication of MSI as a prognostic marker is not clear. A previous study reported that MSI-H was strongly associated with better DFS and OS in rectal cancers.[22] However, other studies indicated that MSI was not a prognostic factor[25] or even a poor prognostic factor in rectal cancers.[18] This discrepancy may be due to selection bias. In addition, the study population was not homogenous, and microsatellite markers used in these studies were not uniform, which can influence on the frequency of MSI-H. It may also be due to ethnic differences. While one study with a high incidence of MSI-H (19%) reported the association of MSI with a good prognosis in rectal cancer,[22] another study with a 2.4% prevalence of MSI-H[18] and the present study with 4.3% showed conflicting results. Finally, treatment may influence the impact of MSI on rectal cancers. Most patients with rectal cancers of stages II or III received CRT with a FL regimen.[26] Because MSI-H showed a poor response to 5-FU chemotherapy,[27] the treatment regimen may dilute the impact of MSI. According to the present study, the prognostic impact of MSI is strong in colon cancer; however, further study is necessary to evaluate the exact value of MSI in rectal cancer.

While the value of MSI as prognostic marker has been well established, the role of MSI as a predictor to treatment response has been more controversial. A previous study reported that MSI-H CRCs did not benefit from 5-FU-based chemotherapy, while MSS/MSI-L CRCs did.[5] This study indicated that 5-FU-based chemotherapy could even be harmful to patients with MSI-H CRCs. However, another study failed to confirm the predictive value of MSI-H in colon cancers from adjuvant therapy trials.[14] A recent meta-analysis reported that 5-FU-based chemotherapy significantly improved prognoses in patients with MSS/MSI-L CRCs, while no clear conclusion was reached for those with MSI-H CRCs because of a large heterogeneity.[24] On the molecular level, an intact DNA repair system was required for 5-FU induced apoptosis, and colon cancer cells with defective DNA repair systems showed resistance to 5-FU.[28,29] Therefore, it is reasonable to regard MSI status as a marker of non-response to 5-FU-based chemotherapy.[13,17]

This study has several limitations. First, a retrospective study design has inherent limitations. Second, because of the small number of MSI-H tumours, the predictive value of MSI-H could not be fully evaluated in patients receiving 5-FU based chemotherapy. A recent study demonstrated that FL plus weekly bolus irinotecan significantly improved 5-year

DFS in patients with stage III MSI-H colon cancers more than in those with MSS/MSI-L.[30] Finally, the predictive roles of the CpG island methylator phenotype (CIMP) and BRAF mutation were not evaluated in the present study. Recent study demonstrated that CIMP-high tumours were significantly associated with good prognosis, regardless of MSI status.[31] MSI-tumours with BRAF mutation showed poor prognosis compared to those with wild type.[32]

In conclusion, we demonstrated that MSI-H tumours had differential phenotypes between colon and rectal cancers. In colon cancers, MSI-H tumours had better OS and DFS than MSS/MSI-L tumours. Therefore, in practice, the MSI assay may be used as a molecular marker of good prognosis in colon cancers. As a marker of predictor, we showed that MSS/MSI-L tumours were good responders to 5-FU-based chemotherapy. Further study is necessary to evaluate the precise role of MSI in rectal cancers and the effect of 5-FU-based chemotherapy in MSI-H tumours.

Conflict of interest statement

None declared.

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