Original Article

The correlation between DNA mismatch repair status and the clinicopathological and molecular features of Chinese sporadic colorectal cancer

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Background: DNA mismatch repair (*MMR*) genes play an important role in cancer development. Deficiencies in these genes may cause microsatellite instability (MSI), which can cause colorectal cancer (CRC). Therefore, we evaluate the relationship between MMR status and the clinicopathological and molecular features of Chinese patients with sporadic CRC.

Methods: We evaluated 1,405 patients who had undergone primary tumour resection, and divided them into MMR deficiency (dMMR) and MMR proficiency (pMMR) groups, according to their *MMR* gene expressions. All clinicopathological and molecular features were obtained from pathology reports.

Results: The dMMR group contained 125 patients and the pMMR group contained 1 280 patients. Patients with dMMR were more likely to be younger (P<0.05), have poorly differentiated tumours (14.6%), tumours with negative peripheral nerve invasiveness (10.2%), and right-side tumours. Multivariate analysis revealed that the significant independent risk factors for dMMR-related CRC were younger age (OR: 0.979, 95% CI: 0.960–0.998), larger tumour diameter (OR: 1.313, 95% CI: 1.162–1.484), poor differentiation, no peripheral nerve invasiveness (OR: 3.018, 95% CI: 1.258–7.239), right-side colon cancer (OR: 10.821, 95% CI: 4.895–23.922), Bcl-2 positivity (OR: 0.209, 95% CI: 0.095–0.458), topoisomerase II negativity (OR: 3.333, 95% CI: 1.563–7.103) and glutathione S-transferase (GST) negativity (OR: 1.748, 95% CI: 1.009–3.027).

Conclusions: Younger age, poorly differentiated tumours, negative peripheral nerve invasiveness, right-side tumours, Bcl-2 positivity, topoisomerase II negativity and GST negativity increased the likelihood of dMMR in Chinese patients with sporadic CRC.

Keywords: Mismatch repair (MMR); microsatellite instability (MSI); colorectal cancer (CRC)

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Introduction

Colorectal cancer (CRC) is the third most common cancer in males and the second in female worldwide (1). Chromosomal instability (CIN) and microsatellite instability (MSI) are two main pathways for the development of CRC (2). The CIN pathway involves the accumulation of mutations in oncogenes, such as *KRAS* and tumour-suppressor genes, especially on *chromosomes 5q* (the adenomatous polyposis coli gene), *17p* (the *P53* gene), *18q* [the deleted in colorectal carcinoma (DCC) and *SMAD4* genes]. Approximately 85% of sporadic CRC cases involve CIN (3). In contrast, the MSI pathway involves a unique molecular alteration that is induced by deficiencies in the DNA mismatch repair (MMR) system, and is characterized by unstable microsatellites. The CpG island methylator phenotype has also recently been reported as a third mechanism of colorectal carcinogenesis (4,5).

The cause of MSI is the inactivation of at least one of the *MMR* genes, which include MLH1, MSH2, MSH6 or PMS2. Germline mutations in the *MMR* genes represent a major cause of the hereditary MSI-high CRCs in Lynch syndrome. The most frequent mutations in the MMR system affect the MLH1 gens (6), which has been identified as the most common cause of the development of hereditary nonpolyposis colorectal cancer (HNPCC). The sporadic CRCs with a high level of MSI account for nearly 3–15% of all CRCs (7), which are mainly caused by promoter CpG island hypermethylation, especially on MLH1 (8). Researchers have demonstrated that immunohistochemistry can be used to test for the loss of *MMR* gene protein expression (9), which offers a highly specific and technically simple alternative to the characterization of MSI tumours.

The correlation between MMR status and the clinicopathological features of CRC have been reported by several researchers. However, few studies have focused on the relationship between the molecular characteristics of CRC and MMR status. Therefore, we investigated the relationship between MMR status and the clinicopathological and molecular features in Chinese patients with sporadic CRC, using a large-scale retrospective analysis. The findings of the present study contribute to our understanding of the relationship between MSI and the clinicopathological and molecular features of CRCs.

Methods

Patients

This retrospective study evaluated 1,405 patients with primary CRC that was diagnosed between 2012 and 2014 at Fudan University Shanghai Cancer Center. Patients who were suspected of having hereditary or familial CRC were excluded from our analysis. All patients had undergone primary tumour resection.

Clinicopathological and molecular features

The clinicopathological characteristics were summarized using data from the patients' medical histories and histopathology reports. These data included age, sex, tumour location, TNM stage, tumour type, histological type, differentiation, tumour size, vascular and peripheral nerve invasiveness. The molecular features were acquired from the immunohistochemistry report, and included the expression of the p53, Bcl-2, topoisomerase II (TopoII), CD44, and glutathione S-transferase (GST) proteins. Patients were classified as having MMR deficiency (dMMR) if they exhibited loss of at least one of the *MMR* genes (*MLH1*, *MSH2*, *PMS2* or *MSH6*).

Statistics

Univariate analysis was performed using the χ^2 test, and the *t*-test was used for continuous variables analysis. Multivariate correlation analysis was performed using the logistic regression test. The statistical analyses were performed using SPSS software (version 20, SPSS Inc., Chicago, IL, USA). Differences with a P value of <0.05 were considered statistically significant.

Results

MMR status and clinicopathological parameters

The present study included 822 (58.5%) men and 583 (41.5%) women, and the average age of the included patients was 59.8 years. We observed dMMR in 125 (8.9%) cases of CRC, and 1,280 (91.1%) cases of CRC exhibited MMR proficiency (pMMR) (*Table 1*). The number of patients with dMMR decreased with increasing age (P<0.05)

Table 1 The relationship between clinicopathological and molecular features and mismatch repair status

Clinicopathological and molecular features	pMMR		dMMR		χ^2	P value
	n	%	n	%		
Sex					0.857	0.354
Male	744	90.5	78	9.5		
Female	536	91.9	47	8.1		
Location					109.532	<0.001
Right-side	262	77.7	75	22.3		
Left-side	452	92.1	39	7.9		
Rectum	566	98.1	11	1.9		
T stage					1.872	0.599
1	77	93.9	5	6.1		
2	210	92.5	17	7.5		
3	645	90.3	69	9.7		
4	339	90.9	34	9.1		
N stage					14.774	<0.001
0	693	88.5	90	11.5		
1	355	94.2	22	5.8		
2	232	94.7	13	5.3		
TNM stage					18.896	<0.001
I	224	91.8	20	8.2		
II	444	86.9	67	13.1		
III	523	94.4	31	5.6		
IV	84	92.3	7	7.7		
Tumour type					3.237	0.356
Protruding	381	90.7	39	9.3		
Ulcerative	798	90.7	82	9.3		
Infiltrating	53	96.4	2	3.6		
Others	43	95.6	2	4.4		
Histologic type					55.234	<0.001
Adenocarcinoma	1,137	93.3	81	6.7		
A + M/S	81	75.5	26	24.3		
M/S	61	78.2	17	21.8		
Differentiation					24.603	<0.001
Good	55	90.2	6	9.8		
Moderate	878	93.8	58	6.2		
Poor	333	85.4	57	14.6		
V ascular invasion					3.395	0.65
No	947	90.3	102	9.7		
Yes	331	93.5	23	6.5		

Table 1 *(Continued)*

Table 1 *(Continued)*

Clinicopathological and molecular features	pMMR		dMMR		χ^2	P value
	n	%	n	%		
PNI					13.567	<0.001
No	1,026	89.8	117	10.2		
Yes	254	96.9	8	3.1		
p21					1.475	0.225
Positive	810	7.7	86	9.6		
Negative	469	92.3	39	90.4		
p53					10.644	0.001
Positive	970	4.3	110	10.2		
Negative	310	95.7	14	89.8		
CD44					4.525	0.033
Positive	1,136	91.7	103	8.3		
Negative	143	86.7	22	13.3		
Her2					0.118	0.731
Positive	522	91.4	49	8.6		
Negative	758	90.9	76	9.1		
E-cadherin						1.000[a]
Positive	1,269	91.7	124	8.3		
Negative	11	91.1	1	8.9		
EGFR					0.086	0.770
Positive	235	90.4	25	9.6		
Negative	997	91	99	9		
Bcl-2					22.379	<0.001
Positive	44	74.6	15	25.4		
Negative	1,216	92.2	103	7.8		
MDR					0.592	0.442
Positive	106	93	8	7		
Negative	1,149	90.8	116	9.2		
TopoII					20.647	<0.001
Positive	1,204	92	105	8		
Negative	60	76.9	18	23.1		
Cox2						0.581[a]
Positive	1,242	91.2	120	8.8		
Negative	38	88.4	5	11.6		
GST					5.071	0.024
Positive	1,039	91.9	92	8.1		
Negative	222	87.4	32	12.6		

[a], Fisher's exact test. pMMR, mismatch repair proficiency; dMMR, mismatch repair deficiency; A, adenocarcinoma; M, mucinous component; S, signet-ring cell component; PNI, perineural invasion; EGFR, epidermal growth factor receptor; MDR, P-glycoprotein; GST, glutathione S-transferase.

Table 2 The correlation between clinicopathological factors and mismatch repair status

Clinicopathological and molecular features	pMMR		dMMR		T test
	n	Mean	n	Mean	P value
Age	1,280	60.095	125	56.816	0.017
Diameter	1,278	4.001	125	5.558	<0.001
Lymph nodes	1,280	16.863	125	22.152	<0.001
Metastatic LN	1,280	1.859	125	1.320	0.082
Frequency of M-LN	1,280	0.117	125	0.069	0.004

pMMR, mismatch repair proficiency; dMMR, mismatch repair deficiency; LN, lymph nodes; M-LN, metastatic lymph nodes.

(*Table 2*). The prevalence of dMMR varied according to tumour stage, with the lowest frequency observed in stage III (5.6%) and the highest frequency observed in stage II (13.1%). As in previous studies, the dMMR phenotype was more common in right-side colon cancer (22.35), compared to in left-side colon cancer (7.9%) and rectal cancer (1.9%); this difference was statistically significant (P<0.001). In addition, dMMR was more prevalent in poorly differentiated tumours, mucinous or signet-ring cell tumours, and tumours with lesser lymph node metastasis (*Table 1*) or a larger tumour diameter (*Table 2*). We also analysed the number of lymph nodes that had been acquired and the frequency of their metastasis, which revealed that more lymph nodes were examined, and a lower metastatic frequency was observed, in cases of dMMR CRCs (*Table 2*).

MMR status and molecular features

The molecular markers that we examined were p21, p53, CD44, Her2/neu, E-cadherin, epidermal growth factor receptor (EGFR), Bcl-2, P-glycoprotein (MDR), TopoII, cyclooxygenase 2 (COX2) and GST. Patients with dMMR exhibited a higher frequency of positive p53 and Bcl-2 expression, compared to patients with pMMR (P<0.01). In addition, patients with dMMR exhibited a higher frequency of negative CD44, TopoII and GST expression, compared to patients with pMMR (P<0.05) (*Table 1*).

Multivariate analysis of factors that were associated with MMR status

Binary logistic regression was performed using age, TNM stage, tumour size, histologic type, differentiation, peripheral nerve invasiveness, p53, Bcl-2, TopoII, CD44 and GST. The independent factors that increased the risk of dMMR-related CRC included younger age (OR: 0.979, 95% CI: 0.960–0.998, P=0.032, <0.05), larger tumour diameter (OR: 1.313, 95% CI: 1.162–1.484, P<0.001), poor differentiation, no peripheral nerve invasiveness (OR: 3.018, 95% CI: 1.258–7.239, P=0.013, <0.05), right-side colon cancer (OR: 10.821, 95% CI: 4.895–23.922, P<0.001), Bcl-2 positivity (OR: 0.209, 95% CI: 0.095–0.458, P<0.001), TopoII negativity (OR: 3.333, 95% CI: 1.563–7.103, P=0.013, <0.01) and GST negativity (OR: 1.748, 95% CI: 1.009–3.027, P=0.046, <0.05) (*Table 3*).

Discussion

In the present study, our multivariate analysis revealed that patients with younger age, larger tumour diameter, poor differentiation, no peripheral nerve invasiveness and right-side colon cancer were more likely to have dMMR tumours. Few studies have reported a significant relationship between age and MMR status, although Park *et al.* (10) have reported that MSI-high colorectal adenoma was more common among younger patients; we also found that dMMR was more common among younger patients. These findings suggest that, when CRC is diagnosed at a young age, clinicians should pay close attention to the patient's dMMR status, especially in cases with stage II CRC.

Regarding the various tumour characteristics, our findings revealed that dMMR tumours had larger diameters. Similarly, Yoon *et al.* (11) evaluated 2,028 tumour samples, and found that MSI-high tumours were typically larger. However, both Sun *et al.* (12) and Faghani *et al.* (13) have reported that there was no significant relationship between tumour size and MMR status. Interestingly, the MMR system can activate cell-cycle checkpoints or apoptosis, which might partially explain the occurrence of over-proliferation in tumours with defective MMR. We also

Table 3 Multivariate analysis of the relationship between clinicopathological or molecular features and mismatch repair status

Clinicopathological and molecular features	OR	95% CI	P value
Age	0.979	0.960–0.998	0.032
Stage			
I	3.115	0.564–17.217	0.193
II	1.272	0.248–6.532	0.773
III	2.561	0.529–12.405	0.243
IV	1		
Diameter	1.313	1.162–1.484	<0.001
Histologic type			
Adenocarcinoma	0.707	0.289–1.729	0.447
Adeno + mucin/signet	1.864	0.704–4.932	0.210
Mucin/signet	1		
Differentiation			
Good	0.472	0.155–1.436	0.186
Moderate	0.498	0.288–0.862	0.013
Poor	1		
N stage			
0	6.330	0.47–85.222	0.164
1	1.522	0.416–5.564	0.526
2	1		
Lymph node	1.032	0.999–1.067	0.061
Frequency of M-LN	2.371	0.176–31.975	0.515
PNI			
No	3.018	1.258–7.239	0.013
Yes	1		
Location			
Right-side	10.821	4.895–23.922	<0.001
Left-side	5.44	2.46–12.028	<0.001
Rectum	1		
p53 (no)	0.712	0.365–1.391	0.320
CD44 (no)	1.318	0.664–2.619	0.430
Bcl-2 (no)	0.209	0.095–0.458	<0.001
TopoII (no)	3.333	1.563–7.103	0.002
GST (no)	1.748	1.009–3.027	0.046

OR, odds ratio; CI, confidence interval; M-LN, metastatic lymph nodes; PNI, periphera

found that poor differentiation and no perineural invasion were characteristics of dMMR tumours, and previous studies have reported similar findings (14-16). However, the specific mechanism(s) for these characteristics require further exploration. Ye *et al.* (17) have reported that dMMR tumours were significantly more common in the right colon (20.5%), compared to tumours in the left colon (9.2%) and rectum (5.1%, P<0.001). We also observed a similar trend. In addition, patients with dMMR tumours had a greater number of examined lymph nodes and less lymph nodes metastasis, although these differences were not statistically significant in the multivariate analysis. Interestingly, Takemoto and Smyrk (18,19) have reported that MSI is characterized by tumour-infiltrating lymphocytes, which may explain our findings regarding lymph node involvement. Thus, lymph nodes that are examined due to dMMR tumours may be associated with colitis. Finally, although dMMR in sporadic CRC is associated with a better prognosis (20), we were not able to evaluate this association, as the patients were not followed-up for a long enough period to conduct the relevant analysis.

Our most important finding was that several molecular biomarkers were related to MMR status in patients with CRC. For example, positive expression of the p53 protein was associated with dMMR status (P<0.05), although this association was only significant in the univariate analysis. Similarly, Christine *et al.* have evaluated the distinctive patterns of p53 protein expression and MSI in human CRC, and reported that p53 overexpression was significantly more frequent among MSI-high CRCs. In contrast, Park *et al.* (10) reported that the loss of hMLH1 or hMSH2 expression was correlated with low p53 expression (P<0.001). The reason for this discrepancy may be related to the relationship between *P53* gene mutation and its protein expression, which has been extensively evaluated. Therefore, because there are numerous types of *P53* gene mutations, it is difficult to use p53 expression to predict P53 mutation(s). The p53 protein acts as a tumour suppressor by triggering cell cycle arrest and then correcting the damage via DNA repair. Interestingly, it has been reported that MMR proteins and p53 have complementary effects on the other's activity (21). For example, MMR and p53 can cooperate to control the cytotoxic effects of cisplatin and limit its mutagenic potential in colon cancer cells. This mechanism may explain why CRC patients with dMMR are resistant to chemotherapy.

Another molecular biomarker that was significantly different related to MMR status was Bcl-2, which is

frequently overexpressed in various types of cancer. This protein enables dysplastic and metaplastic cells to survive, and promotes adenoma development, which can eventually progress to an invasive carcinoma. The relationship between Bcl-2 and MMR was first demonstrated by Youn *et al.* (22), who reported that Bcl-2 expression could suppress MMR activity via hyperphosphorylation of retinoblastoma protein (pRb), which enhanced the E2F-pRb complex and decreased hMSH2 expression. In addition, the role of MMR is to protect against the accumulation of deleterious mutations and maintain genomic stability. Therefore, decreased MMR activity via Bcl-2 may be an underlying mechanism for Bcl-2-promoted oncogenesis, as we found that Bcl-2 expression was more common among dMMR cases, compared to among MMR proficient cases. Similarly, Bendardaf *et al.* (23) have reported that Bcl-2 expression was closely correlated with hMLH1 and hMSH2 expression (P<0.01). Furthermore, their data also suggested that MSI patients with low Bcl-2/MMR exhibited a shorter disease-free survival.

We also found that other molecular biomarkers, such as TopoII and GST, were correlated with MMR status. For example, the absence of TopoII and GST expression was more common in dMMR patients, and these factors were found the independently influence the dMMR phenotype after our multivariate analysis. Interestingly, the expression of these two proteins is related to chemotherapy resistance, as Kaplan *et al.* (24) have reported that decreasing TopoIIA, MSH2 and MLH1 expression may help reduce breast cancer resistance to etoposide chemotherapy. In addition, Tsavaris *et al.* have concluded that levels of TopoII expression were higher in tumours from recurrent CRC (25). Furthermore, Shin *et al.* have evaluated GST genotypes in Korean patients with HNPCC, and reported that the GSTM1 genotype was related to cancer occurrence in family members with hMLH1/hMSH2 mutations (26). However, few studies have reported the specific relationship between those two proteins and MMR status in sporadic CRC, and further studies are needed to clarify this relationship.

In the present study, we found that younger age, poorly differentiated tumours, negative peripheral nerve invasiveness and right-side tumours were significantly associated with dMMR in Chinese patients with sporadic CRC. Moreover, dMMR status was closely related to the positive expression of Bcl-2 and the absence of TopoII and GST expression. Therefore, future research should evaluate how the TopoII and GST proteins interact with MMR proteins.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.11.24). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Fudan University Shanghai Cancer Center (reference number 050432-4-1212B) and written informed consent was obtained from all patients.

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